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INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

IASLC 19th World Conference on Lung Cancer

September 23–26, 2018 Toronto, Canada

Abstracts

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PL02 PRESIDENTIAL SYMPOSIUM - TOP 5 ABSTRACTS
TUESDAY, SEPTEMBER 25, 2018 - 08:15-09:45

PL02.01 OVERALL SURVIVAL WITH DURVALUMAB VERSUS PLACEBO AFTER CHEMORADIOTHERAPY IN STAGE III NSCLC: UPDATED RESULTS FROM PACIFIC

S. Antonia[1], A. Villegas[2], D. Daniel[3], D. Vicente[4], S. Murakami[5], R. Hui[6], T. Kurata[7], A. Chiappori[1], K.H. Lee[8], M. De Wit[9], B.C. Cho[10], M. Bourhaba[11], X. Quantin[12], T. Tokito[13], T. Mekhail[14], D. Planchard[15], Y. Kim[16], C. Karapetis[17], S. Hiret[18], G. Ostoros[19], K. Kubota[20], J. Gray[21], L. Paz-Ares[22], J. De Castro Carpeño[23], C. Faivre-Finn[24], M. Reck[25], J. Vansteenkiste[26], D. Spigel[27], C. Wadsworth[28], M. Taboada[29], P. Dennis[30], M. Özgüroğlu[31]

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PL02 PRESIDENTIAL SYMPOSIUM - TOP 5 ABSTRACTS
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PL02.03 BRIGATINIB VS CRIZOTINIB IN PATIENTS WITH ALK INHIBITOR-NAIVE ADVANCED ALK+ NSCLC: FIRST REPORT OF A PHASE 3 TRIAL (ALTA-1L)

R. Camidge[1], H.R. Kim[2], M. Ahn[3], J.C. Yang[4], J. Han[5], J. Lee[6], M. Hochmair[7], J.Y. Li[8], G. Chang[9], K. Lee[10], C. Gridelli[11], A. Delmonte[12], M.R. Garcia Campelo[13], D. Kim[14], A. Bearz[15], F. Griesinger[16], A. Morabito[17], E. Felip[18], R. Califano[19], S. Ghosh[20], A. Spira[21], S. Gettinger[22], M. Tiseo[23], J. Haney[24], D. Kerstein[24], S. Popat[25]

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PL02 PRESIDENTIAL SYMPOSIUM - TOP 5 ABSTRACTS
TUESDAY, SEPTEMBER 25, 2018 - 08:15-09:45

PL02.05 EFFECTS OF VOLUME CT LUNG CANCER SCREENING: MORTALITY RESULTS OF THE NELSON RANDOMISED-CONTROLLED POPULATION BASED TRIAL

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PL02 PRESIDENTIAL SYMPOSIUM - TOP 5 ABSTRACTS
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PL02.07 IMPOWER 133: PRIMARY PFS, OS AND SAFETY IN A PH1/3 STUDY OF 1L ATEZOLIZUMAB + CARBOPLATIN + ETOPOSIDE IN EXTENSIVE-STAGE SCLC

S. Liu[1], A. Mansfield[2], A. Szczesna[3], L. Havel[4], M. Krzakowski[5], M. Hochmair[6], F. Huemer[7], G. Losonczy[8], M. Johnson[9], M. Nishio[10], M. Reck[11], T. Mok[12], S. Lam[13], D. Shames[13], J. Liu[14], B. Ding[13], F. Kabbinavar[13], W. Lin[13], A. Sandler[13], L. Horn[15]

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PL02 PRESIDENTIAL SYMPOSIUM - TOP 5 ABSTRACTS
TUESDAY, SEPTEMBER 25, 2018 - 08:15-09:45

PL02.09 NINTEDANIB + PEMETREXED/CISPLATIN IN PATIENTS WITH UNRESECTABLE MPM: PHASE III RESULTS FROM THE LUME-MESO TRIAL

G. Scagliotti[1], R. Gaafar[2], A. Nowak[3], T. Nakano[4], J. Van Meerbeeck[5], S. Popat[6], N. Vogelzang[7], F. Grosso[8], R. Aboelhassan[9], M. Jakopovic[10], G. Ceresoli[11], P. Taylor[12], F. Orlandi[13], D. Fennell[14], S. Novello[1], A. Scherpereel[15], U. Von Wangenheim[16], M. Kim[17], J. Barrueco[18], A. Tsao[19]

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PL03.05 IT'S ALL IN THE TISSUE

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Lung cancer therapy has been transformed in recent years, especially for patients with advanced stage non-small cell lung cancer (NSCLC). Our biological understanding of diverse lung cancer types has been enhanced by pathological investigation and molecular analysis of tumours, in turn driving and refining tumour classification. Biological features have become targets of therapy. Eestablished therapeutic approaches of surgery, radiotherapy and chemotherapy still prevail, but their usage has been refined by a better understanding of pathology. New treatment approaches include the inhibition of receptor kinases and therapies which enable an existing but constrained immune response to attack the tumour. All of this progress has been driven by research conducted on tumour tissue. In the lung there are (at least) two pathways of carcinogenesis, involving transformation within two different stem cell populations in the bronchial and peripheral terminal respiratory unit (TRU) epithelium respectively. Our understanding of pre-neoplasia and its morphological progression has informed ideas about adenocarcinogenesis in particular, and improved radiological diagnosis of early lung cancer, and impacted lung cancer screening. These concepts also underpinned understanding of the pathology of squamous cell carcinoma, and adenocarcinoma, and tumours allied to these sub-type genres, and drove changes in the 2015 WHO classification of lung cancer. In 2008, the JMDB trial demonstrated superiority of pemetrexed/platinum in advanced 'de facto' adenocarcinomas, rather than squamous cell carcinoma, making accurate subtyping of NSCLC an issue for the pathologist. Differences in immunohistochemical profiles of lineage markers reflecting tumour origin from bronchial or TRU epithelium became a method of predicting NSCLC subtype when morphology was insufficient. This diagnostic approach features in practice recommendations, and is now standard of care. All of this progress has been driven by research conducted on tumour tissue. The use of tyrosine kinase inhibitors in mutant EGFR oncogene-addicted adenocarcinomas was the first major step in the expansion of personalised, precision medicine in the treatment of advanced stage NSCLC. Targeting ALK fusion gene proteins followed soon after, when it was recognised that ALK tyrosine kinase inhibitors were effective in treating adenocarcinomas bearing an ALK gene rearrangement identified by FISH analysis or multiplex PCR testing to demonstrate abnormal mRNA fusion gene products. Then came the realization that these molecular events were associated with a modest elevation in tumour cell ALK protein, which is the oncological effector driving the tumour, and which is also the target of the drugs. The presence of the protein is associated with, and probably required for, efficacy of these drugs. The same scenario is now unfolding for ROS1 gene rearrangement, its protein product and the use of ROS1 tyrosine kinase inhibitors. BRAF V600 mutation are the latest genetic alteration to be regarded, in many guidelines, as a mandatory test in advanced NSCLC due to the efficacy of BRAF kinase inhibitors. Other targets in a predominantly non-squamous cell carcinoma patient population remain on the 'waiting list' and these may become mandatory pending trial data convincing for efficacy, and approval by appropriate regulatory authorities. The alterations, which have inhibitors targeting kinase activity include MET exon 14 skipping mutations, high levels of MET amplification, RET and NTRK gene rearrangements, and HER2 gene mutations. Some of these alterations represent extremely rare genomic drivers but still represent sufficient patient numbers to justify their investigation. Squamous cell carcinoma presents a rather different scenario. The dominance of tobacco carcinogenesis in this cell type means oncogenic addictive drivers are exceptionally unusual. Most squamous cell carcinomas have a complex genome, exhibiting many mutations, many of which cause loss-of-function in tumour suppressor genes, an unpromising situation for therapeutic intervention. All of this progress has been driven by research conducted on tumour tissue and furthermore, the vast majority of the trial biomarker data and clinical detection if these genomic alterations is based upon detection in tumour tissue samples. Immunotherapy, particular the use of anti-PD1 and anti-PD-L1 agents, has had a major impact on standard of care treatment in advanced stage NSCLC, and biomarker testing to enrich treatment populations for clinical benefit has had a major impact on pathological diagnosis. The principle clinical trial-validated and approved biomarker for these drugs is PD-L1 immunohistochemistry (IHC). Whilst the testing algorithms for the approved drugs, or those drugs in advanced stage of trial validation, all consider PD-L1 expression in tumour cells, the algorithm for atezolizumab also includes expression on tumour-infiltrating immune cells. Other assessments of the tumour microenvironment and tumour inflammation are poorly developed in context of immunotherapy biomarker assessment but there is plenty of scope for pursuing this in the future. A little data exists for NSCLC using mRNA immune gene expression signatures but there is almost nothing based upon morphological assessment of tumour inflammation. Tumour mutation burden, as a surrogate for neoantigenicity is another emerging biomarker in this arena, and is also capable of enriching for effective response. Once again, the vast majority of the trial data, and all validated clinical biomarker assessment is based upon examination of the tumour tissue. Lung cancer pathology has 'come of age' in the last 10 years. Of course, pathologists can rightly argue that it always was important and relevant, but it is only in recent years that it has taken such a pivotal role in predictive biomarker assessment to facilitate personalized, precision medicine for patients with NSCLC. More or less everything we know about lung cancer biology comes from pathological analysis of tumour tissue. Although the so called 'liquid biopsy' is an attractive source of biomarker data, it cannot provide detailed, structural (spatial) pathological information about the patients disease, suffers from sensitivity issues which means it does not work for all patients, and is as abstract assessment – it is presumed findings in the blood relate to the patients tumour, but this may not always be so. In the field of immunotherapy is particular, the tumour microenvironment and cellular relationship are set to assume importance. Pathologists need to work to maximize the amount of data that can be derived from the limited tissue samples that we usually have available.

Keywords: tissue diagnosis, biomarkers

PL03 CALL TO ACTION - CHALLENGES AHEAD
WEDNESDAY, SEPTEMBER 26, 2018 - 08:15-09:45

PL03.06 THE FUTURE OF TARGETED THERAPY

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It is a standard of care to treat patients with non-small cell lung cancer (NSCLC) harboring driver oncogenes with respective tyrosine kinase inhibitors(TKI). The list of the driver genes started with the EGFR gene and now it is further expanding to include ALK, ROS1 and BRAF. Survival of NSCLC patients with EGFR mutations has greatly prolonged since the advent of EGFR-TKI. At the turn of the 21st century, the median survival time of patients with metastatic lung cancer was around on year. However, overall survival of patients with EGFR mutation exceeds 3 years and in some studies, it is close to 4 years. However, acquisition of resistance against EGFR-TKI is almost inevitable and it is exceptional to see patients whose disease are cured. Therefore, although introduction of inhibition of oncogenic tyrosine kinases into lung cancer care was a great progress, it is still on the way from the viewpoint of conquering lung cancer. What is needed for further improving patients' outcome? ***Identification of new targets*** In addition to above-mentioned driver genes to which each targeted therapy is approved by the regulatory agencies, RET, MET, HER2, NTRK1 gene mutations are emerging molecular targets and clinical trials to test each inhibitor for clinical activities are actively conducted. Gene alterations such as KEAP1/Nrf1 whose mutations are relatively frequent in NSCLC is also sought for possibilities to become a therapeutic target other than receptor tyrosine kinase. ***Development of strategies to cope with KRAS*** Although KRAS gene mutation in NSCLC was found nearly 40 years ago and is frequently mutated in NSCLC especially those occurring Caucasian patients. However despite the fact that KRAS mutation is mutually exclusionary with other driver gene mutations., strategies to treat these lung cancers have been unsatisfactory. For example, recent large-scale, SELECT-1 study failed to show a superiority of addition of selumetinib to docetaxel in patients with KRAS mutation. This is partly because not all KRAS mutated cancer cells are fully addicted to mutated KRAS function. Considering the magnitude of the patient population, efficient strategies to treat KRAS lung cancer including the development of small molecules and immunotherapy are eagerly awaited. ***Development of mutation-specific and wild-type sparing TKI*** Osimertinib is the first third-generation EGFR-TKIs that is active for both activating EGFR mutations as well as T790M resistant mutations yet sparing wild-type EGFR function. As a result, it showed superior activity over chemotherapy for lung cancer with acquired resistance due to T790M. Following this, the Flaura study showed longer PFS compared with gefitinib/erlotinib. OS result is immature but promising. Because of low activity against wild-type EGFR, adverse events are in general less frequent. This will make it easier for this compound to combine with other modality of therapy, although the incidence of interstitial lung disease was high when combined with durvalumab in the Tatton study. In the case of ALK, alectinib showed prominent superiority in terms of PFS to crizotinib in the J-ALEX and ALEX studies, with better tolerability. These facts clearly indicate that newer drugs that have a higher activity against mutated version but not against wild-type version further prolong patient survival. ***Development of combination strategies*** To maximize patients' benefit, we have to understand the biology of oncogene-driven lung cancer more in detail. When EGFR mutations were initially discovered, NSCLC harboring EGFR mutations were thought to behave similarly in the patients. However, we soon knew that different EGFR mutations may result in different biological/clinical consequences. For example, exon 19 deletion (Del

19) and L858R are sensitizing mutations, exon 20 insertion mutations are resistant against existing TKIs. Other rarer mutations, so-called uncommon mutations are not that as sensitive as Del19. Furthermore, even though with the same EGFR mutation, lung cancer never behaves same in each patient. There is a great heterogeneity in terms of progression-free survival within patients with the same EGFR mutations when treated with EGFR-TKI. This heterogeneity is now being understood as effects of co-occurring genetic alterations (co-drivers). For example, several investigators found that PFS of patients with EGFR mutation plus TP53 mutation has a shorter PFS than those without. These co-occurring alterations that negatively affect PFS include those of CDK2/4, HER2, TP53. Therefore it is clear that EGFR TKI alone will not be able to achieve long-term disease control, necessitating combination strategy. Recently, NEJ009 trial suggested that carboplatin with pemetrexed followed by pemetrexed maintenance plus gefitinib might prolong overall survival up to over 4 years. This illustrates the importance of chemotherapy as well as EGFR-TKI even for patients with driver gene alterations, probably through inhibition of some activities mediated by co-drivers. ***Role of immunotherapy for NSCLC with driver gene mutations*** PD-1 blockade by pembrolizumab is a standard of care for NSCLC with high PD-L1 expression except those with driver mutations. This is because PD-1/L1 antibodies could not derive benefit for the patients with EGFR/ALK alterations over docetaxel, resulting in omission of these patients in the first-line trial except in the case of atezolizumab. IMpower 150 study showed the superiority of carboplatin/paclitaxel/bevacizumab(CPB) plus atezolizumab over CPB not only in wild-type patients but in EGFR/ALK+ cohorts after first-line TKI therapy. It is not very clear this is because of combination with chemotherapy or bevacizumab or both at this point, and also the mechanism of this efficacy is not known. This study re-opened the door to immunotherapy for these patients, which was once almost closed, In this talk, I would like to envision what has to be done in the next 10 years to further improve the outcome of the patients with driver gene and ultimately to cure their disease.

Keywords: Targeted therapy, driver oncogene, combination therapy

ES01 ADVANCES IN LUNG CANCER SCREENING THROUGH IMAGING
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

ES01.01 IMAGE QUALITY CHARACTERISTICS AND NODULE GROWTH MEASUREMENT, MEDICAL PHYSICS AND MACHINE PARAMETERS

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Modern CT scanners are routinely being used to determine the malignancy potential of small sub-centimeter pulmonary nodules. Increasingly, this involves CT scanning and quantitative volume measurement of lung nodules over short time intervals (e.g. 3 or 6 months) to determine whether a change in nodule size consistent with malignant growth has occurred. Although it may appear that current CT scanners are more than capable of reliably performing these quantitative measurements with high quality due to their ability to obtain sub-millimeter resolution lung images, many clinical sites are not taking the steps needed to achieve consistent high quality small lung nodule measurement results. A study of volume measurement performance in a phase II clinical trial observed multiple clinical sites using CT scanners which resulted in errors in volume change measurements as high as 43% [1]. In addition, a 2016 crowd-sourcing study of CT scanner image quality performance using the site's low dose CT lung cancer screening acquisition protocol revealed that 37% of sites used insufficient slice thickness (<= 1.25mm slice thickness is needed) and only 19% of sites used the needed slice thickness and a reconstruction kernel that avoided excessive smoothing and avoided high levels of edge enhancement [2]. Poor CT image acquisition performance has the potential to result in poor lung nodule volume measurement performance which can negatively impact patient care by contributing to unnecessary biopsies and delays in early lung cancer diagnosis. To address these issues the RSNA's Quantitative Imaging Biomarkers Alliance (QIBA®) has developed the QIBA CT Small Lung Nodule Profile that provides a comprehensive set of specifications to ensure that a clinical site attains a minimum level of quantitative imaging performance necessary to achieve a specified lung nodule volume measurement accuracy. The Small Lung Nodule Profile outlines six fundamental image quality characteristics that are needed throughout the full scanner field of view to support precise volumetric measurement of small lung nodules. These characteristics are (1) Edge Enhancement, (2) Three-Dimensional Resolution, (3) Resolution Aspect Ratio, (4) CT linearity, (5) Spatial Warping, and (6) Noise. In general, CT scanners achieve highest fundamental image quality performance at scanner iso-center with some scanners and image acquisition protocols exhibiting large losses in image quality performance as a function of distance from scanner iso-center [3]. These fundamental image quality properties can now be quickly and easily measured by a technologist at any clinical site using a new image quality measurement phantom and fully automated and cloud-based phantom analysis software. To determine the clinical impact of achieved CT image quality performance, a new set of modeling and simulation tools has been developed that can create simulated CT images given the image quality characteristics for a CT scanner and image acquisition protocol [4]. Quantitative measurement software can then be applied to these images resulting in expected measurement performance for a clinical task, such as the bias and precision of solid lung nodule volume change measurement for virtual lung nodules of different sizes. Having these estimates of a CT scanners performance can further be used to one day quantitatively determine the minimum time interval needed in order to be able to distinguish malignant nodule volume growth from a stable lung nodule. Regularly performing these measurements also has the potential to offer numerous advantages to lung cancer screening sites including the ability to determine if scans from two different CT scanner models will produce sufficiently similar image quality and measurement performance. In summary, a new set of phantoms and cloud-based software tools is available that enables more careful control and optimization of CT lung cancer imaging performance based on fundamental image quality properties. These new tools provide several new opportunities for clinical sites to more precisely perform CT lung cancer imaging studies and measurements. **References** [1] Henschke CI, Yankelevitz DF, Yip R, Archer A, Zahlmann G, Krishnan K, Helba B, Avila R, "Tumor volume measurement error using computed tomography imaging in a phase II clinical trial in lung cancer." Journal of Medical Imaging 3(3), 035505 (Jul–Sep 2016). [2] Avila R, Yankelevitz D, Yip R, Henschke C, "P1.03-021 Initial Results from A Novel and Low Cost Method For Measuring CT Image Quality," January 2017. Journal of Thoracic Oncology 12(1):S554-S555. [3] Avila R, Subramaniam R, Henschke C, Yankelevitz D, "Hot Topic: Clinical Implications of CT Image Quality Variation in Low Dose Lung Cancer Screening Scans," 4th World Congress of Thoracic Imaging Proceedings, Journal of Thoracic Imaging, accepted for oral presentation, 2017. [4] Avila R, Jirapatnakul A, Subramaniam R, Yankelevitz D, "A new method for predicting CT lung nodule volume measurement performance," SPIE Medical Imaging Proceedings, 2017.

Keywords: "lung cancer screening", "Image Quality"

ES01 ADVANCES IN LUNG CANCER SCREENING THROUGH IMAGING
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

ES01.02 IMAGE INTERPRETATION AND ADVANCES FROM THE PERSPECTIVE OF THE RADIOLOGIST

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To a large extent the success of the screening process depends on the algorithm used to manage the findings. Therefore, even though the image production might be identical for two different screening programs, if they differ in the way they manage findings, especially nodules, the comparative results between them would be quite different. It is with this in mind that screening programs develop and choose their workup algorithm. In regard to how these algorithms are chosen, several features must be balanced including the rate of false positives and also potential delays in diagnosing lung cancer. Each of these is associated with a potential cost, the fewer the false positives might be associated with an increase in the number of cases where lung cancer diagnosis is delayed. As we have moved from 5 mm size thresholds to 8 mm size thresholds on the baseline scan we can clearly see how these factors are balanced against each other. The number of false positives dramatically declines as the number of cancers where diagnosis will be delayed by nine months will increase. While it is generally assumed that there is a substantial downside to delaying diagnosis, the challenge is understanding how much the delay actually costs in terms of decrease in the curability of the cancer and this is then considered in terms of how often this might occur. Another major feature of management protocols is their dependence on change in size over time to guide the management protocol. Different protocols apply different criteria for measuring change. One of the main differences is that some recommend the use of 3D volumetric analysis while others still rely on 2D measurements. As a general rule, the 3D approach has inherent advantages in that boundaries for the nodule are automatically chosen by the computer, asymmetric growth can be more easily recognized, and the proportional change for a given amount of change is far greater for volume then for diameter measurements. Nevertheless, there may still be circumstances where volume measures can still be misleading and the radiologist still has a very important role in visually inspecting the nodule to confirm whether change has occurred. Along with the measurement of size change, the time interval between measurements is also important in determining whether growth is meaningful. It is not simply enough to say that a nodule is growing, but rather the intent is to understand its growth rate, and this depends on time, with shorter time intervals between scans introducing greater uncertainty. There are currently many algorithms that have been developed. Some focus solely on screening such as Lung-RADS, while others are designed primarily for the incidentally detected nodules. Differences between the algorithms focus primarily on the size thresholds used to define a positive result, the time intervals between repeat scans, the choice of management for a positive finding, differences in the management of nodule subtypes (solid, part-solid, nonsolid), and differences between baseline rounds and repeat rounds. These different algorithms will be compared and data will be presented in terms of the influence on the rate of positive results. An additional consideration here is also how we define a positive result. Some algorithms define the positivity based on a size threshold, whereas others consider this based on a growth threshold or a combination of size and growth. When these growth thresholds are used, the rate of positive results dramatically decreases. In addition to the finding of lung nodules there are many other findings that commonly occur on the scans such as micro-nodules, areas of atelectasis, perifissural nodules, waxing and waning nodules, endobronchial nodules, presumed pneumonias, that might be found by the radiologist but there are no specific guidance rules for management. Here again the radiologist is confronted with the challenge of attempting to balance excess workup against obtaining a firm clinical diagnosis. While many of these examples have no authoritative guidelines as to how they should be managed, some practical guidance is presented.

Keywords: Screening, False Positives, volumetric

ES01.03 DEEP MACHINE LEARNING FOR SCREENING LDCT

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The first computer algorithms to automatically detect pulmonary nodules in CT scans, based on classical machine learning approaches, were developed almost two decades ago. These systems appeared in commercially available computer-aided detection packages. However, a recent study concluded that such older software systems fail to flag a substantial number of cancerous lesions and have a fairly high false positive rate. Recently, algorithms based on deep learning, in particular, convolutional neural networks, have been developed that report high sensitivity with low false positive rates. Similar deep learning algorithms have been successful in classifying nodules as solid, subsolid or part-solid with accuracy comparable to radiologists, and in estimating the probability of malignancy of nodules. The 2017 Kaggle Data Science Bowl combined these tasks into a single challenge where 2000 teams developed methods to predict, on the basis of a single screening CT scan, whether a patient would be diagnosed with lung cancer within one year of the date of the scan. The 10 best performing solutions are now available under an open source license and form the basis of commercial solutions that show, in recent validation studies, a performance comparable to radiologists. Thorough validation studies are now needed to investigate if the good performance of these deep learning systems can be replicated, independent of CT parameters, and how such systems can be implemented in a lung cancer screening setting. Possibilities include the use of AI software as a second reader, as a concurrent reader, or even a stand-alone reader for a fraction of the cases, when widespread implementation of screening will put a too large burden on scarce radiological resources. In this lecture, I will review the currently available computer solutions and discuss their validation and integration into CT lung screening worksflows.

Keywords: artificial intelligence, deep learning, chest ct

ES01.04 MULTI-PHASIC SCREENING - CAN WE ADDRESS COMPETING CAUSES OF MORBIDITY * MORTALITY SUCH AS CORONARY ARTERY DISEASE AND COPD

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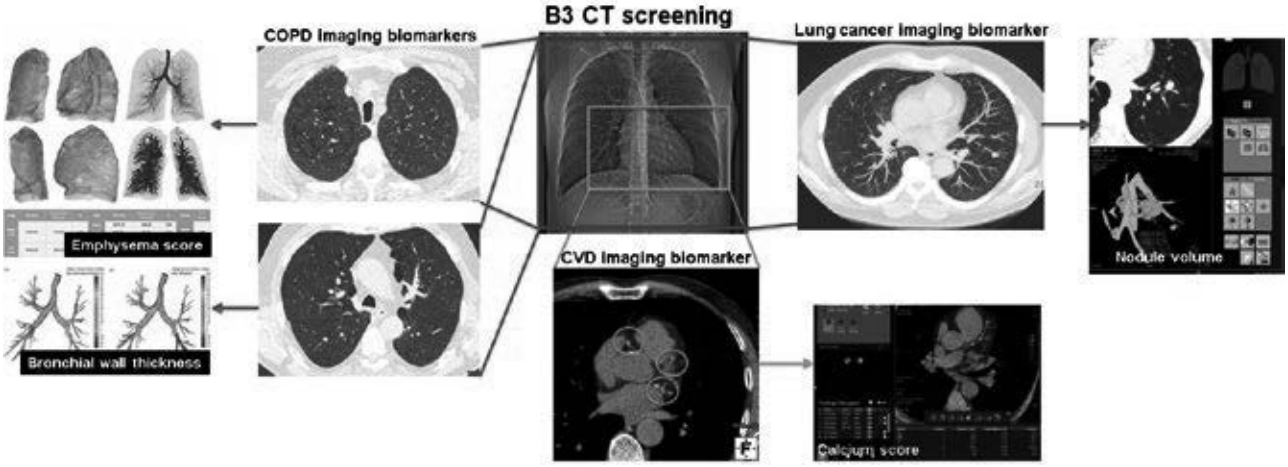
Lung cancer, chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) are highly prevalent in the Western population (annual incidences in the Netherlands: lung cancer n=12,200, COPD n=53,300, and CVD n=101,700). This results in a high burden on the health care system and associated costs, with annual costs of 10 billion euros in the Netherlands alone. Furthermore, lung cancer, COPD and CAD are responsible for a high burden of morbidity, with disability adjusted live year reduction of 2.9, 3.4 and 5.0, respectively. For these so-called Big-3 diseases, treatment is most often initiated at late stages due to late diagnosis after development of symptoms. Early detection and treatment will cure many patients in time, and delay or stop disease progression. Therefore, prevention and early detection are crucial. Currently, no screening is performed for the Big-3. The impact of low-dose computed tomography (CT) lung cancer screening on lung cancer stage shift and reduction of lung cancer mortality has been demonstrated.(1,2) These results have led to recommendations to implement CT screening in high-risk individuals in the USA. Population-based studies have shown the strong relationship between CT-derived extent of CAD and COPD, and mortality, also in lung cancer screening setting.(3-8) However, there is as yet no evidence from randomized controlled trials regarding benefit of CT screening for COPD or CAD. As the high-risk population for the Big-3 is comparable (namely long-term [ex-]smokers), combining imaging biomarkers will likely improve CT screening efficiency. Technological developments in CT allow the determination of early imaging biomarkers for the Big-3, namely lung nodule volume, coronary artery calcium score and lung density/ bronchial wall thickness with low-dose CT (see Figure). Combined evaluation of early signs of the Big-3 diseases has not been extensively explored yet. Major advantages of integrated Big-3 screening can be anticipated due to shared risk factors (in particular long-term smoking) and thus overlapping at-risk population, simultaneous presence of B3 diseases, and the health economic yield compared to a single disease. However, at this moment there is no single CT acquisition that allows for accurate assessment of all Big-3 biomarkers. In particular, calcium scoring based on low-dose chest CT, while providing a good correlation on a population basis, is inaccurate for determining the score on an individual basis.(9) (See below)

Furthermore, there are several challenges that need to be addressed in the preparation and establishment of a B3 screening program. These include the need for evidence of morbidity/mortality reduction for screening of COPD and CAD. Also, B3 imaging biomarkers, particularly for COPD, need validation and standardization. Another hurdle is the labour-intensive work required to obtain B3 imaging biomarkers. Also, education and training for evaluation of B3 CT screening examinations is lacking. Finally, the cost-efficiency of integral B3 screening has not been established. The presentation includes discussion of the background of interest in Big-3 screening, estimated health economic consequences of Big-3 screening, status of imaging biomarker development for the Big-3 diseases, screening population and CT scan protocol, and impediments to Big-3 screening implementation. References: 1. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409. 2. van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med 2009;361:2221-9. 3. Oudkerk M, Stillman AE, Halliburton SS, et al; European Society of Cardiac Radiology; North American Society for Cardiovascular Imaging. 2008. Coronary artery calcium screening: current status and recommendations from the European Society of Cardiac Radiology and North American Society for Cardiovascular Imaging. Eur Radiol. 18:2785-807. 4. Hecht HS, Cronin P, Blaha MJ, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: A report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. J Cardiovasc Comput Tomogr. 2017;11:74-84. 5. Mets OM, Vliegenthart R, Gondrie MJ, et al. Lung cancer screening CT-based prediction of cardiovascular events. JACC Cardiovasc Imaging. 2013;6:899-907. 6. Oelsner EC, Smith BM, Hoffman EA, et al. Prognostic Significance of Large Airway Dimensions on Computed Tomography in the General Population. The Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. Ann Am Thorac Soc. 2018;15:718-27. 7. Mets OM, Buckens CF, Zanen P, et al. Identification of chronic obstructive pulmonary disease in lung cancer screening computed tomographic scans. JAMA. 2011;306:1775-81. 8. Oelsner EC, Carr JJ, Enright PL, et al. Per cent emphysema is associated with respiratory and lung cancer mortality in the general population: a cohort study. Thorax. 2016;71:624-32. 9. Xie X, Zhao Y, de Bock GH, et al. Validation and prognosis of coronary artery calcium scoring in nontriggered thoracic computed tomography: systematic review and meta-analysis. Circ Cardiovasc Imaging. 2013 Jul;6(4):514-21.



ES02.01 EXPANDING PROS IN DAILY PRACTICE

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Lung cancer remains the leading cause of cancer deaths internationally (1). There have been recent improvements in the early diagnosis of lung cancer, with the implementation of lung cancer screening programs in a number of countries and the addition of targeted therapies, which may improve progression free survival for some patients. However, mortality remains high and people living with a lung cancer diagnosis have some of the highest symptom burden experienced across all cancer diagnoses (1,2). Patient reported outcome measures (PROs) can be defined as "any report on the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (3). PROs have been systematically embedded into clinical trials to track side effects and to measure the health related quality of life (HRQOL) of participants. Internationally we are seeing the use of PROs moving into daily clinical practice (4, 5). What are the benefits of using PROs in clinical practice and can they be introduced and embedded into daily practice? PROs can allow patients to highlight to their health care team their current physical and psychosocial issues. In a short clinic appointment with a health care provider the patient may not feel there is time to discuss the most important issues that are affecting them. The health care professional may not ask to right questions to understand the key issues for that person at that time in the context of a short clinic appointment. What is an issue for the patient may not be what the health professional perceives is an issue, leading to barriers in providing truly patient centred care and ensuring shared decision making (6). The utilisation of PROs prior to a clinic appointment can facilitate the therapeutic conversation to ensure the main issues for the patient are addressed at that time. The use of PROs recorded directly into the electronic health record can facilitate communication with the health care team through the receipt of notifications about patient symptoms and function. This can facilitate the management of patient's symptoms in real time, also allowing for the review longitudinal data about a patients PROs over time (7). An RCT into systematic electronic collection of PROs during chemotherapy treatment with automated health care professional e-alerts found the intervention group had better HRQOL, fewer emergency visits and hospitalisations, as well as improved quality-adjusted survival (8). The European Organisation for Research and the Treatment of Cancer (EORTC) QLQ-C30 and the Functional Assessment of Cancer Therapy (FACT-G) are two of the most commonly used general PROs. Both of these PROs have lung cancer subscales, with questions developed and validated for the lung cancer population. In New South Wales, Australia the Edmonton Symptom Assessment Scale (ESAS) and the Hospital Anxiety and Depression Scale (HADS) are being piloted for collection electronically into oncology medical information systems across the state as part of the state-wide collection of PROs in a number of chronic health conditions. Information from these scales will be available for health professionals at the point of care and will also be linked to the NSW Cancer Registry to allow for longitudinal analysis of PROs with specific cancer treatment protocols. The International Consortium for Health Outcomes Measurement (ICHOM) have also developed a lung cancer standard set, using the EORTC QLQ-C30 and EORTC QLQ-LC13 as measures of the degree of health for people with a lung cancer diagnosis (9). With the increasing use of technology, linked e-health records and the understanding of the benefit of the use of PROs in clinical practice cancer centres should be implementing PROs as standard practice in clinical care. This will ensure health care professionals are able to identify and address physical and psychosocial issues for people living with lung cancer at the point of care. References: 1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015;136(5):E359-86. 2. Mohan A, Singh P, Singh S, Goyal A, Pathak A, Mohan C, et al. Quality of life in lung cancer patients: impact of baseline clinical profile and respiratory status. Eur J Cancer Care (Engl). 2007;16(3):268-76. 3. U.S. Department of Health and Human Services. 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Keywords: Patient Reported Outcome Measures, patient centred care, point of care assessment

ES02.02 PRO: TO MEDICATE: MANAGING BREATHLESSNESS

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Breathlessness is a severe symptom that is associated with suffering at end of life. Moderate to severe breathlessness is observed in 20-80% advanced cancer patients, and this symptom is considered as a poor prognostic factor. Currently, opioids (such as morphine) are widely used as first line treatment for reducing the severity of breathlessness in advanced cancer patients. In this session, I will discuss the clinical evidence, involving both efficacy and safety aspects, supporting the routine use of opioids for managing breathlessness.

Keywords: dyspnea, Opioids, breathlessness

ES02.03 CON: NOT TO MEDICATE: MANAGING BREATHLESSNESS

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This presentation will discuss dyspnoea in lung cancer with a focus on non-pharmacological management strategies. Lung cancer is associated with high disease burden and physical hardship. People with lung cancer experience complex symptoms, which can include dyspnoea, fatigue, cough and pain. In lung cancer, multimorbidity is also common, particularly chronic obstructive pulmonary disease (COPD) which is seen in 40-70% of patients, and itself is also associated with chronic dyspnoea. Dyspnoea is the "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity and vary in their unpleasantness and in their emotional and behavioral significance" [1, 2]. It is common in lung cancer, affecting up to 60% of patients. It varies in intensity and is associated with significant unpleasantness [3]. A recent systematic review found that the distress associated with dyspnoea in lung cancer is variable, and there does not appear to be a relationship to disease stage [3]. There are a wide variety of instruments available to measure dyspnoea. It is recommended that assessment includes intensity and sensory quality, distress or unpleasantness, and impact on health-related quality of life [1]. Dyspnoea results in an emotional response and functional consequences [4], including distress and interference with daily activities [5]. Avoidance of triggers, including avoiding physical activity, promotes a vicious cycle of inactivity and functional decline [6]. Whilst the initial focus of managing dyspnoea is to optimise medical and pharmacological management of the underlying lung cancer and comorbid conditions, if dyspnoea persists, there are a range of non-pharmacological strategies that can be considered. There is high level evidence that pulmonary rehabilitation reduces dyspnoea in chronic respiratory diseases, particularly COPD and interstitial lung disease [7]. Similarly, in chronic heart failure, cardiac rehabilitation is also effective at reducing dyspnoea [7]. These outpatient-based exercise rehabilitation programs usually run for 6 to 12 weeks in duration, and include aerobic and resistance exercise training, education and behaviour change. They are associated with reduced self-reported dyspnoea, reduced exertional dyspnoea during exercise, and improved exercise tolerance [1]. The mechanisms in which exercise is thought to reduce dyspnoea in these settings is through system efficiency, reduced dynamic hyperinflation and reduced sensitivity to dyspnoea. There are a range of other strategies for dyspnoea which have been used in a variety of conditions. For short term relief, there is high level evidence for the use of chest wall vibration or walking aids (such as walking frames) [8]. Other strategies, with lower-level or unclear evidence, include breathing exercises (such as pursed lip breathing, breathing control and inspiratory muscle training), music, hand-held fans and acupuncture [8]. Specifically in lung cancer there is less research regarding non-

pharmacological interventions for dyspnoea. In lung cancer, there is growing evidence supporting the role of pulmonary rehabilitation to improve a number of patient outcomes including exercise capacity, muscle strength and fatigue [9]. Studies consistently demonstrate that pulmonary rehabilitation can be applied safely and effectively at all stages of disease [9]. In terms of improving dyspnoea, pulmonary rehabilitation and exercise programs have been shown to be effective, however the impact on dyspnoea has only been studied in a small number of studies to date [10]. Complex interventions for dyspnoea in lung cancer have been successfully tested in a small number of randomised controlled trials. These interventions use a combination of techniques such as patient and carer education, breathing control, activity pacing, relaxation techniques, hand-held fans, psychosocial support and multi-disciplinary input, and are run through nursing or breathlessness clinics. Despite promising evidence regarding the use of non-pharmacological interventions for dyspnoea in lung cancer, these have not been sufficiently implemented into practice [4]. A number of barriers exist including lack of funding for services, the current structure of the multi-disciplinary team, and the need for adequate staff training [4]. Further work is needed to look at how such services can be embedded into lung cancer care. References
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Keywords: dyspnoea, symptoms, pulmonary rehabilitation

ES02 QUALITY CARE IN LUNG CANCER
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

ES02.04 MOLECULAR TESTING 101 FOR NURSES

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Molecular testing in NSCLC is now a standard of care for newly diagnosed non-squamous NSCLC. There are guidelines detailing the appropriate population to test and which tests should be preformed. However, several barriers exist to testing including both medical as well as administrative, making testing rates less than optimal. Several testing platforms exist, and vary internationally. Other challenges for nurses include interpretting the testing results and relaying appropriate information to patients. Also, counseling patients on the value of waiting for results of testing prior to starting therapy can be difficult, and is often performed by the oncology nurse. Utilization of a clinical tissue navigator can make this process more seamless and ensure testing is performed.

Keywords: molecular testing lung cancer

ES02 QUALITY CARE IN LUNG CANCER
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

ES02.05 STRUCTURED APPROACH FOR DEVELOPING AND IMPLEMENTING AND ADVANCED PRACTICE NURSING ROLE IN LUNG CANCER

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Background: Lung cancer patients experience significant physical symptoms, psychological distress and have many supportive care needs impacting their quality of life. In recognition of the complex health needs of patients with lung cancer and the European Partnership for Action Against Cancer recommendations, the University Hospital of Lausanne (CHUV) (Switzerland) aimed to integrate an Advanced Practice Nurse in Lung Cancer (APNLC) within the specialized Multidisciplinary Team (MDT) of the Thoracic Cancer Center. To date, there are limited data on the effectiveness of APNLC interventions for improving lung cancer patient outcomes. Introducing a new Advanced Practice Nursing (APN) role is a complex process and the full integration of this role depends both on successful role development and implementation. International recommendations for developing APN roles recommend pilot testing to assess the feasibility and acceptability of novel APN roles prior to formally assessing the effectiveness of the these roles for patients, providers and organizations. This study aimed to 1) develop and implement an APNLC role within the context of the CHUV Thoracic Cancer Center, 2) explore the acceptability of the new APNLC role from the perspective of a MDT and patients cared for by the APNLC, 3) assess the feasibility of the APNLC consultations and the ability to collect patient-reported outcome measures (PROMs) during first-line treatment, 4) describe changes in self-efficacy for managing lung cancer-related symptoms, symptom intensity/burden and unmet supportive care needs of APNLC patients during first-line treatment. **Methods:** To develop and implement the APNLC role we employed the first 7 phases of the "The Participatory, Evidence-based, Patient-focused process for APN role development, implementation, and evaluation" (PEPPA framework). Focus groups were conducted with nurses (n=5 nurses) and physicians (n=6 physicians) to explore the acceptability of the APNLC role. Additionally, semi-structured interviews were conducted with lung cancer patients (n=4) and the APNLC. The others aims were addressed using a convenience sample of newly diagnosed lung cancer patients receiving systemic therapy with/without radiotherapy. In order to assess the feasibility of the APNLC consultations and the ability to collect PROMs, an exact single-stage phase II design was applied. The study was considered as feasible if at least 55% of patients received all the scheduled APNLC-led consultations and completed PROMs assessments at the three time-points [Baseline, T1 (between day 4-50) and T2 (between day 71-95)]. Descriptive statistics were used to summarize the data and mixed effect models was applied to explore changes in perceived self-efficacy for managing lung cancer-related symptoms, symptom intensity/burden and unmet supportive care needs during first-line treatment. **Results:** Following the first seven phases of the PEPPA framework, the APNLC role was designed based on consensus of key stakeholders within the MDT. The APNLC role focused on providing psychological support, enhancing symptom self-management as well as providing therapeutic education and information about disease/treatments to patients and families. The APNLC role is also tasked with facilitating communication and information exchange within the MDT to improve collaboration and promote continuity of care. The designed APNLC-led intervention included four systematic, alternate face-to-face/telephone consultations with lung cancer patients during first-line treatment. Three main themes emerged describing the acceptability of the APNLC role: "role identification", "role-specific contributions" and "providing flexible service". Physicians and patients alike clearly recognized the APNLC role and emphasized the contribution to continuity of care, providing psycho-social support and enabling symptom self-management. Oncology nurses within the MDT perceived the APNLC role as overlapping with their own role and they expressed concern about losing part of their traditional role. Flexibility in providing care was seen as strength of the APNLC role yet this also posed organizational challenges related to work-load. Among the 46 patients enrolled in the feasibility study, 35 met the feasibility criteria receiving the four APNLC consultations (76%, 95% CI: 0.61-0.87) and 26 completed PROMs assessments at the three timepoints (56%, 95% CI: 0.41-0.71). These initial findings were promising for the feasibility of APNLC consultations and the ability to collect PROMs during first-line treatment. Longitudinal analysis of patient outcomes showed a trend towards improved patient self-efficacy for managing symptoms between baseline and T1, which remained stable at T2. Notably, the intensity of predominant symptoms increased over time yet unmet information needs decreased significantly between baseline and T2 (OR= 0.15 [95% CI: 0.03-0.68] $p<0.01$). **Discussion/Conclusions:** For the first time in Switzerland, we describe the development process of an APNLC role within a multidisciplinary thoracic cancer team. Findings highlight the applicability and the utility of the PEPPA framework as a structured approach for developing and implementing new APNLC roles - particularly in the context of the Swiss health care system where APN roles are yet in early stages of development. Barriers identified during the implementation of the APNLC role were primarily related to intra-professional rather than inter-professional factors. In light of these observations of intra-professional tension, study results underscore the importance of developing a national definition of APN role and regulations guiding APN roles to support their expansion in the country and enhance acceptability of these roles. Initial results were promising in terms of feasibility suggesting that APNLC-led consultations were appropriate and perceived as beneficial for many patients. Indeed, implementation of the APNLC role in the MDT seems to contribute to the improvement and maintenance of patient's perceived self-efficacy for managing symptoms

and decreased unmet supportive care needs. However, to better support lung cancer patients in their symptoms self-management and decrease their symptom burden, findings of this research point to adjustments that could be made to improve the effectiveness of the APNLC role. First, we propose to adjust the dose of APNLC intervention by increasing the frequency and intensity of consultations. Second, we propose to develop an interdisciplinary approach involving joint APNLC-physicians consultations for managing complex lung cancer patients.

Keywords: Advanced practice nursing, Lung neoplasm, supportive care

ES03 HOW TO MANAGE PLEURAL PLAQUES AND PLEURAL EFFUSION WITH NEGATIVE PLEURAL BIOPSY
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

ES03.01 DIAGNOSIS OF MESOTHELIOMA BASED ON CYTOLOGY ALONE

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Historically, the diagnosis of malignant mesothelioma in cytology specimens has been controversial. It is difficult, and some would argue impossible, to make the diagnosis of malignant mesothelioma in cytology specimens since the presence of atypia in mesothelial cells is not specific for malignancy and the lack of architecture inherent in cytology specimens precludes assessment of invasion, which is an important diagnostic feature of malignant mesothelioma. However, relatively recent developments in ancillary tests that aid in the diagnosis of malignancy in mesothelial proliferations have improved our ability to diagnose malignant mesothelioma in cytology specimens. Loss of BAP1 protein expression by immunohistochemistry (IHC) and homozygous deletion of p16/CDKN2a by FISH are specific but not sensitive for malignant mesothelioma (1–4). Recent studies have demonstrated that the combination of both increases the sensitivity for malignant mesothelioma (3–5). Homozygous co-deletion of methylthioadenosine physphorylase (MTAP) occurs in the majority of malignant mesotheliomas with p16/CDKN2A deletions (6-8). MTAP protein expression detected by IHC has advantages over FISH (e.g. not all laboratories perform FISH; truncation artifact can occur with FISH; and IHC requires less time). These ancillary studies, particularly BAP1 IHC and p16/CDKN2A FISH, have become useful in clinical practice for facilitating the diagnosis of malignant mesothelioma in limited samples. Despite these advances, the diagnosis of malignant mesothelioma based on cytology alone remains challenging and there are many cases in which a definitive diagnosis cannot be rendered. References: 1. Churg A, Sheffield BS, Galateau-Salle F. New Markers for Separating Benign From Malignant Mesothelial Proliferations: Are We There Yet? *Arch Pathol Lab Med*. 2015 Aug 19;140(4):318–21. 2. Cigognetti M, Lonardi S, Fisogni S, Balzarini P, Pellegrini V, Tironi A, et al. BAP1 (BRCA1-associated protein 1) is a highly specific marker for differentiating mesothelioma from reactive mesothelial proliferations. *Mod Pathol*. 2015 Aug;28(8):1043–57. 3. Hwang HC, Sheffield BS, Rodriguez S, Thompson K, Tse CH, Gown AM, et al. Utility of Bap1 Immunohistochemistry and p16 (cdkn2a) Fish in the Diagnosis of Malignant Mesothelioma in Effusion Cytology Specimens. *Am J Surg Pathol*. 2016 Jan 1;40(1):120–6. 4. Walts AE, Hiroshima K, McGregor SM, Wu D, Husain AN, Marchevsky AM. BAP1 Immunostain and CDKN2A (p16) FISH Analysis. *Diagn Cytopathol*. 2016 Jul 1;44(7):599–606. 5. Hwang HC, Pyott S, Rodriguez S, Cindric A, Carr A, Michelsen C, et al. BAP1 Immunohistochemistry and p16 FISH in the Diagnosis of Sarcomatous and Desmoplastic Mesotheliomas. *Am J Surg Pathol*. 2016 May;40(5):714–8. 6. Illei PB, Rusch VW, Zakowski MF, Ladanyi M. Homozygous Deletion of CDKN2A and Codeletion of the Methylthioadenosine Phosphorylase Gene in the Majority of Pleural Mesotheliomas. *Clin Cancer Res*. 2003 Jun 1;9(6):2108–13. 7. Krasinskas AM, Bartlett DL, Cieply K, Dacic S. CDKN2A and MTAP deletions in peritoneal mesotheliomas are correlated with loss of p16 protein expression and poor survival. *Mod Pathol*. 2010 Apr;23(4):531–8. 8. Hida T, Hamasaki M, Matsumoto S, Sato A, Tsujimura T, Kawahara K, et al. Immunohistochemical detection of MTAP and BAP1 protein loss for mesothelioma diagnosis: Comparison with 9p21 FISH and BAP1 immunohistochemistry. *Lung Cancer Amst Neth*. 2017 Feb;104:98–105.

Keywords: Mesothelioma, BAP1, cytology

ES03 HOW TO MANAGE PLEURAL PLAQUES AND PLEURAL EFFUSION WITH NEGATIVE PLEURAL BIOPSY
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

ES03.03 WHEN TO REPEAT PLEURAL BIOPSIES

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Malignant pleural mesothelioma (MPM) is a relatively rare and aggressive neoplasm arising from mesothelial cells. Clinical suspicion for MPM may arise in the setting of respiratory symptoms in the context of pleural thickening or an effusion on chest imaging and a history of asbestos exposure. Cytological features in effusions may permit a diagnosis of malignancy but reported sensitivities vary widely. Pleural biopsies are often necessary if a pleural effusion remains undiagnosed after radiological imaging and pleural fluid analysis. Guidelines for optimal ways to diagnose MPM and indications for each of the techniques available (closed pleural biopsy, image-guided cutting needle biopsy, thoracoscopic pleural biopsy) will be reviewed here.

Keywords: pleural biopsies, Mesothelioma, diagnosis

ES03 HOW TO MANAGE PLEURAL PLAQUES AND PLEURAL EFFUSION WITH NEGATIVE PLEURAL BIOPSY
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

ES03.04 ROLE OF CHEMOTHERAPY IN MESOTHELIOMA WITH MINIMAL BULK DISEASE

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Combination chemotherapy is a standard treatment option in management of fit individuals with malignant pleural mesothelioma (MPM) (1). Along with a survival benefit, it is associated with improvements in quality of life. These advantages are in spite of the typical acute side effects experienced with platinum-based regimens. However, the severity of disease-related symptoms relative to a patient's age and comorbid conditions often affect performance status and suitability for chemotherapy. A formal definition of minimal bulk disease has not been established, but descriptions in the literature generally correspond to tumour limited to the pleura, T1 in the latest edition of the AJCC/UICC Staging Handbook. Also implicit in the concept of minimal bulk is pleural thickening that is not bulky, which has been referred to as being less than 10 mm, although a cutoff of 13 mm would be reasonable to adopt based on the revision of the TNM classification (2). Not included in any description of bulk is the size of pleural effusion, if present. Pleural thickening at presentation is less than 10 mm in half of all cases, but one-third have effusions considered moderate or large (3). Categorization as minimal bulk disease gives no indication as to the severity of disease-related symptoms. At diagnosis, the majority with MPM have pleural thickening on CT imaging, as well as pleural effusion, accounting for the most common presenting complaints of chest pain and shortness of breath. Constitutional symptoms such as fatigue and weight loss are indicative of rapidly progressive or more advanced disease. The immediate concern in the majority of patients is implementation of active symptom control: pharmacologic and non-pharmacologic measures for managing chest pain; and thoracoscopy with poudrage or insertion of an indwelling pleural catheter to deal with symptomatic effusions. The effectiveness of these strategies is highlighted in current practice guidelines (1,4). As much as chemotherapy may be of benefit in palliating symptoms such as pain, there is less confidence in its ability to manage pleural effusions. The application of active symptom control strategies addresses the primary palliative needs of the patient, but also facilitates delivery of chemotherapy, if not increase the number of patients suitable for it. For the individual patient with MPM, establishing goals of care is essential to good decision-making. If the main aim is to improve the chance of long-term survival, the bulk of disease may not be relevant to the decision to go ahead with chemotherapy. For others, the preference may be to forego chemotherapy and its side effects, and focus on supportive and palliative measures. In those who are asymptomatic, or whose disease-related symptoms are well controlled, close observation and deferral of chemotherapy is a consideration. There are disadvantages to waiting for symptomatic progression before planning chemotherapy, as early treatment may prolong the time to symptom deterioration and may be associated with a survival benefit (5). However, these differences are probably due to a proportion of those opting to wait never receiving chemotherapy because of a sudden decline in performance status or coming to a personal decision to decline treatment. Deferring chemotherapy may be more appropriate in select cases, such as asymptomatic patients with minimal bulk disease and epithelial histology, where there is an expectation that the disease course could be relatively indolent (1). The aggressive behaviour of MPM in those with elements of

sarcomatoid histology means that the time to symptomatic progression can be expected to be brief, forcing a decision to start chemotherapy. Prognostic indices like the EORTC prognostic model or the modified Glasgow Prognostic Score may be another means of selecting individuals with a better prognosis for close observation (6,7). In summary, patients with minimal bulk disease may have significant disease-related symptoms. Effective palliation requires providing adequate analgesia, and appropriate interventions to manage pleural effusions. Initiation of treatment with chemotherapy will depend on discussion with patients about their goals of care. In select individuals, close observation and deferral of chemotherapy is reasonable. References 1. Kindler HL, Ismaila N, Armato SG 3rd, et al. Treatment of malignant pleural mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018; 36: 1343-1373. 2. Nowak AK, Chansky K, Rice DC, et al. The IASLC Mesothelioma Staging Project: proposals for revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for pleural mesothelioma. J Thorac Oncol 2016; 11: 2089-2099. 3. Seeley JM, Nguyen ET, Churg AM, Muller NL. Malignant pleural mesothelioma: computed tomography and correlation with histology. Eur J Radiol 2009; 70: 485-491. 4. Woolhouse I, Bishop L, Darlison L, et al. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. Thorax 2018; 73 (suppl 1): i1-i30. 5. O'Brien MER, Watkins D, Ryan C, et al. A randomised trial in malignant mesothelioma (M) of early (E) versus delayed (D) chemotherapy in symptomatically stable patients: the MED trial. Ann Oncol 2006; 17: 270-275. 6. Curran D, Sahmoud T, Therasse P, et al. Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. J Clin Oncol 1998; 16: 145-152. 7. Pinato DJ, Mauri FA, Ramakrishnan R, et al. Inflammation-based prognostic indices in malignant pleural mesothelioma. J Thorac Oncol 2012; 7: 587-594.

Keywords: chemotherapy, minimal bulk disease, Mesothelioma

ES03 HOW TO MANAGE PLEURAL PLAQUES AND PLEURAL EFFUSION WITH NEGATIVE PLEURAL BIOPSY
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

ES03.05 ROLE OF SURGERY IN T0 MESOTHELIOMA

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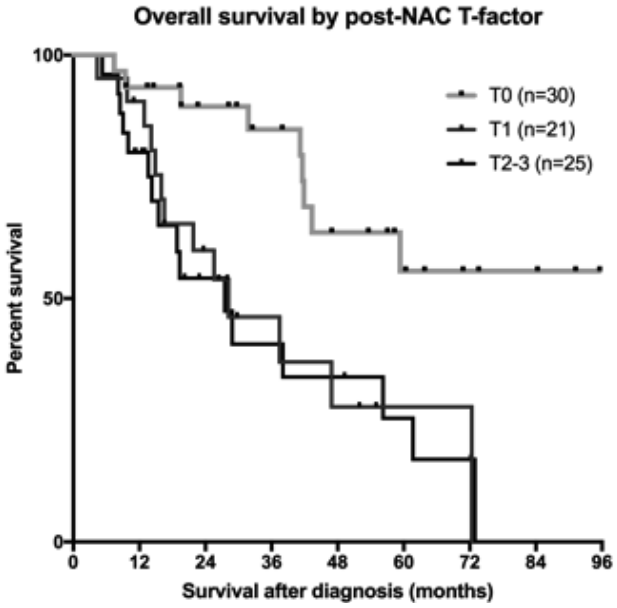
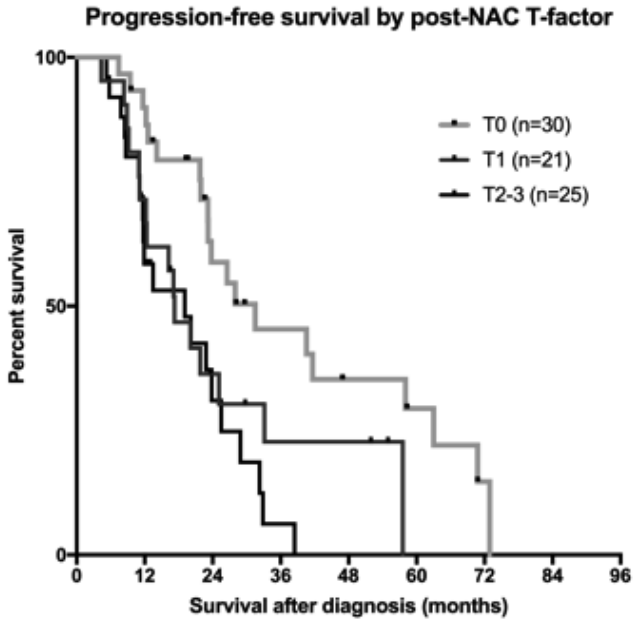
Backgrounds There are increasing number of patients with early malignant pleural mesothelioma (MPM) in Japan. Some part of such early MPM cases have no apparent tumor on preoperative chest CT scan, i.e. radiological T0, but are ultimately staged as clinical T1 on the basis of findings at thoracoscopic biopsy. Currently, more than half of surgical candidates are classified as having clinical T1 disease in our hospital. This situation implies that clinical T1 MPM is not always early disease. In this context, there arise a simple clinical question whether or not patients without visible tumor on preoperative CT have better prognosis in comparison with those with visible tumor. **Hypothesis** Radiological T0 MPM is associated with better survival compared with radiological T1 disease. **Patients and Methods** Definition of radiological T0 Radiological T0 was defined as no apparent tumor with pleural thickness < 5 mm on contrast-enhanced chest CT. Neither of findings from PET/CT nor thoracoscopy were considered. Evaluation of CT was performed by one radiologist (HK) who was blind to any clinical information or survival data. Patients Patients were included in this retrospective study if they had a histologically confirmed diagnosis of non-sarcomatoid MPM, clinical T1N0M0 disease before neoadjuvant chemotherapy (NAC), had contrast-enhanced chest CT both before and after NAC, and underwent curative-intent surgery between October 2008 and December 2017 at the Hyogo College of Medicine. Three courses of platinum plus pemetrexed was employed for NAC and adjuvant chemotherapy Methods Overall survival (OS) and progression-free survival (PFS) were calculated from the day of pathological diagnosis. We used the Kaplan-Meier method to estimate the survival and compared the survivals between groups by Log-rank test. Analysis was based on data updated on June 27, 2018. **Results** A total of 76 patients met the inclusion criteria: 65 males and 11 females; median age of 65 (16-78); 72 epithelioid and 4 biphasic. Patients were categorized into pre-NAC radiological T0 (n=23), T1 (n=29), and T2-3 (n=24), and also post-NAC radiological T0 (n=30), T1 (n=21), and T2-3 (n=25). Of 76 study patients, 27 underwent NAC followed by extrapleural pneumonectomy and postoperative hemithoracic radiation, and the remaining 49 underwent NAC followed by pleurectomy/decortication and adjuvant chemotherapy. Macroscopic complete resection was achieved in 71 patients (93.4%), and the remaining 5 had R2 resection. There was no 30-day mortality. Of 30 patients with post-NAC radiological T0 disease, 12 (40.0%) and 7 (23.3%) were classified as pathological T1 and T2, respectively. In contrast, of 21 patients with post-NAC radiological T1 disease, only one (4.8%) was truly pathological T1 and 15 (71.4%) were classified as pathological T3-4. The median follow-up after diagnosis for survivors was 28.9 months (range 9.6– 95.6 months). For all study patients (n=76), OS and PFS were 41.9 months and 23.2 months, respectively. When analyzed on the pre-NAC CT, survival of patients with radiological T0, T1, and T2-3 were as follows: 2-year OS rate 86.3%, 66.4%, and 55.6%; 5-year OS rate 51.8%, 35.0%, and 29.7%; median survival time not reached, 37.5 months, and 27.5 months; median PFS 26.5 months, 19.1 months, and 22.8 months, respectively. Patients with post-NAC radiological T0, T1, and T2-3 had 2-year OS rate of 89.4%, 59.9%, and 54.2%, 5-year OS rate of 55.6%, 27.7%, and 25.4%, median survival time not reached, 28.2 months, and 27.5 months, and median PFS of 31.5 months, 17.3 months, and 19.1 months, respectively. When analyzed on the pre-NAC CT, no significant difference in OS or PFS was noted between T0 and T1 group. Survival analysis based on post-NAC radiological T-factor revealed that radiological T0 was associated with significant better OS (Figure 1) and PFS (Figure 2) over T1: median survival time not reached vs 28.2 months (P=0.0028, HR=0.30, 95%CI: 0.13 to 0.75); PFS 31.5 months vs 17.3 months (P=0.035, HR=0.51, 95%CI: 0.25 to 1.05). No significant difference in OS and PFS were noted between T1 and T2-3, irrespective on pre- or post-NAC CT. **Comments** Since any type of curative-intent surgery for MPM is highly invasive, development of a predictor for better survival is essential. Current MPM staging system is underpowered to predict long-term survivors. In this context, tumor thickness is considered as a promising T-descriptor and is likely adopted in version 9 IMIG staging system. The present study revealed that post-NAC radiological T0 was associated with significantly better OS and PFS over T1. It is notable that radiological T0 can be re-defined as maximum thickness of zero, and will fit into tumor thickness system. Adoption of radiological T0 may strengthen the next staging system. **Conclusions** Patients with post-NAC radiological T0 MPM were associated significantly better survival in comparison with those with T1 or T2-3 disease. Multimodality treatment with curative-intent surgery is highly encouraged in patients with radiological T0 MPM.





Keywords: Mesothelioma, Surgery, Staging

ES04 LIQUID BIOPSIES IN LUNG CANCER
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

ES04.01 LIQUID BIOPSIES IN LUNG CANCER

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A liquid biopsy in cancer patients generally refers to the sampling and analysis of circulating tumor cells (CTC) or circulating tumor-derived (ct) DNA for the diagnosis and management of patients (1). This contrasts with the traditional tissue biopsy, which still represents the gold-standard to assess the accuracy of liquid biopsies. Liquid biopsy has significant advantage over tissue biopsy as it is more convenient to perform with minimal risk to the patients, thus potentially allows more frequent sampling to monitor disease progression or treatment efficacy (2,3). More recently, liquid biopsy also has been proposed as primary tool for early detection and diagnosis of cancer, or in cancer genotyping to make therapeutic decisions (4). While rapid advances in microfluidic and/or high throughput sequencing technologies have demonstrated the feasibility of quantitative analysis of CTC and ctDNA in advanced stage lung cancer patients, the adoption of these technologies as clinical diagnostics should conform with the accepted principles of laboratory medicine in analytical validity, interpretation, reporting, clinical validity and utility (5). Although circulating tumor cells has been validated and approved by the FDA as a useful prognostic method for many cancer types (6), CTC in lung cancer has not become a clinically useful clinical assay in non-small cell lung cancer (NSCLC), primarily due to the small number of CTC detectable in these patients. In small cell lung cancer patients, CTC has greater number (7), yet its clinical utility still needs to be established. In contrast to CTC, the clinical adoption of ctDNA in lung cancer has occurred rapidly, especially in the detection of T790M resistant mutation during first and second-generation EGFR TKI therapies (8). Since ctDNA represents only a small fraction (<1%) of cell-free (cf) DNA in the blood, most of which are derived from leukocytes, highly sensitive methods are required to detect ctDNA. In general, two methodological approaches are used to "detect" the presence of ctDNA: PCR amplification or hybrid capture of tumor-derived target DNA fragments +/- next generation sequencing. With these techniques, the detection of mutant ctDNA sequences in advanced lung cancer patients with *EGFR* mutated adenocarcinoma has achieved 60-85% sensitivity and >95% specificity, using tissue-based diagnosis as the reference. Many pre-analytical conditions may influence the reliability of results of ctDNA analyses. Additional biological factors (e.g. tumor stage/burden, type, heterogeneity) could also influence the sensitivity of detection of specific tumor genomic aberrations. Since lysis of white blood cells will dilute the ctDNA with leukocyte-derived DNA, it is imperative to collect blood in tubes containing EDTA or leukocyte stabilizing agents (e.g. Streck tube). For the former, blood needs to be processed within 2-4 hours or sooner after collection, while with the latter, they can be kept for up to 48 hours or longer. Plasma is also preferred over serum as clotting increases the amount of non-tumor cf DNA resulting from leukocyte lysis. With the current achievable sensitivity, ctDNA should not be used in treatment naïve patients as the primary method to determine the mutation status of *EGFR* or other actionable driver oncogenes, except when biopsy tissue is insufficient and re-biopsy is not feasible for timely molecular testing. However, despite its suboptimal sensitivity, extensive studies have established the clinical utility of ctDNA for testing T790M in patients with *EGFR* mutant lung adenocarcinoma, who have progressed on first/second generation EGFR TKI therapy (9). The ctDNA assay may include DNA derived from all tumors in the body, thus has the potential of better representation of total body mutation status than tissue biopsy, which usually targets only one of many tumor nodules in metastatic setting. However, the suboptimal specificity mandates that a negative result triggers a tumor tissue re-biopsy to exclude false negative result or to identify other resistant mechanisms, including small cell carcinoma transformation. Other candidate ctDNA assays being studied for their clinical utility in lung cancer include resistant mutations to ALK inhibitors, and tumor mutation burden as predictive biomarker for immune checkpoint inhibitor therapies. Liquid biopsy has generated great excitement among oncologists as it potentially may overcome many of the "tissue is the issue" limitations in current biomarker testing paradigm. However, it is crucial that we apply the same stringency of evidence on liquid biopsy as that has been applied to tissue-based biomarker testing, including the demonstration of clinical validity and utility in clinical trial patient samples. While promising data are rapidly being generated on the roles of ctDNA assay for monitoring and adjusting treatment, or in early detection of lung cancer or residual disease, significant research is still required before they become standards in routine clinical practice. **References:** 1. Crowley E, et al. Liquid biopsy: monitoring cancer-genetics in the blood. Nat Rev Clin Oncol 2013;10: 472–484 2. Sacher AG, et al. Application of Plasma Genotyping Technologies in Non-Small Cell Lung Cancer: A Practical Review. J Thorac Oncol. 2017;12:1344-1356 3. 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Keywords: Diagnostics, Circulating Tumor DNA, blood test

ES04 LIQUID BIOPSIES IN LUNG CANCER
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

ES04.03 OVERCOMING RESISTANCE BY IMPROVING TREATMENT COMPLIANCE

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The use of oral drugs for the treatment of cancer is rising. Over the last two decades, oral antineoplastic agents have increasingly become a primary form of treatment for many cancers. Advances in oral therapies have not only improved outcomes and survival but also have reduced the burden of care by allowing for convenient dosing outside the hospital.[1,2,3] To estimate treatment compliance, it is possible to use some methods, such as: patient self-report, review of patient medical records, family report, residual pill counting, electronic dispensing, prescription refill rates, serum drug, assays to quantify medications or their metabolites and therapeutic outcomes.[2] Despite the notable advantages of using oral medications, there are an array of challenges are created related to patient safety, monitoring of adverse effects, and medication compliance.[1,2] Nonadherence is a problem that has many determinants and the responsibility for compliance has to be shared by health professionals, the health care system and patients. The main factors affecting adherence include, at least, five dimensions: socioeconomic-related factors, health care team/health system-related factors, clinical condition-related factors, treatment-related factors and patient-related factors, as shown in Table 1.[2] Specifically in non-small cell lung cancer (NSCLC), there is a significant fraction of activating-mutations in targetable oncogenes. These include mutations in EGFR (10-40%, depeding on the population)[5], BRAF (~7%)[6], and activating

gene rearrangements involving ALK[7] and ROS1 (1–2%)[7], all of which encode protein kinases, and result in hyperactivation of downstream signaling pathways that drive cell growth, proliferation and survival. The identification of these driver kinases has led to the clinical use of oral kinase inhibitors that suppress these oncoproteins such as erlotinib, gefinitib, afatinib and osimertinib which target mutant EGFR; vemurafenib and dabrafenib for mutant BRAF; and crizotinib, ceritinib, alectinib for ALK and/or ROS1 gene rearrangements. Although targeted therapy agents of NSCLC are directed against tumor cells, they are still associated with toxicities affecting multiple organs. Overall, the side effects described include skin rash, diarrhea, constipation, eyesight alterations, nausea, edema, fatigue, hypophosphatemia, hypokalemia, bradycardia, neutropenia, increased serum ALT and AST, prolonged Q-T interval on EKG, among others. Some studies show that these factors are the main reason for non-adherence. It has become evident that when those side effects are managed appropriately, patients are more likely to want or be able to adhere to established treatment plans.[8,9] The effects of missed doses significantly increase the probability of developing resistance, such as the T790M mutation, which provides tumor resistance against EGFR targeted drugs, and witch is the most frequent mechanism found in NSCLC[5]. Therefore, treatment interruptions and non-compliance may lead to undesirable clinical outcomes: increased morbidity, mortality and also increased health care costs. *Short interruptions or dose reductions, when medically necessary, may not have a negative impact on disease control.*[10] In order to improve compliance, which leads to overcoming resistance and reducing health-related costs, a set of strategies is needed: (1) simplifying the dosage regimen and putting in motion several complex strategies, including: combinations of thorough patient instructions and counseling, reminders, close follow-up, electronic monitoring, supervised self-monitoring, rewards for success, family therapy, couple-focused therapy, psychological therapy, crisis intervention, and manual telephone follow-up; (2) a qualified team acting in the prevention, early identification and management of adverse events; (3) patient awareness and education regarding their treatment; and (4) a health system that facilitate access to oral medications.[2,4] Table 1 - Factors affecting compliance and interventions for improvement.

Factors	Interventions to improve adherence
Socioeconomic	Optimizing the cooperation between services; assessment of social needs;
Health care, team/ health system	Training of health professionals regarding adherence; support to caregivers; multidisciplinary care; supervision in home setting;
Poor understanding of the disease	Eduacation regarding adequate use of medications
Therapy	Simplification of regimens; education on use of medications; giving clear instructions; patient-tailored prescriptions; side effects management
Patient	Education on use of medications; behavioral and motivational intervention; good patient–provider relationship; self-management of disease and treatment; selfmanagement of side-effects

In summary, the number of patients receiving oral chemotherapy is increasing. *However, studies have proved that non-adherence to treatment was associated with poor responses in some diseases, and* there is an urgent need to develop safe and effective systems to administer and manage these agents. *The relationship between noncompliance and outcome in NCLC needs to be better studied.*

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Keywords: Overcoming Resistance, compliance, non-small cell lung cancer

ES05 COLLABORATION BETWEEN STAKEHOLDERS TO IMPROVE LUNG CANCER RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

ES05.02 CAN PATIENT GROUPS AND REGULATORY BODIES WORK TOGETHER TO MAKE CLINICAL RESEARCH EASIER?

A. Ferris
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Background: The lung cancer treatment landscape has rapidly evolved over the past five years, with the U.S. Food and Drug Administration (FDA) approving more than 15 new treatments for advanced-stage non-small cell lung cancer (NSCLC) -- more than in the prior 15 years combined. However, for multiple reasons, including the routine use of overly restrictive eligibility criteria and the difficulty of opening clinical trials in community oncology settings, too many advanced-stage NSCLC patients are unable to participate in clinical trials. As a result, patients do not have early access to potentially life-saving treatments. LUNGevity Foundation is committed to making lung cancer clinical trials more patient-centric and accessible by streamlining the process of conducting studies. **Approach:** In 2015, LUNGevity Foundation began convening multi-stakeholder meetings, the LUNGevity Scientific and Clinical Research Roundtables (SCRTs,) in order to address this complex problem and determine innovative and timely solutions. These Roundtables bring together senior leaders of domestic and international regulatory agencies, clinicians, payers, patient advocates, patients, CROs and trial sponsors to ideate on the most pressing issues confronting the clinical trial landscape, focusing on lung cancer trials as case studies and pilots. The roundtables provide a platform for top officials across sectors to discuss challenges and develop concrete approaches for designing and executing clinical trials that facilitate patient participation and provide earlier access to promising new treatments. **Progress-to-date:** Since its inception, the SCRT program has advanced progress in multiple important areas, developing multi-stakeholder working groups, hosting five in-person stakeholder meetings and three interactive webinars. These efforts have focused on the following workstreams aimed at improving clinical trials from the patient perspective: **Streamlining Lung Cancer Clinical Trials**:

The goal of this roundtable series is to streamline clinical trials and make them more accessible to patients. The three active workstreams include:

· ***Expanding eligibility criteria to allow access to patients that have been historically excluded from lung cancer trials*** - A manuscript was recently published in the Journal of Thoracic Oncology1 presenting recommendations from the multi-stakeholder Expanded Eligibility Working Group on relaxing eligibility criteria to include advanced-stage patients with brain metastasis, poor performance status, and prior malignancies. This Working Group has also identified outdated or unnecessary exclusion criteria frequently seen in lung cancer trial protocols, especially those that may no longer be relevant to current classes of drugs with new mechanisms of action. The group continues to work with regulators and industry partners to revise clinical trial protocols to ensure that such criteria are no longer included in lung cancer trials.

· ***Streamlining reporting of suspected unexpected serious adverse reactions (SUSARs) and adverse events.*** This Working Group has been cataloguing anticipated adverse drug events (ADRs) observed in clinical trials with a goal of advancing understanding of the different types of ADRs and how they should be reported to eliminate excessive and unnecessary reporting.

· ***Creating a prospective real-world control arm for a histological subtype of lung cancer, such as small cell lung cancer (SCLC), where the standard-of-care hasn't changed over the past few decades and the natural history of the disease is well-characterized.*** The goal of this effort is to reduce the numbers of patients needed to complete enrollment for certain trials and maximize the opportunities for patients to access novel therapies. The Working Group is collaborating with health informatics companies to develop and pilot this novel control arm for SCLC trials in the first-line setting. **Patient-Reported Outcomes**:

Due to more patient centric health systems, there has been an increased use and interest in patient-reported outcomes (PROs) to include the patient's perspective in research and clinical practice. With the passage

of the 21st Century Cures Bill, there is a renewed focus and urgency on gathering and incorporating PROs and real-world evidence (RWE) into the drug development process. While PROs have been used for reimbursement decisions outside of the US for many years, there is still limited utilization of PROs to help inform treatment decisions. The Working Group has been focused on improving efforts to gather patient-reported outcomes (PROs) that are meaningful to patients and ensure the information is communicated to patients in a way that is useful in their decision making. The specific questions being asked in this workstream include:

• Why collect PROs and other patient-experience data in cancer trials?

• What PRO concepts should be measured?

• How can PROs be best measured?

• How can we analyze and communicate this data?

Findings from a patient advisory board (comprising 17 lung cancer patients and leaders from the FDA), designed to elicit feedback regarding the core elements of clinical outcome assessments (COA) that FDA previously proposed, will be presented in a manuscript (submitted to The Journal of Thoracic Oncology). The Working Group will continue to synergize with the FDA and industry partners on PRO data collection and use. **Veterans' Access**:

The goal of this roundtable series is to identify barriers and opportunities to ensure that veterans have access to clinical trials through a two-pronged approach –standing up more industry trials within the VA Health Care System and facilitating veteran access to trials outside of the VA health system. These roundtables engage with senior leadership from the Veterans Health Administration, practicing clinicians within the VA, National Association of Veterans' Research and Education Foundations (NAVREF), and industry partners. Ongoing activities include working with the National Program Director for Oncology at the VA on guidance on policies that allow veterans to be referred out to participate in trials outside the VHA, and with the VHA Office of Research & Development and NAVREF on their newly formed Clinical Trials Steering Committee to work on increasing clinical trials within the VHA. **Next topics for action:** LUNGevity Foundation is beginning new workstreams focused on efforts to 1) bring more clinical trials to the community setting, and 2) improve expanded access programs for novel therapies. **References:** 1. Bonomi P, et al. Making Lung Cancer Clinical Trials More Inclusive: Recommendations for Expanding Eligibility Criteria. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. Jun 2018;13(6):748-751.

Keywords: multi-stakeholder, clinical trials, Patient-reported outcomes

ES05 COLLABORATION BETWEEN STAKEHOLDERS TO IMPROVE LUNG CANCER RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

ES05.03 DISCREPANCIES AND SUSTAINABLE ACCESS TO INNOVATIVE THERAPIES: TRANSFORMING PATIENT EXPERIENCE IN TO PATIENT VOICE

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Background Recent years have seen an explosion in new therapies in lung cancer. Research has given us Targeted Therapies, Immunotherapies, minimally invasive thoracic surgery and better directed radiotherapy techniques The challenge is to ensure patients have equitable access to up to date best practice treatment and care, taking advantage of the research developments. There are many reasons for variability in such access - in the main, new therapies cost and Healthcare systems are under enormous financial pressure; resource availability, priority setting and pressures differ between healthcare systems. Furthermore, the pace of change in lung cancer is such that it is difficult to keep up with new developments. Health systems are inherently slow to enact change. Each healthcare system will have its own unique approach to ensuring access to innovative new therapies. In dealing with the reality of finite and scares resources, many countries have developed formal decision making bodies, undertaking Health Technology Assessment (HTA). These processes interrogate both clinical and health economic data. Ethical considerations and patient preference can also be taken in to account. Advocates can work with HTA agencies to ensure that the experience of the patient population impacted by the therapy under review, is part of the assessment. Where assessment processes are not present, advocates can also use the patient experience to work with policymakers in ensuring that a particular disease has enough resources devoted to it. **Using Patient Experience in improving access to new therapies** Through patient experience, advocates have a voice in shaping the process whereby patients access new therapies. There is potential to input across the whole process – designing clinical trials; regulation/licencing; HTA and access procedures. Only people living with a particular health condition can truly describe the challenges they face and the impact that a new therapy will have upon them. Quality of life scores and clinical trial data do not fully reflect patient priorities on aspects of their health and wellbeing. Hence the reason that formal and informal processes have been developed to allow patient advocates to submit the patient perspective to decision makers. In so doing, advocates need to Know the process that is required in their own healthcare system – many Regulators (eg, the FDA) and HTA bodies offer information, training and support to advocates 1. Have the credibility to speak on behalf of their patient community - the ability to contact and survey appropriate patients. 2. Understand the experience of the patient group, receiving the therapy under review. What are the needs and experiences of this patient group? 3. Share patient experience of the therapy under review. What information and data is required to make a contribution? What other therapy options are available? Patient stories can be very powerful. Measuring the **value** which patients attribute to individual therapies, is an area of current interest [1], [2]. This is complex. It can be difficult to define a single set of patient values on a particular therapy. There are many individual patient variables – age, education, expectation, personal finances, social/religious/cultural factors. The focus, therefore, needs to be on inputing a broad range of outcomes, which patients regard as most relevant. **Lung Cancer Patient Specific Issues to consider** In lung cancer, we have a number of specific challenges. Globally, there is a lack of lung cancer patient advocate organisations, who have the ability to engage with this. Lung cancer patients tend to be older, have poorer Performance Status and other co-morbidities. It is often difficult to reach a representative patient group. A better understanding of lung cancer biology and the targeting of therapies, means that new therapies and indications tend to be for smaller, more segmented patient groups. It can be challenging for advocacy organisations to reach these patients in significant numbers. This presentation will, therefore, expand on the areas above and encourage advocates to engage with policy makers to ensure that the lung cancer patient experience is incorporated into decision making on access to new therapies. **References** [1] Narbutas et al, Overview on Patient Centricity in Cancer Care. Frontiers in Pharmacology, Oct 2017; 8: Article 698 [2] Addario et al, Patient value: Perspectives from the advocacy community. Health Expectations. 2018; 21: 57-63.

Keywords: Therapy access, patient voice

ES05 COLLABORATION BETWEEN STAKEHOLDERS TO IMPROVE LUNG CANCER RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

ES05.04 CHALLENGES AND SOLUTIONS IN ENGAGING WITH THE HEALTH TECHNOLOGY ASSESSMENT PROCESS IN CANADA

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Treatment advances in lung cancer have helped increase QoI and survival for lung cancer patients. However, with list prices of over $8000 Cdn per month for recent lung cancer treatments,[1-4] cost can be an insurmountable barrier access for patients. Public coverage offers patients a chance at life-extending treatments that they may not have ability to access. Health Technology Assessment (HTA) bodies are called to answer the value of the new treatment within a context of responsibility to public taxpayer funds. The patient voice within this process is critical to give a "true" assessment of the disease burden which goes beyond ICER's, QALY's and include real world considerations of caregiver time off, and ability to go to treatments by themselves. However patient input into HTA is not standardized and varies across the world. Some countries only accept patient-based evidence that meets scientific standards of collection, or quality of life measures within clinical trials.[5] Canada is fortunate as the Pan Canadian Oncology Drug Review (PCODR-CADTH) is a leader in providing an opportunity for the patient voice in its deliberations by accepting patient group input. HTA within PCODR's deliberative frameworks is based on four quadrants: 1) clinical benefit 2) alignment with patient values 3) cost effectiveness 4) feasibility of adoption into the health system.[6] However treatment advances have challenged the traditional framework, and disease realities have imposed limitations on the patient voice into HTA. These include: 1) Health Canada approval on phase 2 data but positive reimburse recommendations not issued until the release of phase 3 data resulting in coverage delays (some in excess of more than 1000 days) and is challenging in the era of targeted medicine when for some smaller targets, phase 3 trials are not possible 2) Gaps in timing between the trial and HTA submission in a disease with a high mortality 3) Small numbers of patients with experience using the treatment under consideration - especially in the case of targeted medicines 4) Randomized double-blinded trials. Patients

who are on treatment cannot be distinguished from those on comparator By using strategies such as alliances with other cancer patient groups, Lung Cancer Canada has been able to successfully advocate for change to the system. Collaborations with clinicians and using new data sources such as data mining from social media have helped to increase the patient voice within the patient group submission. Other methodologies such as sharing HTA submissions from different countries and strategies employed by other cancer patient groups such as involvement in patient registries can help capture patient reported outcomes and assist in both adopting and increasing the patient voice in HTA deliberations. 1. Canadian Agency for Drugs and Technologies in Health (2018). *Alectinib (Alecensaro) NSCLC (second line)- pERC Final Recommendation*. Retrieved from https://www.cadth.ca/alecensaro-locally-advanced-or-metastatic-non-small-cell-lung-cancer-second-line-details. 2. Canadian Agency for Drugs and Technologies in Health (2017). *Dabrafenib (Tafinlar) Trametinib (Mekinist) NSCLC- pERC Final Recommendation*. Retrieved from https://www.cadth.ca/tafinlar-mekinist-combo-non-small-cell-lung-cancer-details. 3. Canadian Agency for Drugs and Technologies in Health (2017). *Osimertinib (Tagrisso) NSCLC-pERC Final Recommendation*. Retrieved from https://www.cadth.ca/tagrisso-non-small-cell-lung-cancer-details. 4. Canadian Agency for Drugs and Technologies in Health (2016). *Nivolumab (Opdivo) Non-Small Cell Lung Cancer- pERC Final Recommendation*. Retrieved from https://www.cadth.ca/opdivo-non-small-cell-lung-cancer-details. 5. Facey K, Plough Hansen H, Single A (Eds) (2017) *Patient Involvement in Health Technology Assessment*. Singapore: Springer-Nature 6. pCODR-CADTH (2016, March). *pCODR Expert Review Committee Deliberative Framework*. Retrieved from https://www.cadth.ca/sites/default/files/pcodr/The%20pCODR%20Expert%20Review%20Committee%20%28pERC%29/pcodr_perc_deliberative_frame.pdf

Keywords: advocacy HTA patient-input

ES06 OLIGOMETASTATIC DISEASE
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

ES06.01 CURRENT CLINICAL TRIALS IN OLIGOMETASTASES

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Long-term benefit of local ablative treatment in patients with up to 3-5 metastatic sites was seen in several, mainly retrospective, series[1]. In 2012 our group published the first prospective clinical trial in NSCLC patients with synchronous oligometastases [2]. In this single arm phase II study 40 patients with stage IV NSCLC and < 5 metastases, amendable for LAT (radiotherapy or surgery), were enrolled. The 2- and 3-year survival rates were 23.3% and 17.5% respectively. In the last years the concept of oligometastasic treatment evolved. The continuing interest was pushed by the increasing number of available treatment strategies, with widespread introduction of minimal invasive surgery and stereotactic radiotherapy. Several guidelines have described oligometastatic NSCLC as a separate entity. After years of retrospective data and single arm trials reporting on oligometastatic NSCLC, at ASCO 2016 the first randomized phase II trial was presented. Progression free survival (PFS), the primary endpoint, was shown to be significantly superior when oligometastatic NSCLC patients were treated with LAT compared to follow-up or maintenance therapy after treatment with at least four cycles of platinum containing chemotherapy or three months of EGFR-TKI (EGFR mutation) or crizotinib (ALK-rearrangement). These were selected patients as oligometastatic was defined as no progression after this systemic treatment; a maximum of three remaining metastases were allowed. The median PFS were 11.9 and 3.9 months in the LAT and the control group, respectively (HR 0.35, 95% CI 0.18-0.66) [3]. The question arises whether we need additional evidence or whether the randomized phase II trial of Gomez with PFS as primary endpoint will change daily clinical practice. In the meantime another randomized phase II study was recently published, randomizing EGFR/ALK negative, NSCLC patients with up to six extracranial cancer sites (including primary) without progression after 4-6 cycles of chemotherapy to maintenance chemotherapy with or without LAT (radiotherapy) to all tumor sites[4]. Primary outcome was PFS. This study was stopped after an unplanned interim analysis, performed after publication of the Gomez trial. 29 of the 36 planned patients were randomized. The median PFS was 9.7 months in the radiotherapy arm and 3.5 months in the control group (HR 0.30, 95% CI 0.11-0.82, p=0.01). The phase III part of this study is ongoing (NCT03137771) and OS is the primary outcome measure. In addition to both randomized trials, at the 2017 WCLC conference data of a single arm phase II data on pembrolizumab in oligometastatic NSCLC were presented [5]. 45 patients with up to four metastases and no progression after LAT to all known sites were treated with pembrolizumab. The 1-year PFS was 68%. Although the PFS difference is impressive in both randomized phase II studies, there are some concerns to implement this strategy in daily practice. Most importantly the total number of patients enrolled in the two trials combined is very limited (78) and the majority had only one metastatic site. Knowing that assessment of local progression might be a challenge in patients treated with radiotherapy, especially SABR, OS data are needed in order to draw firm conclusions. As patients were randomized after first line treatment baseline characteristics were not known and selection bias might have occurred. What can we expect in the next years? A search on clinical trial.gov learned that ongoing clinical trials all use different definitions of oligometastatic NSCLC and that they require different staging procedures. One of the ongoing trials is the SARON trial (NCT02417662), patients with oligometastatic NSCLC (defined as up to three metastases, FDG-PET and brain imaging mandatory) are registered before treatment initiation and randomized (when no progression after two chemotherapy cycles), between two additional chemotherapy cycles with or without radical radiotherapy to all tumor sites. The number of metastasis and mediastinal lymph nodes are stratification factors. Primary outcome is OS. Hopefully this trial will complete enrolment as it can give the final answer on whether local ablative treatment will improve OS in oligometastatic NSCLC patients. In addition OLIGO-CARE is initiated, a pragmatic observational basket study to evaluate radical radiotherapy for oligo-metastatic cancer patients, a joint project of EORTC and ESTRO. In conclusion, since the trial of Gomez, oligometastatic NSCLC "is there to stay" as some of these patients benefit from systemic treatment combined with LAT. Most trials focus on radical radiotherapy as the LAT modality but optimally trials would also include surgery as an option. However, despite the promising results important aspects have to be addressed. In order to speak the same language we need a uniform definition of oligometastatic NSCLC. The European Organisation of Treatment of Cancer (EORTC) lung cancer group started an initiative to come to a consensus definition of oligometastatic disease for synchronous NSCLC. In addition, these patients have to be accurately staged (i.e FDG-PET and brain MRI/CT), as proposed by the EORTC imaging group[6]. But most important, future trials will have to address predictive factors, as we need a selection tool to identify those patients that will have long-term benefit from LAT. References 1. Ashworth, A., et al., *Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature.* Lung Cancer, 2013. **82**(2): p. 197-203. 2. De Ruysscher, D., et al., *Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450).* J Thorac Oncol, 2012. **7**(10): p. 1547-55. 3. Gomez, D.R., et al., *Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study.* Lancet Oncol, 2016. **17**(12): p. 1672-1682. 4. Iyengar, P., et al., *Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial.* JAMA Oncol, 2018. **4**(1): p. e173501. 5. Bauml, J., et al., *OA 17.08 Phase II Study of Pembrolizumab for Oligometastatic Non-Small Cell Lung Cancer (NSCLC) Following Completion of Locally Ablative Therapy (LAT).* Journal of Thoracic Oncology. **12**(11): p. S1794-S1795. 6. deSouza, N.M., et al., *Strategies and technical challenges for imaging oligometastatic disease: Recommendations from the European Organisation for Research and Treatment of Cancer imaging group.* Eur J Cancer, 2018. **91**: p. 153-163.

ES06 OLIGOMETASTATIC DISEASE
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

ES06.02 INTEGRATING NEW SYSTEMIC THERAPY INTO TRIALS IN OMD

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Significant progress has been made in the treatment of metastatic non-small cell lung cancer (NSCLC) in recent years. The oligometastatic state has been identified and formally adopted by UICC from IASLC recommendations by the creation of the M1b category of the v8 TNM staging system, defining patients with a solitary site of metastatic disease. Parallel to these changes, rapid technical advances in supportive care, minimally invasive surgery, and advanced technical radiotherapy have been implemented alongside a greater biological understanding of NSCLC. Contemporaneously, advances in therapeutics have transformed the face of advanced NSCLC with the routine implementation of personalized molecular oncology into routine care and marked durable responses observed, alongside the recent implementation of immune-checkpoint inhibitor therapy. With the latter, optimal scheduling with radiotherapy has been brought under the spotlight to identify, characterize, and enhance the abscopal effect for maximal clinical benefit. Whilst interactions between systemic chemotherapy and ablative doses of radiotherapy have been established over recent years, significant uncertainty still exist in defining interactions between ablative radiotherapy and novel systemic therapies. Uncertainties include the role of radical consolidation in patients oncogene addicted disease: when to stop tyrosine kinase inhibitor (TKI) therapy and consolidate

with radiotherapy, whether to give traditional radical external beam radiotherapy and risk time off systemic therapy, when (or if) to hold and continue TKI therapy during stereotactic body radiotherapy (SBRT), and if to give ongoing TKI therapy post radiotherapy, and if so, for how long. Similarly for patients with advanced NSCLC suitable for immune checkpoint inhibitor (ICI) therapy, are ICIs the optimal induction agent prior to SBRT, and are they the safest, what risks are observed for combining radiotherapy with ICIs, and does site of oligometastatic disease matter. Finally, should ICIs be given with radical radiotherapy or as consolidation. In this presentation, I will overview ongoing uncertainties in integrating novel systemic therapies into the radical management of the oligometastatic state, discuss current potential treatment strategies contingent on patient scenarios, and highlight presented data to help routine clinical decision-making.

Keywords: NSCLC, Oligometastatic

ES06 OLIGOMETASTATIC DISEASE
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

ES06.04 SURGICAL CONSIDERATIONS IN OMD

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Historically, surgery was reserved for palliation in patients with stage IV NSCLC, but since the 1980s there have been reports of prolonged survival following complete resection of primary tumors and metastatic lesions in select patients with low volume metastatic disease. Hellman and Wechselbaum introduced the term “oligometastasis” to describe an intermediate spread of disease, prior to widely metastatic disease and recognized it as a subset where aggressive local treatments were warranted. Surgery for metastatic NSCLC is increasing in frequency. An analysis from the National Inpatient Sample uncovered a 5.8% average annual percent increase resections of NSCLC metastases between 2000 and 2011.[1]This increase is attributed to several factors, including more efficacious and better tolerated chemotherapies including targeted agents, which have slowed the progression of metastatic spread and altered patterns of resistance. Simultaneously, there have been significant improvements in surgical techniques, with increased minimally invasive approaches, making resection better tolerated and negating long interruption from systemic treatments. The majority of patients considered for resection of oligometastatic NSCLC fall into three categories, isolated metastasis to the brain, adrenal glands, or contralateral lung. Patients who have previously undergone resection of early stage NSCLC and subsequently develope isolated oligometastasis and good performance status should be considered for curative intent resection. Similarly patients with oliogometastsis de novo should be evaluated for curative resection in addition to systemic therapy. **Isolated Brain Metastasis** Some of the oldest series on surgical treatment of oligometastatic NSLC relate to treatment of isolated brain metastasis.[2,3] Up to one quarter of all patients with stage IV NSCLC harbor brain metastasis. Adenocarcinomas are associated with higher rates of brain metastasis, but in 10% of patients with metastatic adenocarcinoma the brain is the only site of involvement.[4] Aggressive curative intent treatment of the primary and metastatic site is encouraged in those with good performance status and in whom both sites are amenable to complete resection or ablation. Curative intent local treatments can only be considered after a thorough search for disease at other sites. Mediastinal lymph node involvement portends poor prognosis and therefore invasive mediastinal staging is recommended prior to starting treatment. Brain MRI is recommended in addition to PET/ CT because of increased sensitivity. Multiple brain metastasis are not an absolute contraindication to this aggressive treatment approach, but most recommend three or fewer lesions.[5] Treatment of the brain lesion can be by resection or radiosurgery ablation. Five year survival following definitive treatment of isolated brain metastasis and primary NSCLC is 15%, and not significantly impacted by synchronous or metachronous presentation. Prognosis is improved in patients who are younger, female, have lower t-stage, and good performance status. Adjuvant whole brain radiation therapy (WBRT) following resection or radiosurgery is recommended. Randomized data on WBRT in this setting is limited, but the sole trial demonstrated a significant decrease brain recurrence.[6] There is also no randomized data specifically addressing the use of adjuvant chemotherapy following complete resection of stage IV disease, but with strong evidence supporting adjuvant chemotherapy for completely resected stage II and III, it is recommended. **Isolated Adrenal Metastasis** In well-selected patients with isolated adrenal metastasis from NSCLC, survival following complete resection is 25%.[7] Similar to those with isolated brain metastasis, mediastinal lymph node involvement portend poor prognosis so invasive staging is recommended. Histology and laterality appear to have no impact on survival and adjuvant chemotherapy is recommended. Synchronous and metachronous tumors have similar long-term survival rates, despite younger age distribution in patients with synchronous presentation.[7] Operative mortality is extremely low in reported series and the majority of patients die of disease progression. **M1a Disease** The appearance of bilateral NSCLC lesions with the same histology is a staging challenge. In the absence of other disease it is difficult to distinguish bilateral primary tumors from stage IVa disease. Analysis of mutational status and genetic clonality difference are being investigated, but not clinically reliable at this time.The clinical judgement of an experienced multi-modality team is essential, [4] and the criteria described by Martini and Melamed in 1975 remains relevant.[8] As with isolated brain and adrenal metastasis, an exhaustive search for additional metastatic disease and invasive mediastinal staging are recommended prior to considering resection. Parenchymal sparing resections are typically recommended when possible in this setting. **Conclusion** Most agree that favorable biology is the primary driver of prognosis in the setting of oligometastasis and the true impact of local interventions on prognosis is unclear. But in an era when local treatments carry minimal morbidity and mortality, the lack of clarity should not translate into a denial of intervention in well-selected patients , but rather another treatment option to prolong survival. **References** 1. Bartlett EK, Simmons KD, Wachtel H, et al. The rise in metastasectomy across cancer types over the past decade. Cancer 2014. 2. Wronski M, Arbit E, Burt M, Galicich JH. Survival after surgical treatment of brain metastases from lung cancer: a follow-up study of 231 patients treated between 1976 and 1991. Journal of neurosurgery 1995;83:605-16. 3. Nakagawa H, Miyawaki Y, Fujita T, et al. 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Keywords: surgery, oligometastasis

ES07 BEYOND THE DIAGNOSIS - COLLABORATIVE CARE FOR CHANGE
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

ES07.01 A MOMENT IN TIME FOR THE UNPLANNED CONVERSATIONS

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Advance care planning (ACP) at its most basic level is a process of a capable person planning for future health care needs and deciding on a substitute decision maker to make health care decisions for them in the event that they become incapable. Over the past several years advance care planning has broadened its definition from a process of a legal document driven approach to one that is individualized, supports patient autonomy and includes a relational approach to ACP. This consensus definition (Sudore et al 2017) is inclusive of engaging adults at any age or stage of illness and their families into conversations that focuses on their goals, values, and preferences for future health care to ensure that patients receive care that is consistent with these values and preferences. It may also include choosing and preparing a trusted person (s) to act on their behalf in the event that they are no longer able to speak for themselves. This definition can also help support clinicians in clinical practice. Lung cancer is the most commonly diagnosed cancer worldwide with eighty five percent of patients being diagnosed at an advanced stage of illness. Despite recent advances in lung cancer treatment it is the leading cause of death from cancer for both men and women in the world. In addition to a significant symptom burden, high mortality and morbidity, patients are faced with complex decisions regarding treatment options, future care and end of life care decisions. Initiating ACP conversations early in a patient’s illness trajectory and revisiting at transition points in a patient’s illness has the potential to ensure they receive care that is consistent with their values, goals and preferences. These conversations may also alleviate the burden on family and reduce conflict with the health care team when patients’ wishes, values and goals are known and honoured. There is overwhelming evidence in the literature that the fear of destroying a patient and family’s sense of hope is one of the primary deterrents for health care clinicians engaging in ACP discussions. Other identified barriers to ACP in the literature are health care clinicians lack of knowledge about ACP, a lack of skills and confidence in how and

when to start these discussions, the fear of causing distress and doing harm, a lack of time and a lack of support from their health care team. A common misconception is that most patients with advanced cancer or advanced illness will talk about ACP related issues if they feel it is important thus putting the onus on the patient rather than the health care clinician (Detering et al 2016, Schickedanz et al 2009). Studies show that a large percentage of nurses and physicians hold the belief that advance care planning conversations should be brought up by the patient and not the care provider as this indicates a readiness to engage in the planning process (Johnson et al 2015). Patient factors to consider prior to initiating an ACP conversation are the patient's readiness and motivation to discuss advance care planning, that families and trusted others can be a motivator or a barrier to ACP and that patients prefer that these conversations are initiated with the health care team that knows them the best. Patients may not initiate these conversations thinking it may not apply to them if their health care team has not initiated the conversation (Sudore et al 2018, Johnson et al 2015). Emerging questions and concerns amongst health care clinicians are; what communications skills are needed, what constitutes an ACP conversation, who should have these conversations, what is the best time in a patient's illness and how do I prepare for it. One of the first things to consider before engaging patients in ACP conversations is to assess your own communication skills and readiness followed by assessing for patient's readiness and motivation. The timing of ACP conversations is important and should be individualized, it may include family or trusted others in the discussion and it should be voluntary. Paying attention to cues from patients can lead to the unplanned conversations. Cues may be implicit or explicit and patients may say…"I always want to be involved in decisions about my treatment and care", "I want everyone to respect what's important to me", "I worry that what I want and don't want will be overlooked", "I am starting to wonder how long I may have to live" and "I don't want to be a burden to my family". The use of patient's own words can help to guide the conversation. Clinician skills are important to have successful conversations that result in positive patient outcomes. Clinicians should have knowledge of ACP, be able to establish a therapeutic alliance, create a safe space for expression of emotion as ACP conversations can be difficult and emotional for the patient, family and the health care clinician, tailor the discussion to individual needs and determine what the patient and family know about the illness and what they know about ACP, an educational approach may be useful. Communication skills and tools can help to support clinicians in their practice. The use of open ended questions or phrases can to help to start the conversation. Some examples are; what is your understanding of your illness, how do you like information to be communicated to you, what brings quality to your life, what do you value most in your life, and is their someone in your life that you trust to make health care decisions for you if you are not able to speak for yourself? The success of having these unplanned conversations relies on knowing the literature, knowing the patient, knowing yourself and having the courage to do it.

Keywords: advance care planning, unplanned conversations, communication

ES07 BEYOND THE DIAGNOSIS - COLLABORATIVE CARE FOR CHANGE
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

ES07.03 SPECIAL NEEDS AND WELLNESS IN LUNG CANCER PATIENTS - EUROPEAN PERSPECTIVE

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Early palliative care among patients with metastatic lung cancer can lead to improvements in various aspects such as quality of life, emotional stability and supportive environment. An integrative care, which combines the standard medical treatments of a palliative care, is considered to be the optimal care. The Palliative care discipline aims to improve patients' quality of life and support their families, as they face a life-threatening illness. A key ingredient of this approach is the ability to identify and to map patients' needs and to address them in a holistic and systematic way. Each individual patient may have different needs, which include symptoms management, patient and family coping, information, social support, etc. This type of care requires the involvement of multidisciplinary team including Oncologist, Radiation unit, palliative team, Psychologist, social worker, spiritual guidance, community services such as home care unit or family physician, inpatient departments and day care treatment units. The need for multi-team effort makes the task of coordination and integration significantly challenging. In order to achieve this goal, the role of the nurse coordinator is both to be the actual coordinator of the various disciplines involved, as well as to mediate the massive amount of information to the patient and his main caregivers. Performing these tasks can reduce patients' confusion, frustration and exhaustion, and remove bureaucratic barriers. As part of this mission, the nurse coordinator builds a treatment plan with the patients and his / her family and main caregivers. During the dialogue, the nurse coordinator informs them about the various aspects of the diagnosis, treatment and the variety ways of coping. In addition, the nurse coordinator is responsible to implementing this multidisciplinary plan. One of the main challenges is maintaining the palliative treatment through a long term illness. As cancer medications might prolong life expectancy and improve patient's well – being, the sense of urgency of palliative care decreases along the patient's journey, despite its utmost importance in prevention of and coping with a commonly seen future deterioration. Whereas in Israel and some European countries the "nurse-coordinator" is inseparable unit in lung cancer case management, other sites are still in the process of adopting this approach. In my talk I will demonstrate this approach through a patient case From Sheba Medical Center in Ramat Gan, Israel.

Keywords: Early palliative care ,nurse coordinator, patients' quality of life

ES07 BEYOND THE DIAGNOSIS - COLLABORATIVE CARE FOR CHANGE
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

ES07.04 LEVERAGING SOCIAL MEDIA TO CHANGE THE PUBLIC CONVERSATION ON LUNG CANCER STIGMA

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The reality of lung cancer stigma is tangible and has a profound impact on people living with this disease. Further, stigma remains a highly significant barrier to fulfilling the clinical promise of advancements in lung cancer treatment, early detection, and reduced lung cancer burden.[1-2] Lung cancer stigma can have far-reaching effects that range from reduced involvement in interventions targeting prevention and early detection efforts such as smoking cessation and screening, impaired patient-clinician communication, delayed access to diagnosis and treatment, negative psychosocial responses, and even more broadly, to limited public support of and actual research funding. The phenomenon of lung cancer stigma is multilevel involving that of the individual, persons in the individuals' immediate environment, persons in the healthcare system, and society at large, which shapes public perceptions and decisions that impact lung cancer patients (e.g., public attitudes, media campaigns, policy, research funding). Stigma is mainly social in nature. It is commonly a perceived or felt stigma as well as internalized by the individual patient influencing patient behavior. The stigma of lung cancer is perpetuated by the public's perception that this is a 'smoker's only' disease. However, many people are not aware that approximately 20% of lung cancer patients diagnosed each year are never smokers.[3] It is imperative that innovative and novel approaches to changing the public perception of lung cancer and its associated stigma are pursued. If you have lungs, you can get lung cancer. As opposed to the prevailing perspective of blame that highlights a lifestyle choice fueled by addiction (i.e., smoking), we need to change the public conversation around lung cancer to one that focuses on early diagnosis, treatment, research dollars that match the magnitude of this deadly disease, and compassion. Comprehensive tobacco control efforts over the past five decades have been lauded as one of the leading public health successes. Specifically, restrictions to smoking in public buildings and spaces, increased tobacco-related taxation, and public health national media campaigns primarily delivered through fear-based messaging have all led to diminished social acceptance of smoking as an appropriate lifestyle behavior. Collectively, this has contributed to the overall success of decreasing U.S. adult smoking rates from 43% in 1964 to the current 15.5% U.S. adult smoking rate.[4] Unfortunately, the demonization of tobacco has had the unintended consequence of stigmatizing the disease of lung cancer negatively impacting those at risk for and living with the disease. Just as the stigmatization of lung cancer did not happen in isolation, addressing this phenomenon requires broad strokes, so to speak, to change the public conversation about lung cancer. We have a unique opportunity to leverage social media platforms like Twitter, Facebook, and Instagram to change this conversation by crafting messaging that empowers rather than further stigmatizes both patients living with lung cancer as well as those at risk. The purpose of this presentation will be to discuss: (1) social media as a platform to change the public dialogue around lung cancer, and subsequently, its associated stigma; (2) how successful traditional population-based marketing can be adapted to the social media platform to target stigma; and (3) future directions in this new communication landscape for evidence-based psychosocial interventions targeted toward decreasing lung cancer stigma. **References** 1. Jacobsen MM, Silverstein SC, Quinn M, et al. Timeliness of access to lung cancer diagnosis and treatment: A scoping literature review. *Lung Cancer.* 2017;112:156-164. doi:10.1016/j.lungcan.2017.08.011. 2. Hamann HA, Ostroff JS, Marks EG, Gerber DE, Schiller JH, Lee SJC. Stigma among patients with lung cancer: a patient-reported measurement model. *Psychooncology.* 2014;23(1):81-92. doi:10.1002/pon.3371. 3. American Cancer Society. Lung cancer risks

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Keywords: Social Media, Lung Cancer Stigma

ES07 BEYOND THE DIAGNOSIS - COLLABORATIVE CARE FOR CHANGE
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

ES07.05 RESEARCH UPDATE: PATIENT'S PERSPECTIVE ON LIVING WITH MALIGNANT PLEURAL MESOTHELIOMA

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Malignant pleural mesothelioma (MPM) is an aggressive, rare cancer due to exposure to and inhalation of asbestos (Odgerel et al 2017). Incidence is higher in certain occupational groups including asbestos mining and disposal and construction industries (Rake et al 2009). Rates vary within and across countries. The UK has approximately 2700 new diagnosis a year, one of the highest internationally. Rates of MPM show no signs of reducing and global incidence and burden is likely to be underreported due to poor data capture in some countries. Whilst asbestos use has drastically reduced in developed countries, significant amounts of asbestos are still used in India, China, Russia, and some developing countries (Frank&Joshi 2016) The latency period for MPM varies from 30 and 50 years with an average of 40. Occasionally exposure to diagnosis can be 10 years or less, but this is uncommon. MPM is an incurable cancer but there are new treatments offering promise in terms of length of life and palliation of symptoms. New radical surgical procedures are being performed and novel drug treatments provide better patient outcomes. In addition there are new procedures for the consequences of MPM such as trapped lung and malignant pleural effusion (MPE). Although showing no signs of the global burden reducing, and the increase of new treatment and procedures, there is little research exploring the experience of living with mesothelioma from the perspective of the person with the disease and their family. This presentation will shine a light on existing research, and provides us with an understanding of the experiences of living with MPM. It will draw on the wider literature as well as recent and current studies being conducted by the author and colleagues. International literature will be included but many references will be to the UK context. The journey of the person with MPM will provide the structure for the presentation. Starting with the long road to diagnosis, the experiences of coming to terms with and understanding the diagnosis will be considered. This will be followed by research on people's experiences of treatment and trials and care related to end of life. An underpinning theme will be balancing the bleak with the positive. The diagnostic process is a challenging experience for patients. Many people describe it as a long and winding road, full of dead ends and false trails, as other possible diagnosis are offered prior to confirmation of MPM. For others whose first symptom is a MPE the distress of the symptoms are compounded by the shock of being delivered a terminal diagnosis. Although challenging, for some actually getting a diagnosis confirmed has the benefit of the end of uncertainty. Understanding and coming to terms with a MPM diagnosis is fraught and perplexing. Not only is the diagnosis life limiting, it was due to exposure to asbestos many years ago. The extent to which people remember and expected consequences of this exposure will impact upon ability to accept the diagnosis. It is not uncommon for people to have never heard of MPM and people can struggle to understand the nature of the tumour and their prognosis. Many people see cancer as a solid tumour or lump, so a diffuse cancer such as MPM is difficult for people to understand. Balancing the needs of patients and family members can be difficult especially if they conflict in terms of the nature of information and the time in the pathway it is requested. Prognostic facts are an example as patients and family carers may differ when and if they want such information. For those with a MPE, there is an urgency to have that treated. Unless the MPE and related symptoms are addresses, people are unable to assimilate information about the underlying diagnosis of MPM. This highlights the importance of timing related to information delivery. As new treatments become available, this will increase the information burden for patients. There are also challenges regarding decision making and tolerating the burden of treatments and interventions (Hughes&Arber 2008, Clayson et al 2005). People will have to understand procedures and eligibility criteria for treatments and face the consequences of being eligible or not eligible. Finding themselves not eligible can be experienced as a 'failure' as well as a loss of hope. For those receiving aggressive treatments they will have to endure any potential side effects and consequences. Legal and compensation processes add additional challenges to the patient journey. Again there may be a time pressure for people to resolve this for family members before the person with MPM dies (Hughes&Arber 2008). Finally research findings regarding end of life are considered, including the access to timely palliative care, pressures on family members in coping with MPM as an industrial disease requiring post-mortem and coroner involvement (Clayson et al 2005). Psychosocial impacts emerge across the pathway as patient's and carers deal with stress, shock, changes to identify, relationships and the demands of managing uncertainty. Throughout the pathway, research indicates the need for people with MPM to balance out the bleak with the positive (Taylor 2018). Understanding this can help health professionals better meet the needs of patients and family. Much of the research on MPM experience highlights the enormity and range of information people have to take on board. Some of this has a time pressure as it is linked to treatment or trial decisions. In conclusion, the contribution of Relationship-centred care' (RCC) will be considered. This expands on and enhances the notion of person-centred care. The proposition is that RCC will help address the complex and challenging nature of improving the MPM patient and carer experiences (Taylor et al 2018). The experience of patient and family carers experiences of MPM is relatively unexplored. We need more evidence to help us understand what is important to them and how care priorities can best be met. At the impact of increased asbestos use in developing countries emerges, with an increase in asbestos related diseases, research to illuminate patients perspectives and experiences in those nations will be required.

Keywords: patient experience, Mesothelioma, quality of life

ES08 THE PATHOLOGIST - AN ESSENTIAL MEMBER OF THE PATIENT CARE TEAM
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

ES08.02 IMMUNOTHERAPY

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Lung cancer is the leading cause of cancer death worldwide with low response rates to conventional chemotherapy. Nevertheless, new therapies have emerged recently based on PD-1 immunity check point inhibitors, such as nivolumab and pembrolizumab, or PD-L1 inhibitors, such as atezolizumab, durvalumab, and avelumab. Numerous standardized PD-L1 assays performed on dedicated platforms have been validated in clinical trials, each antibody being associated to one specific PD1 or PD-L1 inhibitor. The prescription of pembrolizumab for advanced stages non-small cell lung carcinoma (NSCLC) patients requires the demonstration of PDL1 expression by tumor cells immunohistochemistry (IHC) (minimum of 50% of positive tumor cells is required for first-line setting, and of 1% for second-line and beyond) and PD-L1 assay is now considered as a companion diagnostic tool for this drug. To date, four standardized PD-L1 immunohistochemistry Dx assays are available: 22C3 and 28-8 pharmDx assays on Dako platforms, and SP142 and SP263 on Ventana platforms; each assay was developed in combination with a particular anti-PD-1 or anti-PD-L1 drug for testing of patients in clinical trials (pembrolizumab, nivolumab, atezolizumab and durvalumab, respectively). These assays differ in terms of characteristics of the primary monoclonal antibodies, the immunohistochemistry platform type, the detection system used, the interpretation of staining and the relevant positivity thresholds identified in clinical trials. Several recent studies have shown a close analytical performance of the 22C3, 28-8 and SP263 assays with respect to tumor cells staining in NSCLC, whereas the SP142 assay stained a lower percentage of tumor cells. These results lead to the conclusions that 22C3, 28-8 and SP263 were interchangeable tests for PD-L1 expression assessment in tumor cells (ref 1- 7). Accordingly, SP263 assay has been proved by the FDA as a complementary diagnostic test for nivolumab and companion diagnostic tests for pembrolizumab in NSCLC. However, not all pathologists have access to the dedicated platforms and the high cost of these assays is still a limitation to their implementation; in addition, the small size of the NSCLC tumor samples does not allow to perform at the same time multiple assays for multiple drugs. The use of laboratory developed tests seems feasible but their validation must guarantee the same sensitivities and specificities as standardized tests. To date, two studies revealed that nearly half of LDT were not efficient enough to give optimal stain in reference to Dx assays, the other LDT giving acceptable results providing they had been developed according to guidelines for the validation of a theranostic assay. The other limitation of the PD-L1 test is the reproducibility of the interpretation of the staining by pathologists, but this is clearly improved when pathologists are sufficiently trained and experienced (ref 8). Overall, PD-L1 test is of great help to select patients who could benefit for ICO and most pathologists have included this test their daily practice for advanced stages NSCLC, along with ALK and ROS1 IHC. Very useful guidelines have been provided to pathologists (ref 9-10) but there is still a need of more LDT standardization and validation recommandations, training sessions and quality assurances programs. **References** 1. Hirsch FR, McElhinny A, Stanforth D et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. J. Thorac. Oncol. Off.

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Keywords: assays, laboratory developed test, PD-L1 immunohistochemistry

ES08 THE PATHOLOGIST - AN ESSENTIAL MEMBER OF THE PATIENT CARE TEAM
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

ES08.03 MESOTHELIOMA, THYMIC EPITHELIAL TUMORS AND OTHERS

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The role of the pathologist in the patient care team (in particular in relation to multidisciplinary meetings) has increased dramatically in the last decade, in particular in relation to the revolution in targeted treatment for lung cancer. The management of other thoracic tumours is now evolving in similar fashion. For all tumours, the role of the pathologist still has to (a) make the correct diagnosis using the current (2015) WHO classification,[1] but also has to (b) identify increasing numbers of clinically relevant subtypes, often related to molecular findings, (c) stage tumours according to current TNM systems and potentially grade, and (d) manage tissue and ensure relevant molecular testing occurs for targeted therapies. **Mesothelioma** Tumours are divided into epithelioid, biphasic and sarcomatoid types, but accurate diagnosis requires knowledge of the numerous morphologic variants, ranging from tubulopapillary to pleomorphic. These lead to a wide range of potential differential diagnoses and the pathologist needs to know how to distinguish epithelioid mesothelioma from metastatic carcinoma and sarcomatoid mesothelioma from metastatic sarcomas, as well as distinguish reactive mesothelial hyperplasia and reactive fibrous pleuritis from neoplastic proliferations. Until recently, the last of these was predominantly a morphologic assessment of cell morphology and distribution, with limited assistance from immunohistochemistry, although recent data have shown that loss of BRCA1-associated protein (BAP-1) staining and p16 deletion are useful markers of neoplasia.[2] Tumour subtypes may also have relevance in planning management, in particular consideration for surgery in epithelioid versus non-epithelioid variants.[3] Morphologic variants may also have prognostic significance, and a grading system has been proposed. In relation to predictive markers, there are none for standard chemotherapy. However there are several ongoing trials in relation to immunotherapy, with expression of PD-L1 associated with poor prognosis and non-epithelioid variants.[4] Work is however still required in relation to identifying clinically relevant staining cut-offs.Other putative markers that the pathologist may be required to assess are mesothelin expression, as well as genetic alterations in BAP1, NF2 and p16.[5] **Thymic Epithelial Tumours** Accurate histologic classification is again important, with recognition of types A, AB, B1-3 thymoma requiring distinction from thymic carcinoma as well as other mediastinal tumours such as carcinoids, diffuse large B-cell lymphomas and germ cell tumours.[1] Accurate staging is also important, using the 8th TNM system, this having greater prognostic significance than histological subtype.[6] Assessment of completeness of resection is also vital, and may require discussion with the surgeon. However, histological subtyping may be more important in relation to patients who have recurrence.[7] In relation to targeted therapies, there is no evidence for use of EGFR-related drugs, although there are isolated cases showing response to sorafinib and sunitib, which may be related to c-KIT and PDGFR status. However there are no routine immunohistochemical or molecular assessments at the present time. One putative marker is mesothelin, where strong expression has been associated with improved overall survival. In relation to immunotherapy, PD-L1 positivity within tumour cells is associated with high stage and more aggressive histologic subtypes and trials are ongoing. It seems likely that pathologists will be required to undertaken these assessments in the near future. **Other Thoracic Malignancies** Throughout the mediastinum, pleura and lung, a multitude of other malignant tumours may occur. Although rare, the pathologist needs to be aware of these possibilities when faced with unusual histologic features in patients clinically suspected to have either lung cancer, mesothelioma or a thymic epithelial tumour. Even within this group, knowledge of the molecular characteristics is important, with several mesenchymal tumours and lymphoproliferative diseases as well as rarer epithelial malignancies having characteristic genetic abnormalities that aid in diagnosis and may provide targeted therapeutic options (Table 1). Some abnormalities may also point towards considering genetic screening of relatives (e.g. pleuropulmonary blastoma and DICER1 mutations).[8]

Rare thoracic tumours and molecular abnormalities	
1-8 Other carcinomas	
NUT-carcinoma	**NUT translocations**
1-9: Salivary gland-type tumours	
Mucoepidermoid carcinoma	**MECT1-MAML2 gene rearrangement**
1-12: Mesenchymal tumours	
PEComatous tumours	**TSC gene mutations in LAM**
Inflammatory myofibroblastic tumour	**ALK/ROS/RET rearrangements**
Epithelioid haemangioedothelioma	**WWTR1--CAMTA1/YAP1-TFE3 fusions.**
Pleuropulmonary blastoma	**DICER-1 mutations**
Synovial sarcoma	**X:18 translocation**
Pulmonary myxoid sarcoma...	**...with EWSR1-CREB1 translocation**
Myoepithelial tumours	**EWSR1 and FUS fusions**
Localized fibrous tumour	**NAB2-STAT6 gene fusion**
1-13: Lymphoproliferative disorders	
Langerhans cell histiocytosis	**BRAF mutation**
Erdheim Chester disease	**BRAF mutation**

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Keywords: Mesothelioma, Molecular, Thymoma

ES08 THE PATHOLOGIST - AN ESSENTIAL MEMBER OF THE PATIENT CARE TEAM
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

ES08.04 NEOADJUVANT THERAPY

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Currently, neoadjuvant cytototic and radiation therapies are used in standard of care surgically resectable non-small cell lung carcinoma (NSCLC) aiming to improve recurrence free and overall survivals after surgical resection. There is no prospectively conducted clinical trial addressing the role of the pathological response after neoadjuvant chemotherapy in lung cancer. A pathology-based retrospective study demonstrated that a major pathological response (MPR) defined as ≤10% viable malignant cells correlated with significantly improved disease free and overall survival in patients with stages II and III NSCLCs [1]. Importantly, pathological response did not correlate with tumor size changes determined by CT imaging [2]. This study utilized a systematic sampling with serial sections through a resected tumor followed by averaging. Unfortunately, despite the proposals by Pataer *et al* [1] and modified by Hellman *et al* [3], there are not established validated protocols and guidelines to process surgical resected tumors and assess pathological response in NSCLC after neoadjuvant therapy. Recently, with the advent of immunotherapy in lung cancer, several phase II and III clinical trials are ongoing assessing the benefit of PD-L1/PD-1 immune checkpoints blockade in the neoadjuvant setting. Several of these immunotherapy clinical trials adopted the chemotherapy MPR criteria of ≤10% viable cells as endpoint, while others are using recurrence rate. Early results in a limited number of patients has up to 45% MPR when treated with anti-PD-1 therapy and several cases showed of complete response [4]. However, as for chemotherapy, for immunotherapy there is no validated operational standard procedures (OSP) or guidelines on how best process the tumor gross specimens and to microscopically assess pathological response. There are several ongoing initiatives in the pathology community to establish these guidelines with participation of the multidisciplinary lung cancer care team. **References** [1] A. Pataer, N. Kalhor, A.M. Correa, M.G. Raso, J.J. Erasmus, E.S. Kim, C. Behrens, J.J. Lee, J.A. Roth, D.J. Stewart, A.A. Vaporciyan, Wistuba, II, S.G. Swisher, Histopathologic Response Criteria Predict Survival of Patients with Resected Lung Cancer After Neoadjuvant Chemotherapy, J Thorac Oncol 7(5) (2012) 825-832. [2] W.N. William, Jr., A. Pataer, N. Kalhor, A.M. Correa, D.C. Rice, Wistuba, II, J. Heymach, J.J. Lee, E.S. Kim, R. Munden, K.A. Gold, V. Papadimitrakopoulou, S.G. Swisher, J.J. Erasmus, Computed tomography RECIST assessment of histopathologic response and prediction of survival in patients with resectable non-small-cell lung cancer after neoadjuvant chemotherapy, J Thorac Oncol 8(2) (2013) 222-8. [3] M.D. Hellmann, J.E. Chaft, W.N. William, Jr., V. Rusch, K.M. Pisters, N. Kalhor, A. Pataer, W.D. Travis, S.G. Swisher, M.G. Kris, Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint, Lancet Oncol 15(1) (2014) e42-50. [4] P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, D.M. Pardoll, Neoadjuvant PD-1 Blockade in Resectable Lung Cancer, N Engl J Med (2018).

MTE01 PRECLINICAL MODELS OF LUNG CANCER (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE01.01 GEMM OF LUNG CANCER

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The primary induction of lung cancer is difficult to study in humans because patients often present very late in the course of their disease. Genetically engineered mouse models (GEMMs) have therefore emerged as crucial bridging strategies between understanding pathogenic mechanisms and clinical translation. Importantly, they reveal insights on the events and processes underlying tumor initiation and progression, studies which are not possible when employing transplantation or chemically-induced model systems. The recent advent of next-generation sequencing technologies has provided us with an in-depth characterization of the cancer genome of lung adenocarcinoma (LUAD) (1), squamous cell carcinoma (LUSC) (2) and small cell lung cancer (SCLC) (3). While these studies have highlighted the genetic complexities of lung cancers, attention is now focused on elucidating "driver" mutations that confer a growth advantage, from "passenger" mutations that have little impact on malignant transformation. Investigating the loss or gain-of-function of individual genes, alone or in combination, can be directly addressed using GEMM systems. The "gold-standard" lung cancer models are based on *Cre-LoxP* recombination technology that enable the formation of autochthonous tumors from a limited number of somatic cells in a spatial and temporal fashion. Critically, tumors arise sporadically within the lung, in the setting of an intact immune microenvironment. GEMMs are designed to harbor genetic mutations frequently identified in human lung cancer. Cre-inducible alleles are engineered to disrupt tumor suppressor genes (*LoxP* sites flanking key exons (*floxed*), that are removed upon recombination) and/or activate oncogenes (*LoxP*-flanked stop codons (*lox-stop-lox)* that result in gene expression upon recombination). Cre-recombinase is delivered to the lung via inhalation or intra-tracheal injection of a recombinant adenovirus (Ad5) expressing *Cre*-recombinase under the control of a ubiquitous cytomegalovirus (CMV) promoter. Expression of *Cre*-recombinase directs the recombination of floxed alleles in a variety of epithelial cell types in the adult mouse lung (4,5). Utilizing this approach enabled investigators to interrogate the functional consequences of genetic alterations found in human lung cancer through the generation of models of LUAD, SCLC and more recently lung LUSC (6). Moreover, the recent advent of CRISPR-Cas9 gene-editing technology now enables us to interrogate the functional interaction between multiple genetic alterations in a high-throughput setting (7). Furthermore, the generation of cell type specific Ad5-Cre viruses, that restrict *Cre* expression, and thus recombination, to alveolar type II (ATII) (Ad5-SPC-Cre), club (Ad5-CC10-Cre), neuroendocrine (Ad5-CGRP-Cre) and basal (Ad5-K5-Cre, Ad5-K14-Cre) (8) cells, have provided insights into the cellular origins of different subtypes of lung cancer (9,10). Critically, unlike patient-derived xenograft (PDX) models, one additional advantage of GEMMs is the ability to interrogate the interplay between tumor cells and immune cells present in the tumor microenvironment. Such studies are crucial given the success of immune checkpoint inhibitors in lung cancer patients. This presentation will outline lung cancer GEMMs commonly used in the field and how these models can be utilized to identify cancer initiating cells, understand the molecular pathways underlying tumorigenesis, the immune microenvironment of lung cancer, and importantly to identify vulnerabilities that can be exploited for the design of improved treatment modalities for patients. **References** 1. The Cancer Genome Atlas Research Network, *Comprehensive molecular profiling of lung adenocarcinoma* (2014) Nature, 511 (7511) 543-550. 2. The Cancer Genome Atlas Research Network, *Comprehensive genomic characterization of squamous cell lung cancers* (2012) Nature, 489 (7417) 519-525. 3. George *et al.*, *Comprehensive genomic profiles of small cell lung cancer* (2015) Nature, 524 (7563) 47-53. 4. 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Sutherland *et al.*, *Multiple cells-of-origin of mutant K-Ras-induced mouse lung adenocarcinoma* (2014) Proc. Natl. Acad. Sci. USA, 111 (13) 4952-2957.

Keywords: cell-of-origin, GEMM, tumor development

MTE01 PRECLINICAL MODELS OF LUNG CANCER (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE01.02 LUNG PATIENT DERIVED XENOGRAFT AND ORGANOID

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Establishment of preclinical lung cancer models that closely match patient tumor biology is imperative for developing therapeutic strategies with the most translational relevance. Non small cell lung cancer (NSCLC) cell lines grown under 2D conditions or as cell line-derived xenografts (CDXs) are the most widely used models. They have been complemented with murine models engineered to develop lung cancer after introduction of specific genetic alterations (GEMMs). Lung cancer cell lines are readily amenable to mechanistic studies and economical high-throughput drug screening. However, for many NSCLC cell lines, the spectrum of mutations and copy number alterations have drifted considerably relative to patient tumors [1]. This finding, in conjunction with long-term adaption to heterologous in vitro growth conditions, raise concerns about the extent to which cell line biology and potential drug responses may have deviated from clinical tumors. GEMMs are powerful tools for studying specific oncogenic mechanisms in isolation in vivo, but these models lack the intratumoral heterogeneity of patient tumors, which is thought to play a major role in the development of drug resistance. Furthermore, ideally, GEMMs should be constructed using the appropriate cell of origin context, which is challenging, as there are differences in the compositions of human and murine airways, and the cellular origins for most forms of lung cancer have not been established. NSCLC patient-derived xenografts (PDXs) overcome some of the limitations of these other models. They show much less genetic drift than cell lines, and their mRNA expression and the phospho-tyrosyl proteome more closely match patient tumors [1, 2]. We have established a large collection of NSCLC PDXs from surgically resected tumors and endobronchial ultrasound-guided (EBUS) and CT-guided biopsies. Tumor specimens were initially implanted in the subcutaneous flanks of NSG mice (NOD SCID gamma, non-obese diabetic severe combined immunodeficiency, gamma). The PDX tumors have been viably cryopreserved and can be serially passaged in NOD SCID mice. Most of our collection comprises the major histologic subtypes of NSCLC [52 adenocarcinomas (LUAD) and 62 squamous cell carcinomas (LUSC)]. They, along with the primary patient tumors, are being molecularly profiled at multiple levels so that they can be optimally used for personalized medicine studies and novel integrated approaches to understand NSCLC pathogenesis, prognosis, and treatment.
These levels include copy number variations, exome mutations, DNA methylation, mRNA and miRNA expression, and proteomics. In general, the PDX models recapitulate the mutation spectrum, copy number variations, and gene expression of matched patient histologies. They also recapitulate sensitivity and resistance to known targeted therapeutics (e.g. EGFR inhibitors), and thus, can be used to dissect mechanisms underlying differential drug responses. Such studies are ongoing, including investigation of potentially new biomarker-targeted therapeutic combinations. We have also found that not all patient tumor fragments engraft successfully, and that successful engraftment correlates with poor prognosis of the patient [3]. We are using this relationship to discover a new molecular fingerprint to predict clinical outcome, as well as understand the bases that distinguish less and more aggressive tumor behavior. In parallel, we have developed methods to grow organoids from primary patient tumors and PDX models in 3D culture using Matrigel (PDO and XDO, respectively). For LUAD, both the PDO and XDO success rate of establishing bona fide organoid models is ~20%. Our stringent criteria include a minimum capacity of 10 passages and a split ratio of at least 1:3. LUSC has been more difficult to establish as organoid models, with a success rate of 17%, and only from PDXs, so far. Using these methods, we have established 4 models of each histology, which we have confirmed

form tumors when transplanted into mice. Molecular profiling indicates that the organoids maintain the same mutation spectrum and copy number variations of their parental tumor tissue. These models offer distinct advantages over PDXs and cell lines. As compared to standard 2D cultures, they recapitulate the appropriate tissue histology, and thus, possibly clinically relevant growth control mechanisms, even while growing ex vivo. This notion is further supported by the ex vivo conditions supporting gene expression patterns, which allows the organoids to be segregated into their respective tumor histologies when using signatures derived from patient or PDX material. Given the low cost, rapid growth rates, and ease of in vitro manipulation, these models are ideally suited for rapid discovery and testing of new therapeutic strategies that can be matched to specific patient molecular profiles. In summary, generation of molecularly profiled PDX and organoid models offer great opportunity for translational and personalized medicine in NSCLC. 1. Gao, H. *et al.* High-throughput screening using patient-derived tumor xenografts to predict clinical trial drug response. *Nat. Med.* **21**, 1318-1325 (2015). 2. Wang, D. *et al.* Molecular heterogeneity of non-small cell lung carcinoma patient-derived xenografts closely reflect their primary tumors. *Int. J. Cancer* **140**, 662-673 (2017). 3. John, T. *et al.* The ability to form primary tumor xenografts is predictive of increased risk of disease recurrence in early-stage non-small cell lung cancer. *Clin. Cancer Res.* **17**, 134-141 (2011).

Keywords: Organoid, model, Xenograft

MTE02 UPDATE ON WHO CLASSIFICATION AND STAGING OF LUNG CANCER (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE02.01 UPDATE ON WHO CLASSIFICATION AND STAGING OF LUNG CANCER

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The most significant changes in the 2015 WHO classification of the lung tumors include classification criteria for small biopsy and cytology specimens, use of immunohistochemistry, integration of molecular testing, adoption of the IASLC/ATS/ERS adenocarcinoma classification and a strict definition of large cell carcinoma limited to surgical resection specimens only. [1,2] Tumors that show unequivocal morphology of adenocarcinoma or squamous cell carcinoma on a small specimen should be diagnosed without immunohistochemistry. Immunohistochemical work up of poorly differentiated tumors should be limited to TTF-1and p40/p63, while neuroendocrine markers should be used only if morphologically indicated. This approach should reduce the diagnosis of NSCC, NOS to less than 5 % and preserve tissue for molecular testing. [1,2] Major changes in the adenocarcinoma classification for resected specimens include addition of adenocarcinoma in situ (AIS) to preinvasive group that already includes atypical adenomatous hyperplasia. Minimally invasive adenocarcinoma (MIA) defined as a solitary, lepidic predominant adenocarcinoma presenting measuring in gross size 3 cm or less and with invasion of $\leq$ 5 mm was added as a new category. These tumors are also recognized by the 8th edition of the AJCC staging of lung cancer and include Tis(adenocarcinoma) and T1a-mi. T stage of non-mucinous lepidic predominant adenocarcinomas is based on the microscopic size of invasion, but gross size should be recorded in the pathology reports. Multifocal ground glass opacities/lung nodules most frequently present as MIAs and should be classified by the T category of the lesion with the highest T along with the number of lesions (#) or simply (m) for multiple indicated in parentheses, and with a single N and M category that applies to all of the multiple tumor foci. This approach should be applied to grossly or microscopically identified lesions occurring in the same or in different ipsilateral or contralateral lobes.[3] For non-lepidic adenocarcinoma T stage is determined by gross size in 1.0 cm increments as each size subgroup carries prognostic significance. Former mucinous BAC are reclassified as invasive mucinous adenocarcinoma, excluding tumors that meet criteria for AIS or MIA. Signet ring and clear cell carcinomas are considered to represent cytologic variants rather than specific subtypes. Invasive adenocarcinomas should be subtyped by semi-quantitatively estimating the percentage of the various subtypes in 5% increments. [1,2] Reproducibility for lung adenocarcinoma predominant subtypes among pulmonary pathologists was good to moderate (κ-values 0.44 to 0.72).[4] For untrained pathologists, κ-values were lower ranging from 0.38 to 0.47, but these improved after a training session and particularly for individual reviewer. [5] The 2015 WHO classification defines large cell carcinomas based on morphology, as carcinomas without morphologic evidence of glandular, squamous or neuroendocrine differentiation, and also based on null immunophenotype and genotype. [1]This change in definition reflect what was already happening in the pathology practice. According to National Cancer Institute (NCI) Surveillance Epidemiology and End Results registry the diagnosis of large cell carcinoma started to decline about the time that TTF-1 was introduced into clinical diagnosis. 6 References: Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: International Agency for Research on Cancer, 2015. Travis WD. Et al. The 2015 World Health Organization Classification of Lung Tumors Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015; 10 (9); 1243-1260 Frank C. Detterbeck, MD et al. The IASLC Lung Cancer Staging Project: Summary of Proposals for Revisions of the Classification of Lung Cancers with Multiple Pulmonary Sites of Involvement in the Forthcoming Eighth Edition of the TNM Classification . J Thorac Oncol 2016;11(5): 639-650 Thunnissen E, Beasley MB, Borczuk AC, et al. Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study. Mod Pathol 2012;25:1574–1583. Warth A, Cortis J, Fink L, et al.; Pulmonary Pathology Working Group of the German Society of Pathology. Training increases concordance in classifying pulmonary adenocarcinomas according to the novel IASLC/ATS/ERS classification. Virchows Arch 2012;461:185–193. Lewis DR, Check DP, Caporaso NE, Travis WD, Devesa SS. US lung cancer trends by histologic type. Cancer 2014;120:2883–2892.

Keywords: lung carcinoma- WHO classification- staging

MTE02 UPDATE ON WHO CLASSIFICATION AND STAGING OF LUNG CANCER (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE02.02 UPDATE ON WHO CLASSIFICATION AND STAGING OF LUNG CANCER

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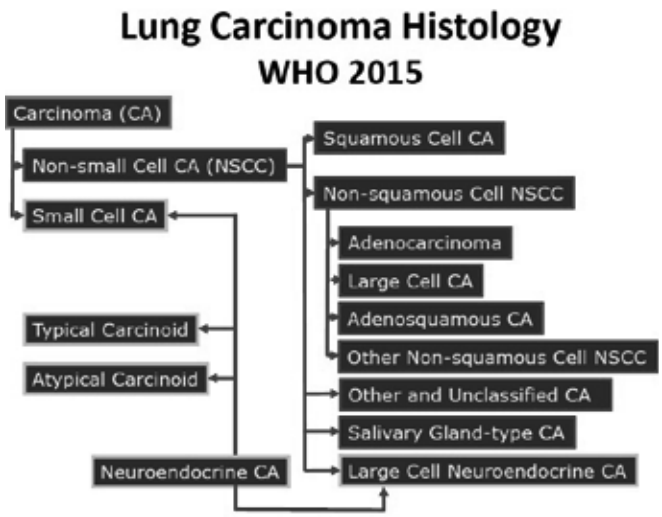
Squamous cell carcinoma comprises approximately 20% of lung cancer cases and is classified into keratinizing, non-keratinizing and basaloid types (1,2,3). The p40 (or p63) immunohistochemical stain is helpful in diagnosing squamous cell carcinoma, if keratinization of the tumor cells is not appreciable. Neuroendocrine tumors comprises of four categories: small cell carcinoma, large cell carcinoma, typical carcinoid and atypical carcinoid (1), with variable degrees of malignant potential. Small cell carcinoma comprises approximately 14% of lung cancer cases and is further categorized into small cell carcinoma and combined small cell carcinoma (1,4,5). The tumor is composed of densely packed small-size tumor cells with scant cytoplasm, finely granular chromatin, and absence of distinct nucleoli. Mitotic figures and apoptotic bodies are frequently seen. Nuclear molding and smearing may be observed. Rosette formation and peripheral palisading, characteristics of neuroendocrine tumors, are consistently found. Large cell neuroendocrine carcinoma has the cytological morphology of large cell carcinoma and the growth pattern of neuroendocrine tumor. Both small cell carcinoma and large cell neuroendocrine carcinoma are high grade tumors. Carcinoid tumors are usually centrally located with endobronchial growth and are further divided into two categories: typical carcinoid (intermediate grade) and atypical carcinoid (low grade). Adenosquamous carcinoma is rare and comprises 0.4-4% of lung cancer cases (1,6,7). Presence of both adenocarcinoma and squamous cell carcinoma components and each component comprising more than 10% is required. Sarcomatoid carcinoma comprises less than 1% of lung cancer cases and is further subcategorized into pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma (1,8). Given the marked histological heterogeneity, sarcomatoid carcinoma need to be thoroughly sampled before the final diagnoses are made. Salivary gland-type carcinomas include mucoepidermoid carcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma, arising from the salivary-type glands of the bronchial mucosa (1). In summary, the major types of lung carcinomas are outlined in **Figure 1**.

(See next page)



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Keywords: Lung, Carcinoma, Classification

MTE03 CLINICAL TRIAL DESIGN WITH NOVEL LUNG CANCER THERAPY (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE03.01 INCLUSION/EXCLUSION UPDATES (CNS METS, MULTIPLE PRIOR CANCERS, ORGAN DYSFUNCTION)

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Introduction Randomized clinical trials (RCTs) represent the gold standard trial design for the evaluation of treatment interventions. Advancing knowledge in oncology has relied heavily on data from high quality RCTs focusing on important outcomes such as overall survival (OS) and more recently progression free survival (PFS). Many examples exist, even in recent times, where the use of alternate study designs, such as cohort and case control series, have concluded benefit for a therapy that was subsequently disproven by RCTs. Nevertheless, an increasing number of therapies are being approved by licensing authorities such as the FDA, based on intermediate outcomes such as objective response rate (ORR) from phase II clinical trials. *Pragmatic versus explanatory trials* RCTs can be either explanatory or pragmatic. Explanatory trials evaluate a treatment intervention under ideal conditions. They tend to have more restrictive inclusion and exclusion criteria to minimize the potential for confounding due to coexistent health problems. Pragmatic trials, on the other hand, evaluate treatment interventions in real life practice conditions. Inclusion and exclusion criteria are generally less restrictive and the results are considered more generalizable to the broad population of people with the underlying condition. RCTs in oncology are often explanatory in design. Inclusion criteria generally limit eligibility to the highest functioning patients. They often specify the type of diagnostic material needed and require samples to be available for correlative studies. Trials are generally very restrictive in regard to prior therapy that patients may have received and most trials require normal, or near normal organ function for eligibility. Exclusion criteria contain lengthy lists of criteria that make patients ineligible. Many trials exclude patients with brain metastases unless they have been treated and stable for some time. There are often lengthy lists of coexistent health problems, such as cardiac disorders, that commonly coexist in patients with lung cancer, that make an individual ineligible. The end result is that the generalizability of many RCTs is limited and healthcare providers need to extrapolate trial findings to a large proportion of their patients who might not have met inclusion and exclusion criteria for the trial generating the evidence of efficacy. *Why should we rethink our current approach* Historically, most advances from RCTs in lung cancer have represented small incremental gains in OS or PFS. Under these conditions, dependence on explanatory trials with multiple inclusion and exclusion criteria may well have been appropriate to minimize the confounding effects from intercurrent problems. However, many changes have taken place in therapeutic options for lung cancer patients over the last decade. Our understanding of underlying molecular abnormalities important in lung cancer development and growth has increased greatly. Multiple agents targeting underlying molecular abnormalities have demonstrated ORR almost twice that of conventional chemotherapeutic agents, with similarly impressive improvements in PFS. Additionally, many newer agents have been developed that cross the blood brain barrier and have demonstrated significant anti-tumor activity in patients with CNS metastases as well. Given the improved tolerability of these agents and increased expectation of benefit from therapy, less stringent inclusion and exclusion criteria should be considered. Trials of targeted therapies should include a broader spectrum of patients including those with lower performance status and untreated CNS disease. Criteria focusing on organ function should be limited to known toxicity concerns for the therapy under evaluation. The emergence of treatments targeting activation of the immune system also represents a significant therapeutic advance. Some trials evaluating immune checkpoint inhibitors have been very restrictive for patients with CNS metastases. Nevertheless, responses are seen in patients with CNS metastases, questioning the need for such restrictive exclusion criteria. Patients with underlying autoimmune disorders are excluded from the majority of trials of immunotherapy agents. Some emerging data exists though suggesting that these agents may be safely given to patients with underlying autoimmune diseases. These findings highlight the need to modify inclusion and exclusion criteria for trials of immunotherapy agents to gain information of safety and efficacy in these populations of patients and to increase the generalizability of trial findings. *Conclusions* The advancement of knowledge in oncology remains dependent on well conducted RCTs. However, we need to question the rigidity of a number of common inclusion and exclusion criteria in an attempt to improve the pragmatic aspect of many trials and increase the generalizability of current RCTs.

MTE03 CLINICAL TRIAL DESIGN WITH NOVEL LUNG CANCER THERAPY (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE03.02 NOVEL TRIAL DESIGN FOR PRECISION MEDICINE

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Trial design for precision medicines has shifted to increasing use of platform protocols, 'liquid' biopsy and the practice of co-clinical trials using patient or circulating tumour cell derived (PDX/CDX) models. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors were the first class of precision medicine approved for advanced non-small cell lung cancer (NSCLC) but initially for unselected patients following the traditional convention of phase I evaluation in heavily pretreated populations, phase II evaluation also in pretreated, 'all comers', and then in large, randomised, phase III, double blind, placebo controlled studies versus best supportive care. The linkage between sensitising EGFR mutations and their prediction for efficacy came later. It now seems remarkable that these agents made it through to standard of care and is questionable whether they would have been approved for all comers in the current health economic climate. The 'EGFR story' catalysed the current goal to integrate drug-target linkage early in clinical development. This was achieved for the first in class ALK inhibitor, crizotinib, initially developed as a MET inhibitor but on discovery of ALK gene fusion and its potency for ALK a strategy to enrich for patients with tumours positive for ALK gene fusion by fluorescent in situ hybridisation (FISH) ensued. The phase I trial (PROFILE 1001) led to accelerated approval within 4 years on the basis of response rate, setting the paradigm of 'enrichment' studies for precision medicine development. (2) In parallel, platform studies using 'umbrella' or 'basket' protocol designs emerged to screen prospectively for multiple targets simultaneously and enrol the patient to a study arm designed for the target/biomarker(s)

present. The first of these studies to be conducted in lung cancer was the BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trial (3) and subsequent examples ongoing are the Lung Master Protocol (Lung-MAP)-A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400 (4) and the National Lung Matrix Trial in the UK (5). Obvious strengths for umbrella studies are a single protocol, screening for a panel of molecular alterations simultaneously and flexibility to add new study arms (and testing modalities) but criticisms include a high attrition rate both due to sample inadequacy for molecular testing and lack of a study arm for the biomarker(s) identified. Regardless of the study design, translational science to rigorously evaluate serial predictive biomarkers of response and resistance is crucial and in this regard new technologies for liquid biopsy are proving transformational, overcoming the reliance on tissue biopsy that can be a barrier to participation in trials (6), and in the resistance setting may not be representative due to evolution and heterogeneity. Of note the 3rd generation EGFR-TKI, osimertinib, designed to target the EGFR T790M resistance mutation, was developed in trials that included serial tissue and 'liquid' biopsy for analysis of plasma circulating tumor DNA (ctDNA). While the application of 'liquid biopsy' proved the clinical utility of this approach and is now a standard of care (7), the high response rate rendered the second biopsy on treatment uninformative in many patients (8). A further use of tissue and liquid biopsy in precision medicine trials that is likely to increase is the practice of so-called 'co-clinical trials'. This involves obtaining a fresh tumour biopsy and/or a circulating tumour cell sample from blood to establish as a xenograft mouse model from a patient at study entry and again on progression. The resultant patient derived or CTC derived explant model (PDX or CDX) is used to identify molecular mechanisms and candidate predictive biomarkers for subsequent clinical validation and is particularly applicable to trials for patients with small cell lung cancer (SCLC) (9,10). Although traditional, all comer, early phase study designs may soon be obsolete new designs of precision medicine trials will only be as effective as the enrichment strategy, scientific rationale and pharmacology underpinning them. To this end 'team science' approaches with close collaboration between academia and pharma will be essential for the golden age of precision medicines to be fully realised for lung cancer. (1) Tan DSW et al. The International Association for the Study of Lung Cancer Consensus Statement on Optimizing Management of EGFR Mutation–Positive Non–Small Cell Lung Cancer: Status in 2016. JTO 2016 Vol 11, Issue 7, Pages 946–963 (2) Blackhall F and Cappuzzo F. Crizotinib: from discovery to accelerated development to front-line treatment. Ann Oncol. 2016 Sep;27 Suppl 3:iii35-iii41. (3) Kim ES et al. The BATTLE trial: personalizing therapy for lung cancer. Cancer Discov. 2011 Jun;1(1):44-53. (4) Herbst RS et al. Lung Master Protocol (Lung-MAP)-A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400. Clin Cancer Res. 2015 Apr 1;21(7):1514-24. (5) Middleton G et al. The National Lung Matrix Trial: translating the biology of stratification in advanced non-small-cell lung cancer. Ann Oncol. 2015 Dec;26(12):2464-9. (6) Lim C et al. Patients with Advanced Non-Small Cell Lung Cancer: Are Research Biopsies a Barrier to Participation in Clinical Trials? J Thorac Oncol. 2016 Jan;11(1):79-84. (7) Oxnard GR et al. Association Between Plasma Genotyping and Outcomes of Treatment With Osimertinib (AZD9291) in Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2016 Oct 1;34(28):3375-82. (8) Thress KS et al. Modulation of Biomarker Expression by Osimertinib: Results of the Paired Tumor Biopsy Cohorts of the AURA Phase I Trial. J Thorac Oncol. 2017 Oct;12(10):1588-1594. (9) Lallo A et al. Circulating tumor cells and CDX models as a tool for preclinical drug development. Transl Lung Cancer Res. 2017 Aug;6(4):397-408. (10) Drapkin BJ et al. Genomic and Functional Fidelity of Small Cell Lung Cancer Patient-Derived Xenografts. Cancer Discov. 2018 May;8(5):600-615.

Keywords: precision medicine trials

MTE04 COMPARISON OF VARIOUS RISK MODELS (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE04.01 COMPARISONS OF RISK MODELS

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Lung cancer unfortunately remains the leading cause of cancer death in the world. Lowering lung cancer mortality in the near term while efforts continue to halt the tobacco use epidemic would result from early detection with low-dose helical CT screening in countries with the health care resources to support this complex endeavor. Current guidelines from groups like the United States Preventive Services Task Force (USPSTF), the Centers for Medicare and Medicaid Services (CMS) and the Canadian Task Force on Preventive Health Care follow criteria for entry to screening that mimic the National Lung Screening Trial entry criteria. Many researchers have shown that these guidelines may not be optimal for achieving the maximal lung cancer mortality reduction attainable through screening. Also, there is variability from country to country in lung cancer risk depending upon demographics, ethnic and racial mix, smoking intensity patterns and types of tobacco products. Individual risk models that have been validated in the country and population group in which they will be used will assist in optimizing effectiveness and efficiency. Where to set the risk-threshold will be a function of cost-effectiveness and other considerations and will be the subject of a separate presentation. What are the components of a risk model and how do the various risk models compare, and which ones are available to use? This talk will review the risk models published to date. Also, several groups have compared several of the risk models with each other demonstrating some advantages to certain models. The complexities of these model comparisons will be elucidated. Country to country variability will also be discussed. Models also differ in the number of variables they include. There are advantages to the parsimonious models as they may be easier to use in practice. However, they may do less well in better defining risk. Given that different racial and ethnic groups have different risk profiles it should be important to characterize this risk and have one useable model that incorporates it rather than separate models for different groups. Another major issue is how to incorporate risk models into facilitating entry into screening programs. What are the strengths and limitations of electronic medical records for this process? CMS requires an "informed decision making" visit with a health-care provider prior to lung cancer screening. What ideally should this include and how should risk be discussed? As the field of oncology moves to a "precision medicine" approach lung cancer screening can be at the forefront of this effort. The goal of an effective and efficient strategy will hopefully translate into the most numbers of lives saved for the screenings done. It is a challenge our community can meet.

Keywords: lung cancer risk; CT screening; risk-based screening

MTE04 COMPARISON OF VARIOUS RISK MODELS (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE04.02 WHERE SHOULD HEALTH PROGRAMS SET THRESHOLD FOR TAILORED SCREENING?

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Since the publication of the U.S. Preventive Services Task Force recommendation statement on lung cancer screening much discussion has focused on what is the critical information required to make an informed decision regarding the benefit of undergoing thoracic CT screening (1). Ever more sophisticated modeling approaches are being developed to better characterize the risk: benefit consequences of screening. This session will explore the current state of this complex issue. Yet as screening implementation builds momentum, more information is emerging about the information gleaned from thoracic CT obtained in a population of heavily tobacco-exposed individuals that may profoundly effect the screening health benefit discussion. A comprehensive analysis of diseases, injuries and risk factors across the United States from 1990 to 2016 was recently reported by a jointly sponsored consortium from the National Institutes of Health and The Bill and Melinda Gates Foundation, as a guide to investment for research, care and public health policy in the United States (2). According to that report, lung cancer including both the trachea and the bronchi was and remains the second leading cause of years of life lost across the 26 year time interval of that study due to an increase by 26.8% in the number of lung cancer deaths. In that analysis, the most lethal disease process was ischemic heart disease (IHD) which accounted for over 544,000 deaths in 2016. Even though, there was a 15% reduction in IHD mortality since 1990, ischemic heart disease still results in over 2.84 times more deaths than lung cancer. However, for both of these diseases, the age-standardized death rate is fortunately declining. In contrast for the third leading cause of death, chronic obstructive pulmonary disease (COPD), over that same 26 year interval, the total number of deaths has increased by 86.9%. Collectively, these three diseases, IHD, lung cancer and COPD account for over 44% of the mortality from the top 25 causes of years of life lost in 2016. As we consider risk developing risk models for lung cancer screening, it is useful to step back and consider the information being shared with the individual considering their screening benefit. Currently, in the United States that person being screened is most likely an over 55 years old, current or former smoker with over 30 pack year exposure to tobacco combustion products. As we have just reviewed, the most likely determinants of that individual's life expectancy are the three most lethal diseases, IHD, lung cancer and COPD. Even as we are beginning to screening tobacco-exposed populations, we know that there large numbers of individuals found in the course of their lung cancer screening CT, who will also be found that have asymptomatic but objective evidence of COPD or coronary calcification (3-7). For both IHD and COPD, NIH is encouraging measures to improve the early detection of these two major diseases so that pre-emptive strategies can be

employed, before the development of symptoms and avoid the disabling burden of largely incurable advanced disease. Guidelines have already been published for managing the extent of coronary calcium found on thoracic CT scans as promulgated by cardiac professional societies (8). In parallel developments, the pulmonary community is also finding compelling evidence for cardiovascular disease when evaluating for COPD (9). Finding from both of these thoracic CT-detected diseases are frequently being reported on the radiologists' report for lung cancer screening. Considerable progress has been made in developing predictive risk models for lung cancer in the screening setting (10, 11). However, from a screening subjects' perspective, a lung cancer-only risk analysis does not include the vast majority of risk-for-death information that is relevant to a heavy smoker that could be available on their screening CT in regard to the first and third leading cause of death (IHD or COPD) (2-9). Therefore when considering developing future risk outcomes tools for an individual deciding on whether or not to undergo CT screening for lung cancer, we perhaps need a more inclusive evaluation of health outcomes that consider the major knowable consequences of extensive tobacco exposure. The most recent Surgeon General's Report released in 2014 and summarizing 50 years of studying tobacco health consequences, reaffirmed the causal inference of tobacco smoke to a lengthy list of diseases including most prominently, cancers, cardiovascular disease and chronic obstructive pulmonary disease (12). In discussions about other major chronic diseases such as diabetes or hypertension, people are educated about the multi-organ involvement of these diseases, so they have the information to better protect their health. The three leading causes of loss of life (IHD, lung cancer and COPD) in the United States cumulatively account for over 13,500 years of loss of life per year. However, from a heavily tobacco-exposed individual's perspective, lung cancer only accounts for 26% of this mortality burden. A thoracic CT scan can provide actionable risk information for all three leading tobacco-related causes of death. The most recent draft research plan for the United States Preventive Services Task Force is explicitly evaluating lung cancer screening outcomes for impact on all-cause mortality. It is a critical time to consider more comprehensive tools to transparently inform about the relevant health information available with the use of thoracic CT imaging in heavily tobacco-exposed individuals. **References:** 1) Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014 Mar 4;160(5):330-8. doi: 10.7326/M13-2771. 2) PMID: 24378917The Burden of Disease Collaborators; Mokdad AH, Murray CJL, Khan AR, et al. 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Implications of Nine Risk Prediction Models for Selecting Ever-Smokers for Computed Tomography Lung Cancer Screening. Ann Intern Med. 2018 May 15. doi: 10.7326/M17-2701. [Epub ahead of print]. 12) US Department of Health and Human Services, The Health Consequences of Smoking: 50 Years of Progress: a Report of the Surgeon General, 2014 Atlanta, GAUS Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

MTE05 ROLE OF PNEUMONECTOMY IN N2 DISEASE (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE05.01 ROLE OF PNEUMONECTOMY IN N2 DISEASE

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Stage III non-small cell lung cancer (NSCLC) presents a significant treatment challenge. Patients are treated with curative intent, but only 20-30% achieve that goal, and acceptable treatment plans vary dramatically. Chemotherapy-based multimodality is the standard of care, but the ideal local therapy is unclear. Definitive concurrent chemo-radiotherapy without surgery is accepted by many as the treatment of choice, but local relapse is the first site of failure in up to >30%. Therefore, adding surgery to improve outcomes is attractive. Lung resection following induction chemo-radiotherapy to 45 Gy has been prospectively shown to be safe in numerous clinical trials. The use of pneumonectomy after induction therapy has been far more controversial. Multiple single institution series report on the safety of pneumonectomy following induction chemo-radiotherapy, even to doses of 60Gy, but results from multi-institutional prospective trials have not been as good, with reported peri-operative mortality up to 20-25%. The Intergroup trial 0139 was designed to evaluate the utility of adding surgery to chemo-radiotherapy for the treatment for N2+ IIIA NSCLC. The primary endpoint was improved overall survival, but was not met despite a significant improvement in progression-free survival. Some of this discrepancy was due to a high number of patients undergoing pneumonectomy and excessive mortality following pneumonectomy. Some of this was felt to be attributed to lack of surgical expertise both for pre-operative and intra-operative decisions. A recent evaluation of two prospective RTOG trials (0229 and 0839) which evaluated full-dose induction chemo-radiotherapy to 60 Gy followed by resection, reported increased peri-operative mortality (19%) with extended resections (pneumonectomy or bilobectomy). Results were complicated by the use of an EGFR antibody in the induction therapy, since 60% of grade 5 Adverse Events occurred in those who received both the EGFR antibody in addition to an extended resection. It is important to note that two large European prospective trials concentrated at experience surgical centers, reported excellent peri-operative outcomes with no increase in surgical mortality with use of pneumonectomy after induction chemo-radiotherapy. Stage IIIA NSCLC is a heterogeneous cohort of patients and treatment decisions need to be tailored to the individual patient and tumor. A pneumonectomy required for a large or central tumor with small volume nodal disease is distinct from tumors with bulky or infiltrative mediastinal nodes that require a pneumonectomy both in terms of short and long-term outcomes. Similarly outcomes vary by laterality, with mortality nearly twice as high for those on the right. While pneumonectomy needs to be used judiciously in this setting, eliminating it from all treatment decisions reduces the ability to achieve local control and long-term cure in a significant population.

Keywords: lung cancer, stage III, pneumonectomy

MTE05 ROLE OF PNEUMONECTOMY IN N2 DISEASE (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE05.02 ROLE OF PNEUMONECTOMY IN N2 DISEASE

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The therapeutic management of stage IIIA-N2 non-small cell lung cancer (NSCLC), which represents a locally advanced disease with ipsilateral mediastinal lymph node involvement, remains controversial despite the results of several randomized controlled trials [1-2]. By definition, stage IIIA-N2 represents a very heterogeneous population ranging from incidental discovery of N2 disease during surgery, through single mediastinal nodal involvement to bulky N2 disease where individual lymph nodes are difficult to identify and resect. Thus, treatment algorithms are controversial and guidelines are ambiguous. Patients with proven or suspected clinical stage IIIA-N2 NSCLC, are staged with contrast chest computed tomography (CT), integrated positron emission tomography – computed tomography (PET-CT) and brain magnetic resonance imaging (MRI) or CT. Additionally, before any treatment, histological proof of nodal involvement should be obtained either by a minimally invasive (EBUS) or invasive technique (mediastinoscopy). This is justified by the relatively high rate of false positive nodes [3] and also for complete mediastinal staging which includes the number of positive stations and the type of nodal infiltration. Proper lung cancer staging allows precise oncological treatment. When N2 disease is detected during surgery, in an entirely staged patient, this is referred as incidental, unsuspected or "surprise" N2 [4]. Here, if complete oncological resection can be achieved through lobectomy or pneumonectomy, the surgeon should proceed with the procedure. Adjuvant chemotherapy

prolongs survival and is currently recommended in this setting. Major controversy occurs when N2 disease is confirmed either by staging EBUS or mediastinoscopy. A properly staged mediastinum has biopsies of stations 4R, 7 and 4L. Due to the absence of internationally accepted definition, the term "potentially resectable N2" is usually applied when mediastinal involvement is limited and surgery can potentially offer R0 resection. According to guidelines, patients in this sub-group should be treated by definitive concurrent chemo-radiotherapy or neoadjuvant therapy followed by surgery or definitive radiotherapy. In the recently published Swiss Cancer League trial, no significant difference was found when comparing those two strategies [5]. Specific controversy exists regarding the role of surgery versus radiotherapy and the acceptable extent of resection post-induction therapy. The Intergroup trial [6], a randomized study published in 2009 and comparing neoadjuvant chemoradiotherapy plus surgery to chemoradiotherapy alone, issued caution regarding pneumonectomy in the context of multimodality therapy. This was largely due to inexplicable surgical results in this series, which demonstrated morbidity and mortality higher than published averages (26%). Yet pneumonectomy continues to be advocated in this setting by high volume centers that achieve superior surgical morbidity and mortality [7-10]. A systematic review of pneumonectomy followed by neoadjuvant therapy was published in 2012 [11]. The report included 27 studies from 1990–2010, and included 4 randomized controlled studies, including the Intergroup trial. Mortality at 30 days was 7% and at 90 days was 12%, suggesting traditional reporting of 30-day mortality may not be the ideal marker of perioperative mortality for pneumonectomy patients. The ideal treatment for patients with locally advanced NSCLC, who require pneumonectomy for resection, remains controversial. Reference: 1. Eberhardt WE, De Ruysscher D, Weder W, Le Péchoux C, De Leyn P, Hoffmann H et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol 2015; 26:1573-88. 2. Eberhardt WE, Pöttgen C, Gauler TC, Friedel G, Veit S, Heinrich V et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA-N2 and selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). J Clin Oncol 2015; 33:4194-201. 3. De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg 2014; 45:787-98. 4. Van Schil P. Stage IIIA-N2 non-small-cell lung cancer: from "surprise" involvement to surgical nightmare. Eur J Cardiothorac Surg 2016; 49:1613-4. 5. Pless M, Stupp R, Ris HB, Stahel RA, Weder W, Thierstein S et al. Induction chemo-radiotherapy in stage IIIA/N2 non-small cell lung cancer: a phase 3 randomised trial. Lancet 2015; 386(9998):1049-56. 6. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-86. 7. Kim AW, Faber LP, Warren WH, et al. Pneumonectomy after chemoradiation therapy for non-small cell lung cancer: does "side" really matter? Ann Thorac Surg 2009;88:937-43; discussion 944. 8. Weder W, Collaud S, Eberhardt WE, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. J Thorac Cardiovasc Surg 2010;139:1424-30. 9. Krasna MJ, Gamliel Z, Burrows WM, et al. Pneumonectomy for lung cancer after preoperative concurrent chemotherapy and high-dose radiation. Ann Thorac Surg 2010;89:200-6; discussion 206. 10. Cerfolio RJ, Bryant AS, Jones VL, et al. Pulmonary resection after concurrent chemotherapy and high dose (60Gy) radiation for non-small cell lung cancer is safe and may provide increased survival. Eur J Cardiothorac Surg 2009;35:718-23; discussion 723. 11. Kim AW, Boffa DJ, Wang Z, et al. An analysis, systematic review, and meta-analysis of the perioperative mortality after neoadjuvant therapy and pneumonectomy for non-small cell lung cancer. J Thorac Cardiovasc Surg 2012;143:55-63.

Keywords: Stage III-N2, Pneumonectomy, lung cancer

MTE06 SYMPTOM MANAGEMENT IN MESOTHELIOMA (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE06.02 HOW TO REGISTER TOXICITY AND GUIDE PATIENTS

L. Darlison
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There are 125 million people exposed to asbestos in the workplace and it causes over 100,000 deaths annually (IOSH 2018). The UK has the highest incidence of Malignant Mesothelioma in the world with 2697 cases in 2015 (CRUK 2018). Approved treatment in the UK has not changed for over a decade with Pemetrexed and Cisplatin being the only standard treatment widely available. However the last 2 years has seen an increase in clinical trial opportunities using both targeted and immunotherapy drugs. To help promote equitable access, Mesothelioma UK publishes a regular clinical trials update listing all trials that are open to recruitment (Mesothelioma UK 2018). These new treatment options have brought with them new challenges in terms of patient expectation, accessing treatment and side effects.McCambridge et al (2018) describe 2017 as a year characterised by several important advances in the field although only a minority are considered practice changing. This results in patients feeling anxious about the ongoing limited treatment options and frustrated by difficulties experienced in trying to access new treatment modalities. This presentation will briefly review current treatment options in the UK and how patients and health care professionals are kept informed about treatment and trial opportunities. Approaches to managing treatment expectation are explored and finally how health care professionals and patients are educated about side effects from new treatment modalities in and out of clinical trials. **References** IOSH 2018 (Institute of Occupational Safety and Health) No Time to Lose Campaign https://www.iosh.co.uk/VP/Home/Toolkit/IOSH-No-Time-to-Lose-Campaign.aspx (Last viewed June 18th 2018) CRUK 2018 (Cancer Research UK) Mesothelioma Incidence Statistics https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/mesothelioma/incidence (Last viewed June 28th 2018) Mesothelioma UK 2018 Clinical Trials http://www.mesothelioma.uk.com/information-support/information/clinical-trials/ (Last viewed July 4th 2018) McCambridge AJ, Napolitano A, Mansfield AS, Fennell DA, Sekido Y, Nowak AK, Reungwetwattana T, Mao W, Pass HI, Carbone M, Yang H, Peikert T, 2018. Progress in the Management of Malignant Pleural Mesothelioma in 2017. *Journal of Thoracic Oncology* Vol 13 No 5 606-623.

Keywords: Mesothelioma - accessing treatment

MTE07 MANAGEMENT OF PLEURAL RECURRENCE (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE07.01 FROM RADIATION ONCOLOGY PERSPECTIVE

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Radiation therapy (RT) plays an important role in the multimodality management of thymic malignancies and is an effective local treatment modality with the goal of reducing the risk of local recurrence. It can be employed in the neoadjuvant, adjuvant, definitive or palliative setting. It is important to evaluate the role of RT for pleural recurrence in the context of surgery and systemic treatment options as part of a multimodality approach and carefully coordinate the three modalities for optimal outcomes. Studies on the specific role of RT in pleural recurrences are sparse. However, there are several recent large database and population-based studies that indicate which patient subsets may benefit the most from RT. The indication and clinical setting for RT (perioperative versus definitive RT) depends on surgical resectability and operability of the patient. The adjuvant setting is the most extensively studied setting for RT in thymic malignancies. The greatest benefit of adjuvant RT appears to be in patients with newly diagnosed locally advanced stage III and IV thymomas, including patients with pleural dissemination.[1-4] For thymic carcinomas the impact of adjuvant RT appears more significant.[5-7] For incompletely resected thymic tumors there is a stronger rationale for adjuvant RT based on emerging data and general oncologic principles. The principles of adjuvant RT may be applied to surgically resected pleural recurrences as well. A range of modern radiation therapy techniques is available to aid the radiation oncologist in optimally targeting the tumor bed, while maximally reducing the radiation dose to surrounding organs at risk.[8,9] The radiation technique should be uniquely tailored to the needs of each individual patient's presentation. Techniques include 3D conformal radiation therapy, intensity-modulated radiation therapy, proton therapy and intraoperative radiation therapy using high dose rate brachytherapy or low dose rate seed implantation. The extent of the radiation treatment field will depend on the intraoperative findings, pathologic results, proximity to and dosimetric assessment of critical organs at risk. This may vary from treatment of a small tumor bed of a single pleural metastasis to hemithoracic pleural RT following an extrapleural pneumonectomy or lung-sparing pleurectomy/decortication in select cases. For inoperable or unresectable patients definitive RT is an excellent treatment option. A subset of patients is technically or medically inoperable, due to invasion of critical structures such as the heart, great vessels, spine, esophagus etc. or comorbidities. In general, thymic malignancies are radiosensitive, allowing for long-term local control rates, even when treated with definitive RT in the absence of surgery. Stereotactic ablative RT may be used for oligometastatic disease as an alternative to surgical resection and has been shown to be a highly effective treatment modality with >90% long-term local control rates and minimal morbidity in multiple histologies of intrathoracic metastases, including thymic tumors.[10] Lastly, palliative RT should be considered whenever surgical management or definitive radiation treatment options are not feasible. Conventional palliative RT is an important modality to improve quality of life by alleviating pain, treating SVC syndrome,

airway compression and other symptoms. 1. Fernandes AT, Shinohara ET, Guo M, et al. The role of radiation therapy in malignant thymoma: A surveillance, epidemiology, and end results database analysis. *Journal of Thoracic Oncology.* 2010;5(9):1454-1460. 2. Rimner A, Gomez DR, Wu AJ, et al. Failure patterns relative to radiation treatment fields for stage II-IV thymoma. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer.* 2014;9(3):403-409. 3. Rimner A, Yao X, Huang J, et al. Postoperative Radiation Therapy Is Associated with Longer Overall Survival in Completely Resected Stage II and III Thymoma-An Analysis of the International Thymic Malignancies Interest Group Retrospective Database. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer.* 2016;11(10):1785-1792. 4. Modh A, Rimner A, Allen PK, et al. Treatment Modalities and Outcomes in Patients With Advanced Invasive Thymoma or Thymic Carcinoma: A Retrospective Multicenter Study. *American journal of clinical oncology.* 2016;39(2):120-125. 5. Ahmad U, Yao X, Detterbeck F, et al. Thymic carcinoma outcomes and prognosis: results of an international analysis. *J Thorac Cardiovasc Surg.* 2015;149(1):95-100, 101.e101-102. 6. Omasa M, Date H, Sozu T, et al. Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II and III thymic epithelial tumors: the Japanese Association for Research on the Thymus Database Study. *Cancer.* 2015;121(7):1008-1016. 7. Ruffini E, Detterbeck F, Van Raemdonck D, et al. Thymic carcinoma: a cohort study of patients from the European society of thoracic surgeons database. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer.* 2014;9(4):541-548. 8. Gomez D, Komaki R. Technical advances of radiation therapy for thymic malignancies. *Journal of Thoracic Oncology.* 2010;5(10 SUPPL. 4):S336-S343. 9. Gomez D, Komaki R, Yu J, Ikushima H, Bezjak A. Radiation therapy definitions and reporting guidelines for thymic malignancies. *Journal of Thoracic Oncology.* 2011;6(7 SUPPL. 3):S1743-S1748. 10. Baschnagel AM, Mangona VS, Robertson JM, Welsh RJ, Kestin LL, Grills IS. Lung metastases treated with image-guided stereotactic body radiation therapy. *Clinical oncology (Royal College of Radiologists (Great Britain)).* 2013;25(4):236-241.

Keywords: Thymoma, radiation, pleural recurrence

MTE07 MANAGEMENT OF PLEURAL RECURRENCE (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE07.02 FROM SURGICAL PERSPECTIVE

R. Korst
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The pleural space represents the most common location for recurrence following resection of thymic epithelial tumors (TET). The rationale to include surgical resection in the management plan for these patients is based on small case series and reports, many of which demonstrate long periods of survival following pleural metastasectomy. Two large, retrospective series of patients with pleural disease have been recently published, both of which reflect pooled data from multiple institutions; one from Europe and the other from Japan[1,2]. Despite this, little prospective data address this issue. In addition, the management strategy for pleural disease in patients with TET is extrapolated from the management of primary TET in the mediastinum, where surgical resection plays an important role. Prognostic factors after surgical resection for pleural disease mirror those that are most consistently reported for primary mediastinal TET. Most case series of patients undergoing resection for pleural disease (either recurrence or initial presentation) suggest that the ability to completely resect the disease is an important prognostic factor. Indeed, both of the aforementioned larger series confirm that complete resection is associated with enhanced survival[1,2]. The Japanese report of 136 cases of pleural dissemination of thymoma at initial presentation (not recurrence) also determined that lower disease burden in the pleural space positively affects survival[2]. Although the large European Society of Thoracic Surgery (ESTS) Thymic Working Group Project (152 patients with either pleural recurrence and pleural disease at initial presentation) did not report disease burden, it confirmed the importance of complete resection in maximizing survival[1]. This later study also determined that thymic carcinoma patients experienced significantly shorter survival after resection of pleural disease than patients with thymoma. Thymic carcinoma, pleural disease burden and the ability to perform a complete resection can all be considered surrogates for individual tumor biology, which may be the most important underlying prognostic factor. Surgical approaches for patients with TET that has spread to the pleural space include metastasectomy and extrapleural pneumonectomy (EPP). The surgeon's goal is the complete gross resection of disease, which is dependent on the burden and location of disease. In cases of pleural recurrence, the surgical approach is typically through a lateral thoracotomy since this incision provides the best exposure of the entire pleural space and the mediastinal tumor has already been resected at an earlier time. More recently, video assisted thoracic surgery (VATS) approaches have been used selectively to approach these patients depending on the expertise of the operator. The surgeon wishes to perform the least amount of resection possible while still rendering the patient grossly disease free. Metastasectomy may range from the resection of a single pleural lesion to an extensive parietal pleurectomy with or without pulmonary resection(s) for visceral pleural involvement of metastatic deposits. On occasion, the surgeon may explore the chest of a patient with the intent of performing metastasectomy, but instead encounters diffuse innumerable visceral and parietal pleural metastatic deposits. In this case, EPP may be the only option to render the patient grossly disease free. The surgeon should always be prepared for this development whenever operating on a patient for metastatic TET, so that an educated decision can be made to proceed with EPP at the time of exploration, if necessary. EPP, however, may not be a good option for patients with thymic carcinoma that has metastasized to the pleural space given the magnitude of this approach combined with the significantly worse survival after resection in patients with metastatic pleural disease, when compared to thymoma. Pleural treatments used as an adjunct at the time of surgical resection for patients with pleural metastases from TET are becoming more popular. Heated intrapleural chemotherapy (HIPC) represents the most commonly used modality in this regard. After resecting all gross disease, the surgeon perfuses the hemithorax with heated chemotherapy for a period of time ranging from one to two hours. This strategy has been demonstrated to be safe with an acceptable complication rate in several small case series of patients with TET[3]. Although survival rates appear to be encouraging, definitive data demonstrating a survival benefit to HIPC are lacking. Intrathoracic photodynamic therapy (PDT) has also recently been reported for patients with TET that has metastasized to the pleural space[4]. Although the use of neoadjuvant chemotherapy has been reported in several case series of patients with pleural metastases at the time of initial presentation[5], data are lacking specifically in the scenario of pleural recurrence. The rationale for this approach mimics that for locally advanced TET in the mediastinum – to reduce the disease burden in hopes of increasing the likelihood of complete resection. Once again, this strategy appears to be safe and associated with encouraging rates of complete resection and survival, but definitive data confirming a benefit are lacking. In summary, the surgical resection of pleural recurrence of TET is associated with prolonged survival in selected patients, as reported in many case series. However, given the lack of controlled studies, it is unclear if prolonged survival is a direct result of the surgical approach or simply selection of patients with more forgiving tumor biology. Despite this, a rational approach may be to invoke a surgical approach as the initial strategy in patients with thymoma whose disease appears to be resectable. Once surgical options have been exhausted, or the disease is clearly unresectable, systemic therapy and/or radiotherapy can be utilized to achieve further disease control. References: 1. Moser B, et al. Surgical therapy of thymic tumours with pleural involvement: an ESTS Thymic Working Group project. Eur J Cardiothorac Surg 2017;52:346-55. 2. Okuda K, et al. Thymoma patients with pleural dissemination: Nationwide retrospective study of 136 cases in Japan. Ann Thorac Surg 2014;97;1743-9. 3. Maury J-M, et al. Intra-thoracic chemo-hyperthermia for pleural recurrence of thymomas. J Thorac Dis 2017;9:E1137-9. 4. Chen K-C, et al. 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Keywords: Thymoma, Surgical resection, pleural recurrence

MTE08 ENHANCING THE NURSE'S ROLE IN TOBACCO PREVENTION AND CESSATION: NEW CHALLENGES (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE08.01 ENHANCING THE NURSE'S ROLE IN TOBACCO PREVENTION AND CESSATION: NEW CHALLENGES

L. Sarna
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The purpose of this presentation is to discuss strategies for enhancing the nurses' role in tobacco control, including the implementation of smoking cessation interventions in oncology practice settings as part of routine care. The experiences of the Tobacco Free Nurses Initiative to accelerate nursing involvement in tobacco control in multiple countries will be used to illustrate key strategies. Healthcare professionals are effective in increasing quit attempts and long-term cessation; however, few patients receive the necessary support. Although more healthcare providers are identifying smoking status in the patient record and providing advice to quit, fewer actively assist patients who smoke with a quit attempt and arrange for follow-up. During this presentation, an evidence-based smoking cessation intervention based on the 5 As (i.e., Ask, Advise, Assess, Assist and Arrange) will be reviewed along with strategies for facilitating implementation in the clinical setting. The

oncology team needs adequate knowledge and skills in the delivery of a tobacco dependence treatment intervention. Although many healthcare providers may know about the devastating health effects of smoking and tobacco use, including lung cancer, few received the necessary training to deliver an evidence-based intervention. Many educational resources are available as listed in Table 1. Basic content of educational programs to support delivery of a smoking cessation intervention includes information about health risks of smoking and exposure to secondhand smoke, nicotine dependence and withdrawal, health benefits of quitting, evidence-based methods for supporting tobacco dependence treatment including behavioral interventions (i.e., social support and skills training), identification of triggers for relapse and how to manage withdrawal symptoms and cravings, and knowledge of FDA-approved pharmacotherapy, including side effects and toxicity. With the advent of the electronic medical record (EMR), tobacco use is often included as core information at patient intake with reminders to providers increasing the rates of advice and assessment. The EMR may be tailored to include easy-to-use prepopulated "Smart sets" for intervention with information about approved medications and referral options as well as downloadable materials for patients and families. The EMR can push alerts to clinicians to prompt treatment. Inpatients who are identified as smokers can be offered nicotine replacement therapy (NRT) to alleviate withdrawal symptoms, regardless of their desire to quit long-term. Changes in the healthcare environment also can support implementation of these recommendations. These include adopting smoke-free policies in healthcare settings, beyond the inpatient hospital, and supporting quit efforts of healthcare providers. Although smoking is declining among healthcare providers, this may be an issue in some settings and in some geographic areas. Smoking of the healthcare provider has been associated with decreased interventions and confidence in providing a patient with intervention. Promoting the smoking cessation support services provides an opportunity to support the quit efforts of healthcare providers as well. Providers' support of patient quit efforts is essential regardless of the smoking status of the individual clinician. Table 1. Resources to support implementation of tobacco dependence treatment in oncology clinical settings

Title	Organization	Information
Agency for Healthcare Research and Quality	Treating Tobacco Use and Dependence: 2008 Update https://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html	Section for clinicians and system decision makers, including systems change information for integration of tobacco dependence in clinical practice
American Society of Clinical Oncology	Tobacco cessation tools and resources https://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/tobacco-cessation-control	Comprehensive information regarding the 5 As for a cessation intervention and wide-ranging tobacco control policies
Centers for Disease Control and Prevention	Health Care Providers: How you can help patients quit https://www.cdc.gov/tobacco/campaign/tips/partners/health/hcp/index.html	Provides general information for healthcare providers based on the Tips for Former Smokers®Campaign
Centers for Disease Control and Prevention	Smoking cessation and cancer https://www.cdc.gov/tobacco/campaign/tips/diseases/cancer.html	Specific examples of the impact of smoking and exposure to second-hand smoke on cancer. Videos from the TIPs campaign with cancer to promote motivation to quit
North American Quitline Consortium	State telephone support lines for smoking cessation http://www.naquitline.org/	Provides information about availability and details of telephone quitlines for smoking cessation across the United States including electronic referral, other resources, and availability of nicotine replacement
Oncology Nursing Society	Tobacco control policy recommendationsfor oncology nurses https://www.ons.org/advocacy-policy/positions/policy/tobacco	Also endorsed by the International Society of Nurses in Cancer Care
Smokefree partner toolkit	Smoke-free.gov https://smokefree.gov/help-others-quit/health-professionals	Provides comprehensive list of evidence-based resources, guides and government reports aimed for clinicians, including smokefree mobile interventions
SRNT, Society for Research on Nicotine and Tobacco	Resources for Clinicians https://www.srnt.org/?page=Resources_Clinicians	Provides many science-based resources and a searchable index for abstracts related to cardiovascular disease
Tobacco Free Nurses	Resources for nurses to enhance to tobacco control https://tobaccofreenurses.org	Multiple webcasts in different languages, including many focused on oncology nursing and tobacco control
University of Wisconsin- Center for Tobacco Research and Intervention	Providers overview of tobacco dependence treatment https://ctri.wisc.edu/providers/providers-overview/	Offers tobacco treatment training through webinars, onsite videos or online programs. Updates on the evidence for electronic cigarettes, including vaping regulations by state

References Treating Tobacco Use and Dependence:2008 Update. Clinical Practice Guideline.https://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html EK, Strouse R, Hall J, Kovac M, & Schroeder SA. (2010). National survey of U.S. health professionals' smoking prevalence, cessation practices, and beliefs. *Nicotine Tob Res*, **12** (7), 724–733. doi: 10.1093/ntr/ntq071. Sharpe T, Alsahlanee A, Ward K & Doyle F. (2018). Systematic review of clinician-reported barriers to provision of smoking cessation interventions in hospital inpatient settings. *J Smok Cessat*, 1-11. Doi.10.1017/jsc.2017.25 Sarna L, Bialous SA, Ong MK, Wells M, Kotlerman J. Increasing nursing referral to telephone Quitlines for smoking cessation using a web-based program. *Nurs Res*. 2012 Nov-Dec;61(6):433-40. doi: 10.1097/NNR.0b013e3182707237. Thomas D, Abramson MJ, Bonevski B, George J. System change interventions for smoking cessations. *Cochrane Database Syst Rev*.2017 Feb 10;2:CD010742. doi: 10.1002/14651858.CD010742.pub2. Boyle R, Solberg L, Fiore M. Use of electronic health records to support smoking cessation. . 2014 Dec 30;(12):CD008743. doi: 10.1002/14651858.CD008743.pub3. Review. PMID 25547090 Rigotti NA, Regan S, Levy DE, Japuntich S, Chang Y, Park ER, Viana JC, Kelley JH, Reyen M, Singer DE. Sustained care intervention and postdischarge smoking cessation among hospitalized adults: a randomized clinical trial. *JAMA*.2014 Aug 20;312(7):719-28. doi: 10.1001/jama.2014.9237

Keywords: Cancer, tobacco, smoking, nurses

MTE09 MANAGEMENT OF ADVANCED WILD-TYPE LUNG CANCER IN SPECIAL SITUATIONS (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE09.01 EVIDENCE BASED MANAGEMENT OF THE PATIENT OVER 80

E. Quoix
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Lung cancer is the first cause of death by cancer in the entire world. In US the estimated number of new lung cancer cases in 2018 is 234030 with an estimated number of deaths of 154050 (25% of all cancer deaths) (1). Due to the conjunction of two factors (increased incidence of cancer with age and increase of life expectancy), median age at diagnosis is now 70 years in the US. The probability of developing a lung cancer is 6.1% after 70 years of age in males and 4.8% in females to be compared with respectively 1.9% and 1.4% between 60 and 69 years (1). Seventy years is also the cutoff most frequently used to define older adults in clinical trials of systemic treatments (2) (3) (4) Although, octogenarians represent a non negligible part of the patients, lung cancer is most frequently diagnosed among people aged 65-74 years (33.4% of the cases) whereas

26.8% are diagnosed between 75 and 84 years and 9.4% after 84 years (https//seer.cancer.gov/statfacts/html/lungb.html) . Non-small cell lung cancer (NSCLC) represent 85% of the cases whatever the age of diagnosis and, between 2007 and 2013, 57% of them were diagnosed at a metastatic stage (1). Thus systemic treatment to be applied in older patients is of paramount importance. Patients without targetable mutations and with a PDL1 expression <50% should be considered for chemotherapy whereas those with a PDL1 expression > 50% should be considered for immunotherapy by Pembrolizumab as first line therapy (5). Recommendations for fit patients with no targetable mutations are to give a platin-based doublet (4 to 6 cycles) followed by a maintenance therapy in patients with no progressive disease at the end of the induction cycles. In non-squamous cell carcinoma, bevacizumab may be added in the absence of contra-indication (5). Regarding chemotherapy for older adults, we have some specific trials (table 1). The first point of these studies is that elderly patients do beneficiate of chemotherapy. Second point is that a non platin-based doublet does not provide any survival benefit compared to single agent therapy and third, carboplatin-based doublet (especially monthly carboplatine + weekly paclitaxel) provides an important survival benefit over single agent alone for elderly patients with PS 0-2 (4). In this study subgroup analysis showed that the survival benefit of a doublet compared to single agent therapy was also observed in the octogenarians. We have no data regarding maintenance therapy in elderly patients. The benefit/risk ratio is not in favor of bevacizumab after 70 years (6). The case of immunotherapy in elderly patients is of importance as the increased incidence of cancers in this population may be due to immune dysfunction (7). However, we do not have studies dedicated to elderly patients and data are obtained from subgroup analyses of studies with no upper limit of age (with the risk of selection biases). Pembrolizumab was compared to chemotherapy in patients with PDL1 expression > 50% and resulted in a survival benefit (8). Moreover in a recently published trial, addition of Pembrolizumab to chemotherapy as first-line therapy resulted also in a survival benefit compared to chemotherapy alone (9). Although there were some patients aged 80 years and more in these trials, specific studies are lacking and should be implemented. With reference to second line treatment, there are also no specific trials for elderly patients although erlotinib was due as second line therapy in one randomized trial (10) with similar results as observed in the pivotal study (BR21 comparing placebo to erlotinib after a first line consisting in a platin-based doublet). Regarding immunotherapy as second line, 4 phase III trials (docetaxel versus nivolumab in squamous and non-squamous cell carcinoma, docetaxel versus pembrolizumab and docetaxel versus atezolizumab) which are all in favor of the immunotherapy, included some elderly patients but with a median age around 62-64 years and although the eldest patients were 85 years old the proportion of patients aged 75 and more was below 12%. Thus, if recommendations regarding chemotherapy in elderly patients are now clear, there is a need for specific studies of immunotherapy in elderly patients especially those aged over 75 years either in first line therapy or second line therapy. **Table I Randomized trials dedicated to elderly patients with advanced NSCLC**

Author (year)	Drugs	N° patients	Response rate (%)	Median survival (months)	1-year survival rate (%)	P
Gridelli (1999)	VNR BSC	76 75	19.7 ------	6.5 4.9	32 14	0.03
Frasci (2000)	VNR VNR+-Gem	60 60	15 22	4.5 7	13 30	<0.01
Gridelli (2003)	VNR Gem VNR+-Gem	700	21 16 18.1	8.5 6.5 7.4	42 28 34	Ns
Kudoh (2006)	VNR Doc	92 90	9.9 22.7	9.9 14	NR NR	Ns
Quoix (2011)	VNR or Gem Carbo + weekly Pacli	226 225	10 27	6.2 10.3	25.4 44.5	0.0004
Tsukada (2015)	Doc CDDP + Doc	63 63	26.2 55	10.7 17	45.2 66.6	0.0384
Abe (2015)	Doc CDDP + Doc	134 138	24.6 34.4	14.8 13.3	58.2 54.5	Ns
Corre (2016)	CGA or standard allocation	243 251		6.1 6.4	NR NR	

Abbreviations : VNR : vinorelbine; BSC : best supportive care; Gem : gemcitabine; Carbo : carboplatin; Doc : docetaxel; CDDP : cisplatin; CGA : comprehensive geriatric assessment; ns : not significant; NR : not reported **References** 1. Siegel RL Cancer statistics, 2018. CA Cancer J Clin 2018;68:730. 2. Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. Elderly Lung Cancer Vinorelbine Italian Study. The oncologist. 2001;6 Suppl 1:47. 3. Pallis AG. Management of elderly patients with NSCLC; updated expert's opinion paper: EORTC Elderly Task Force, Lung Cancer Group and International Society for Geriatric Oncology. Ann Oncol 2014;25:127083. 4. Quoix E. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011;378:107988. 5. Hanna N. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017;35:3484515. 6. Ramalingam SS. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599 J Clin Oncol. 2008 Jan 1;26(1):60-5 7. Ferrara R. Immunosenescence and immunecheckpoint inhibitors in non-small cell lung cancer patients: Does age really matter? Cancer Treat Rev 2017;60:608. 8. Reck M. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:182333. 9. Gandhi L. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378:207892. 10. Quoix E. Second-line therapy in elderly patients with advanced nonsmall cell lung cancer. Eur Respir J 2014;43:2409.

Keywords: non-small cell lung cancer, systemic treatment, elderly

MTE09 MANAGEMENT OF ADVANCED WILD-TYPE LUNG CANCER IN SPECIAL SITUATIONS (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE09.02 MANAGEMENT OF THE PS 2 PATIENT

J. Schiller
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Patients with poor performance status (PS) of 2 represent a heterogeneous group of patients and a large proportion of the non-small cell lung cancer patient population (about 30-40 percent). Assessment is complicated by the influence of comorbidities versus disease burden on performance status and treatment outcome. The treatment of PS 2 patients was of particular interest in the late 20th/early 21st century. Studies evaluating that impact of performance status on outcome have shown that a poor performance status is also a poor prognostic indicator. ECOG 1581 showed that patients with a performance status of 0, 1, or 2 and median survivals of 36 weeks, 26 weeks, and 10 weeks, respectively. The toxic death rate was 3 percent, 2 percent, and 10 percent respectively (1) . Despite their poor prognosis, studies have shown that PS 2 patients do benefit from chemotherapy. Gridelli et al randomized patients 70 years or older with a PS of 0-1 to best supportive care versus a single vinorelbine (2). A statistically significant improvement in overall survival was observed (relative hazard ratio of death for vinorelbine-treated patients was 0.65). Other studies compared single agent versus doublet therapy in PS2 patients. Obasaju et al (3) randomized patients to single agent gemcitabine versus gemcitabine plus carboplatin in a US oncology trial in PS2 non-small cell lung cancer patients. Median survival was 5.2 months in the single agent arm versus 6.9 months in the doublet arm; overall response rates were 11.5 % versus 36%, respectively. Another trial (4) (Reynolds, JCO, 2009) also randomized PS2 patients to gemcitabine versus carboplatin and gemcitabine and also found an improvement in response rate, progression free survival, and overall survival, although only the difference in response rate was statistically significant. Dr. Lilenbaum reported the results of CALGB9730, a study of single agent pemetrexed versus carboplatin and pemetrexed. Patients with PS 2 who were treated with carboplatin and paclitaxel had a 4.7 month survival versus 2.2 months in PS2 patients treated with paclitaxel alone. In 2013, Zukin and colleagues presented the results of a phase 3 comparison of single agent pemetrexed versus combination pemetrexed plus carboplatin chemotherapy in patients with performance status is 0- 2

and no prior chemotherapy (5). The response rates were 10.3% for single agent pemetrexed versus 23.8% for the combination of carboplatin and pemetrexed. In the attempt to treat population, the median PFS was 2.8 months for single agent pemetrexed and 5.8 months for the combination. Median overall survival was 5.3 months for pemetrexed and 9.3 months for the combination; one-year survival rates were 21.9% and 40.1 %, respectively. Toxicity was acceptable. Doublet therapy has also been compared in PS2 patients. ECOG 1599 was a phase 2 randomized trial for PS2 patients, in which patients were randomized to dose attenuated carboplatin plus paclitaxel or gemcitabine plus cisplatin. Disease control rates (RR and SD), time-to-progression (TTP), progression free survival (PFS) and survival results are similar for the two regimens. PCB yielded more grade 3–4 neutropenia, neuropathy and grade 1 arthralgia/myalgia. GC caused more grade 3 thrombocytopenia, fatigue, nausea and grade 1 nephropathy. (6) There is less data as to how these patients respond to immunotherapy, since they have been excluded in many clinical studies. However, several nivolumab studies have included patients with a performance status of 2. CheckMate 171 was a European, single arm, phase II study in previously treated patients with metastatic squamous cell carcinoma of the lung which included patients 70 years and older or with poor performance status. (7). A total of 809 patients were enrolled, 98 of whom had a performance status of 2. Baseline characteristics and prior therapy in the PS2 subgroup were consistent with those in the overall ambulation, with the exception that the PS2 subgroup had fewer complete or partial responses as best response to most recent therapy. The safety profile of nivolumab was also comparable between the overall patient population and those with a performance status of 2, including a rate of 6% grade 3 or 4 treatment related AE's (TRAEs), and 5% TRAEs leading to discontinuation. Overall survival was low were in the PS2 patients (median 5.4 months compared to a median of 9.9 months in the total patient population.) 14 percent of all patients had a complete or partial response compared to 11 percent of PS2 patient. CheckMate 153 was a Phase ¾ study which evaluated the safety of nivolumab monotherapy in patients with previously treated metastatic non-small cell lung cancer in the US and Canada. 1375 patients were enrolled, 123 of whom had a performance status of 2. The frequency of grade 3 or four adverse events was 12% in patients with a performance status of zero or one compared to 10% in patients with a PS of 2. Grade 5 events were less than 1% in the PS 0-1 patients and was 2% in the PS 2 patients. Six-month and 1 year overall survival rates in the PS2 subgroup were lower than those in the PS 0-1 subgroup (10.5 months versus 3.9 months, respectively) and one year overall survival rates of 44 percent versus 17 percent. Significant improvements in symptoms burden were observed in the PS2 patients at most time points, with improvement in quality of life starting at week 6 onward. (8) CheckMate 169 was an expanded access program involving nivolumab in previously treated patients with advanced non-small lung cancer in 161 patients. Baseline characteristics were generally the same in the PS2 patient population as the overall patient population. The safety profile was also comparable, with rates of any grade or grade 3-4 TRAEs, and TRAEs leading to discontinuation were also similar. Median survival was 5.9 months in the PS2 patients and 9.1 months in the overall patient population. (9) Taken together, these studies show that patients with advanced non-small cell lung cancer and a poor performance status have a poor prognosis than those with a PS of 0 or 1. The data regarding TRAEs is more variable, with some studies suggesting they are comparable to those observed in PS 0 or 1 patients, while others report a higher incidence of TRAEs in PS 2 patients. Despite this, however, PS2 patients derive a benefit from chemotherapy when compared to no therapy, and doublet therapy vs single agent. Randomized trials with immunotherapy are lacking; however, retrospective data suggests that the toxicity data is comparable compared to patients with a better performance status. References

1. Ruckedeschel J. C., et al. A randomized trial of the four most active regiments for NSCLC. Journal of Clinical Oncology 1986 4:1, 14-22 2. Gridelli C., et al, *Annals of Oncology*, Volume 15, Issue 3, 1 March 2004, Pages 419–426, 3. Obasaju C.K., et al ASCO Article-Abstract A-7533. 4. Reynolds C.; JCO.2009.27, 5808-5815. 5. Zukin M., et al. *JCO* 31, no. 23 2849-2853. 6. Tester W.J., et al; ECOG 1599: *JCO* 22, no. 14_suppl 7055-7055. 7. Popat S., et al;. Presented at the 17th World Conference on Lung Cancer; December 4-7; Vienna, Austria. 1303 PD. 8. Spigel D., et al; Presented at the 17th World Conference on Lung Cancer; December 4-7; Vienna, Austria. P3.02c-026 9. Juergens R., et al;. Presented at the 18th World Conference October 15-18, 2017; Yokohama, Japan. PO2.07-029

MTE10 EMERGING TECHNOLOGIES FOR SMALL AND SMALLER LESIONS - UPDATE ON ABLATION VIA ENDOSCOPY VS PERCUTANEOUS (TICKETED SESSION)
MONDAY, SEPTEMBER 24, 2018 - 07:00-08:00

MTE10.01 EMERGING TECHNOLOGIES FOR SMALL AND SMALLER LESIONS - UPDATE ON ABLATION VIA ENDOSCOPY VS PERCUTANEOUS

F. Herth

Dept. of Pneumology and Critical Care Medicine, Thoraxklinik at University of Heidelberg and Translational Lung Research Center (TLRC), Heidelberg/DE

A solitary pulmonary nodule (SPN) is a round or oval opacity smaller than 3 cm in diameter that is completely surrounded by pulmonary parenchyma. Workup of these nodules is rather expensive and emotionally burdensome, especially when the patient has risk factors for bronchial carcinoma. SPNs are noted in up to 0.2% of chest radiograph, whereas 27.3% of patients undergoing the national lung screening trial (NLST) had at least one SPN with a diameter of more than 4mm on their CT examination. Numerous articles/papers have been published addressing the optimal strategy of evaluating individuals with lung nodules, including the published ACCP guideline for the diagnosis and management of lung cancer. Those strategies are generally based on the individuals' risk of developing lung cancer, the pulmonary nodule characteristics and the capability of the current diagnostic and therapeutic approaches. Standard bronchoscopy has been limited in the evaluation of the peripheral pulmonary nodules, with diagnostic yields ranging from 19% to 68%. The addition of tools such as electromagnetic navigational bronchoscopy (ENB), radial endobronchial ultrasound (r-EBUS), and several other navigation technologies have been used and increased the diagnostic yield. Actual, The Transbronchial Parenchymal nodule access (TPNA) has shown the best results. Radiofrequency ablation (RFA) and Microwaves (MW) are promising alternative treatment method for early-stage lung cancer in non-surgical patients. They can also be used for oligometastasis from distant cancer or as a therapy for the local control of tumors. Compared to their percutaneous approach, in the lung, percutaneous ablation is associated with severe complications, including pneumothorax, hemothorax, bronchopleural fistulas, and pleural effusions. Therefore a bronchoscopic approach seems to be as effective with reduced complications.

Keywords: ablation, solitray pulmonary nodule, endoscopic navigation

MTE11 BIOLOGY OF SMALL CELL LUNG CANCER (TICKETED SESSION)
TUESDAY, SEPTEMBER 25, 2018 - 07:00-08:00

MTE11.01 NOVEL THERAPEUTIC TARGETS IN SCLC

J. Sage

Pediatrics and Genetics, Stanford University, Stanford/CA/US

Small cell lung cancer (SCLC) remains the most lethal form of lung cancer, in part because of its rapid growth and dissemination, and also because of its ability to evade therapy. In the last few years, however, a number of studies have taken advantage of improved pre-clinical mouse models of SCLC as well as increased access to primary human samples to identify novel candidate therapeutic targets against SCLC. Some of these new therapeutic targets include activation of the immune system (T cells, NK cells, or macrophages), as well as cell-intrinsic signaling pathways that often act in autocrine or paracrine manners (e.g. Hedgehog or Notch signaling). This presentation will put these different approaches in context and discuss signaling pathways that may not be mutated in SCLC but can still significantly contribute to the proliferation and the survival of SCLC cells during SCLC progression and metastasis.

Keywords: SCLC, kinase, metastasis

MTE11 BIOLOGY OF SMALL CELL LUNG CANCER (TICKETED SESSION)
TUESDAY, SEPTEMBER 25, 2018 - 07:00-08:00

MTE11.02 BIOLOGICAL SUBSETS OF SCLC

C. Rudin

Memorial Sloan Kettering Cancer Center, New York/NY/US

Small cell lung cancer (SCLC) is an exceptionally lethal cancer for which new therapeutic approaches are needed. Over the past few years several research teams have applied global profiling approaches to characterize the SCLC genome, epigenome, transcriptome, and proteome. Despite the seemingly homogeneous microscopic appearance of SCLC, these studies have consistently suggested the presence of biologically distinct subsets of disease. Parallel studies across libraries of patient-derived xenografts and in a diversity of genetically engineered mouse models of SCLC have

validated these subset distinctions. Some models suggest that these subsets reflect parallel programs of oncogenesis, perhaps emerging from distinct cells of origin. Conversely, other data imply a temporal hierarchy among disease subsets, or at least that transition from one phenotypic subset to another is possible. Most exciting from a treatment perspective, several research groups have reported unique therapeutic vulnerabilities among these subsets. Several of these therapeutic strategies are being actively tested in SCLC patients, and emerging correlative data further confirm the predicted differential sensitivities among SCLC subsets. Together, these studies advocate for a very different approach to clinical translation in SCLC than that taken to date. Rather than treating all SCLC the same, a more successful approach may be to consider focused trials among biomarker-selected subsets of disease, exploiting the distinct dependencies and vulnerabilities of biologically relevant subsets. This presentation will highlight some of the recent preclinical studies that have defined determinants of these subsets, together with recent clinical work emphasizing their importance to the field, and to our patients.

Keywords: subsets, omics, small cell lung cancer

MTE12 IO IN THE REAL WORLD - HIGH RISK POPULATIONS AND PATIENT SUPPORT (TICKETED SESSION)
TUESDAY, SEPTEMBER 25, 2018 - 07:00-08:00

MTE12.01 IS IO AN OPTION FOR PATIENTS WITH CONTRAINDICATIONS (AUTO-IMMUNE DISEASE, PULMONARY FIBROSIS, HIV, HEPATITIS, TRANSPLANT ETC)

A. Robinson
Oncology, Queens University, Kingston/ON/CA

This session will focus on an approach to making informed decisions for patients largely excluded from the pivotal clinical trials of immunotherapy. The non-comprehensive presentation will focus on some distinct clinical entities (HIV, Hepatitis B&C, Tuberculosis), select auto-immune diseases (AID's), and organ transplant patients, and illustrate an approach to use clinically. Information from reports of similar patients treated with immunotherapy is informative[1, 2], however caution is required in interpreting these reports as both selection and reporting bias may occur. There are six key questions that need to be considered prior to starting therapy – accepting that many of these answers have a high degree of uncertainty. Decisions are based on close collaboration with disease experts; evidence from published and presented studies and reports; and biologic plausibility/pathogenesis. **1:** What is the benefit and toxicity of this therapy compared to it's alternatives in the absence of contraindications? **2:** How may the underlying condition impact the benefit and toxicity? An understanding of the condition and co-management with other specialists is desirable. Is there a potential for benefit or harm from activating T-cells? The potential impact is estimated from: critically reading cohort studies/case series/case reports; discussions with specialist colleagues for understanding disease pathogenesis; and understanding where the patient is in the spectrum of their comorbid disease. Consider possible effects on the organ at risk, but also other organs (i.e. extra-colonic manifestations of ulcerative colitis; extra-articular manifestations of rheumatic disease etc.), and whether there is any impact on toxicities unrelated to underlying condition. For auto-immune disease, the cohort studies of Leonardi et al and meta-analysis of Abdel-Wahab are informative. Leonardi et al included 56 patients with NSCLC and a history of auto-immune disease treated at several large treatment institutions over 3 years. Most patients were asymptomatic from their AID at baseline. Abdel-Wahab et al included 123 patients, but did not restrict to lung cancer, and included patients treated with both CTLA-4 and PD-1 inhibitors. For Leonardi et al, 5 of 10 patients who were symptomatic had a disease flare or worsening, while 8/46 who were not symptomatic at baseline had a flare. The vast majority of these patients were treated in second or above line (84%). The Abdel-Wahab paper revealed 75% of patients had a disease exacerbation or immune related adverse even or both, however 46% of patients were symptomatic from their AID at baseline. Case reports and small series are available for solid organ transplant, while prospective cohorts and retrospective cohorts are available for some chronic infections. Given the significant biases inherent in these case series and reviews, a prudent approach to most auto-immune diseases is to assume that disease may worsen/recur, and to monitor and intervene early. Also assume that there are some patients who will not worsen, either because of a lack of functioning remaining immune system/burning out of initial disease/or other reasons. Disease specific recommendations and considerations (Multiple Sclerosis, Guillian-Barre, Crohn's/UC, and inflammatory arthritises) will be discussed in the session. **3:** How may concomitant medications impact the benefit and toxicity, what are the alternatives (if any) to these medications? This impact is estimated from cohort studies, case reports, biological rationale, and discussion with specialist colleagues regarding alternative therapies with potentially less impact on T-cell function. While cohort studies have been varied in showing an impact of immuno-suppressive medications on immune therapy response, the data remain extremely sparse and biologic rationale is used for decision making. A general approach would be to use the lowest dose feasible with the most targeted approach feasible for the underlying disease. It is plausible that gut-specific therapy for IBD (i.e. vedolizumab), will have less effect on Tumor T cells than systemic steroids, anti-TNF agents, etc. There is very little collective published experience in this area. **4:** If this patient requires immune suppression for toxicity, are there special considerations or risks? Information from clinical trials and population studies help determine the likelihood of immune suppression. Expertise from specialist colleagues may be required to understand how to mitigate the effect of immunosuppression before or during immunosuppression. This is particularly true for infectious diseases that may have exacerbations with prolonged courses of immunosuppression (hepatitis B, TB etc). Suppressive or eradicative anti-infectious medications may improve safety of subsequent immunosuppression and may be considered. **5**: Does the patient have the reserve to tolerate the expected or possible toxicities of the immunotherapy? Physician judgement/experience and a knowledge of how clinical trials toxicities translate to the 'real' world are needed. Patients with certain immune or non-immune underlying conditions that result in a decreased patient/organ reserve may be less likely to tolerate toxicities. For instance, an asymptomatic pneumonitis (Grade 1 toxicity) in a relatively fit patient may translate to a grade 4/5 toxicity in a patient who at baseline is oxygen dependent with near end-stage pulmonary disease. **6**: If I proceed with IO therapy, how do I monitor to intervene early if complications arise? Other than 'routine' monitoring; How do I monitor for the infectious disease; transplant rejection; or auto-immune flare? Most of the published experience with toxicity suggests that reversibility of toxicity may occur with early intervention. Thus, monitoring is required and will be disease specific. Ideally, a monitoring plan agreed upon by both the oncologist and the disease specialist will be explicit. Patient education is crucial, as many of these diseases will present clinically and not through testing. REFERENCES 1. Ostios-Garcia, L., et al., *Safety and Efficacy of PD-1 Inhibitors Among HIV-Positive Patients With Non-Small Cell Lung Cancer.* J Thorac Oncol, 2018. 2. Abdel-Wahab, N., et al., *Use of Immune Checkpoint Inhibitors in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease: A Systematic Review.* Ann Intern Med, 2018. **168**(2): p. 121-130.

Keywords: auto-immune, comorbid disease, real world practice

MTE12 IO IN THE REAL WORLD - HIGH RISK POPULATIONS AND PATIENT SUPPORT (TICKETED SESSION)
TUESDAY, SEPTEMBER 25, 2018 - 07:00-08:00

MTE12.02 HOW CAN WE MINIMIZE TOXICITY FOR OUR HIGH RISK PATIENTS?

M. Nematollahi
William Osler Health Center, Brampton/CA

This session will focus on strategies and innovative approaches to minimize cancer immuno-therapy toxicities. Immune checkpoint inhibitors (ICI) are a new class of anti-neoplastic agents termed immuno-therapy and are now standard of practice for lung cancer population including elderly with comorbidities. These agents have significantly impacted patient outcomes by offering durable responses. However, the effective and safe delivery of these agents require expertise in understanding the unique characteristics of the ICI (Immune Checkpoint Inhibitors) that differ from cytotoxic chemotherapy. Certain immunotherapy protocols may have up to 50% rate of developing severe irAEs. The number of indications of ICI treatment is rapidly evolving and broadening thus being proactive in developing a specialized clinic for these patients would not only centralize care and optimize efficacy but minimize toxicities in high risk population. Currently there is a large unmet need for an education class for patients prior to starting immunotherapy. Many centers have "chemotherapy teaching class" which are attended by all patients prior to starting chemotherapy, however the information regarding toxicities does not apply to ICI and could lead to under reporting of IrAEs particularly in high risk population with comorbidities and elderly. At William Osler Health Center, under supervision of Dr. Parneet Cheema an immune-oncology clinic has been established. Objective: The objective of this initiative is to generate a standardized, reproducible, and safe implementation immunotherapy program that could be easily recreated at any community cancer center. This presentation will discuss the clinic design, immunotherapy teaching class, logistics and standardized ICI delivery, care monitoring, and follow-up.

Keywords: Elderly with comorbidities, Immunotherapy clinic

MTE14.01 NODULE MANAGEMENT (PRO CON DEBATE AND CASE PRESENTATIONS)

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A recent observation study on the management of lung nodules 8 mm to 20 mm by community pulmonologists in the US showed a high benign biopsy rate of 62% and benign surgical resection rate of 35%. Furthermore, the surgical resection rates were similar irrespective of the pre-test probability of malignancy risk.[1] The study suggested there is a lack of adherence to nodule management guidelines. However, there are a number of lung nodule management guidelines and lung nodule malignancy risk prediction tools.[2-6] Some are based on 2D diameter size measurement while others used volumetric measurement or a combination of both. New nodules with a prior negative CT have a higher probability of malignancy even at a smaller size.[7-9] Compares to baseline screen, the malignancy risk of new nodules is higher for nodules <8mm.[9] Computer assisted diagnostic (CAD) tools facilitates volume measurement and reduce inter-observer variability but they may not be generally available. Volumetric measurement is particularly useful for comparison of serial scans for evidence of growth. Growth independent nodule characteristics such as right upper lung and central distribution may further improve volume based new nodule malignancy prediction. Nodule size and growth are the most important parameters for malignancy. To measure size accurately especially to determine changes in volume, it is necessary to address standardization of technical requirements related to the scanners and image acquisition protocols.[10] The action thresholds for early recall CT imaging study, PET/CT or biopsy vary in different guidelines with major differences for non-solid nodules making it difficult for clinicians to remember or apply. Therefore, a lack of adherence to guideline recommendations could be related to a lack of clarity of guidelines. To facilitate implementation, there is a need to have an integrated nodule malignancy risk tool that takes into account prior LDCT history when there is more than a baseline LDCT. In this session, the important issues regarding which risk model should be applied and which nodule management approach should be used (e.g. diameter or volume) for baseline and new nodules will be discussed through case presentations. References: 1. Tanner NT, Aggarwal J, Gould MK, Kearney P, Diette G, Anil Vachani A, Fang KC, Silvestri GA. Management of Pulmonary Nodules by Community Pulmonologists. A Multicenter Observational Study. Chest 2015:148(6):1405-1414. 2. MacMahon H, Naidich DP, Goo JM, *et al* (2017). Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology*; 284; 228-243. 3. American College of Radiology. Lung CT Screening Reporting and Data System (Lung-RADS). Accessed 23rd June 2017 from www.acr.org/quality-saftey/resources/lungRADS. 4. Callister MEJ, Baldwin DR, Akram AR *et al* (2015). BTS guidelines for investigation and management of pulmonary nodules. *Thorax*; 70:ii1-ii54. Doi: 10.1136/thoraxjnl-2015-207168. 5. Horeweg N, van der Aalst CM, Vliegenthart R, et al. Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial. Eur Respir J 2013;42:1659-67. 6. McWilliams AM, Tammemägi MC, Mayo JR, *et al* (2013). Probability of cancer in pulmonary nodules detected on first screening CT. *N Eng J Med*; 369: 910-919. 7. Walter JE, Heuvelmans MA, Bock GH, Yousaf-Khan U, Groen HJM, Aalst CMV, Nackaerts K, Ooijen PMAV, Koning HJ, Vliegenthart R, Oudkerk M. Characteristics of new solid nodules detected in incidence screening rounds of low-dose CT lung cancer screening: the NELSON study.Thorax. 2018 Apr 16. pii: thoraxjnl-2017-211376. doi: 10.1136/thoraxjnl-2017-211376. [Epub ahead of print] 8. Walter JE, Heuvelmans MA, de Jong PA, Vliegenthart R, van Ooijen PMA, Peters RB, Ten Haaf K, Yousaf-Khan U, van der Aalst CM, de Bock GH, Mali W, Groen HJM, de Koning HJ, Oudkerk M. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. Lancet Oncol. 2016 Jul;17(7):907-916. 9. Paul F. Pinsky PF, Gierada DF, Nath PH, Munden R. Lung Cancer Risk Associated With New Solid Nodules in the National Lung Screening Trial. *AJR* 2017; 209:1009–1014. 10. Alexander A. Bankier AA, MacMahon H, Goo JM, Rubin GD, Schaefer-Prokop CM, Naidich DP. Recommendations for measuring pulmonary nodules at CT: A Statement from the Fleischner Society. Radiology 2017 Nov;285(2):584-600.

Keywords: lung cancer screening

MTE15.01 IDENTIFYING HIGH RISK PATIENTS: WHAT MAKES A PATIENT TOO HIGH RISK FOR SURGERY AND WHO DECIDES?

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Thoracoscope is, by its original meaning, defined as an endoscope to observe intrathoracic space, just like a bronchoscope for bronchial lumen. But today this endoscope has been widely accepted as a surgical instrument to perform various kinds of intrathoracic procedures which had been otherwise done with open thoracotomy. **Video-assisted thoracic surgery (VATS)** has been expected to reduce the surgical burden, and already applied for the complex surgeries such as those for lung cancer. It is now a part of our routine procedures. However, despite the minimally invasiveness of the procedure, VATS may become a risky surgery in several special situations. Not only the surgeons, but also pulmonologist, medical oncologist, or radiation oncologist should know the nature of the surgery, and the situations in which VATS should be rather avoided. In this MTE sessions, I would like to present the special situations in which the VATS procedures are at too high risk, and therefore, and are not considered to be performed. **HIGH-RISK SURGERY** When dose the surgery become at high risk? In what situation, we should think the surgery is at high risk? Generally, there must be two kinds of situations each alone or both combined, which make the surgery at high risk. One is **the patients at high risk for surgery** even for a routine lobectomy, with a limited pulmonary reserve. The other is **the difficult, complex surgery** such as the extended pulmonary resection. Technical limitations of a VATS procedure are generally related to several different situations, which are described below. In this MTE session, I would like to focus upon the surgical, technical risks for the VATS procedures. **VATS LUNG RESECTRIONS AT TECHNICALLY HIGH RISK** 2-1. DIFFICULT ONE-LUNG VENTILATION. **One-lung ventilation**, collapsing the one entire lung of the operative side, is an indispensable part of the stable VATS procedure. Thoracic cavity is usually filled with expanded lung, and only very limited space is left when the lungs are airated. To make VATS procedures possible, deflation (collapse) of the lung on affected side is indispensable, which provides the space for observation and working of surgical instruments. Therefore, for patients who do not tolerate to the one-lung ventilation because of the limited pulmonary reserve or previous history of lung resection, VATS is generally not indicated. For these patients, we consider routine open thoracotomy with intermittent collapse of the operative side of the lung. 2-2. TIGHT ADHESIONS. Tight adhesions might exist within the thoracic cavity, especially for patients with the history of pleurisy or surgery. As seen previously, the working pleural space is an indispensable element of a VATS procedure. Surgeons are concerned about such history in case VATS resection is indicated. There are several types of adhesions which make VATS procedure difficult. Examples for these conditions are as follows: **1) Previous pleurisy.** If intrathoracic adhesion, mostly due to the previous pleurisy, is extensive, it is impossible to have an enough working space. In fact, lysis under thoracoscopy can be done, but it is usually time-consuming with significant amount of blood loss. There might be even a higher risk of damaging the visceral pleura and lung parenchyma, which may cause prolonged air leakage especially in the elderly with bullous lung. Therefore, except for a localized one, the extensive symphysis of pleura should be respected as a contraindication and a case which should be converted to the open thoracotomy. **2) Adhesions at pulmonary hilum ("Frozen hilum").** In some cases with past history of infection such as tuberculosis, the hilar nodes are tightly adhesive to the bronchovascular structures. This is extremely difficult situation even for routine lobectomy. VATS resection for such cases are hardly considered. **3) Previous thoracotomy.** Major lung resection after previous lung resection involving the hilum (for example, a completion right lower lobectomy after middle lobectomy) is one of the most challenging surgery even by open thoracotomy. Also, for these operations, VATS resection is rarely indicated. 2-3. COMPLEX PROCEDURES. Among various procedures in thoracic surgery, complex procedures are thought to be done safely by open thoracotomy, and not by VATS. These might include the following: such as bronchovascular plasty, combined resection with neighboring structures, pneumonectomy, and pleuropneumonectomy. 2-4. OTHER SITUATIONS WHICH MAKE VATS PROCEDURE AT HIGH RISK **1) Complex anatomical variation.** When complex anatomical variations are found during the surgery, the procedure should be converted to open thoracotomy without hesitation. **2) Large lesions.** Any large intrathoracic mass, wherever it is located, have a trouble in being retrieved from the thoracic cavity. Not only they inevitably require enough extension of the trocar port or access thoracotomy, but also, they might be crushed during being extracted, which may result in tumor dissemination. **3) Special locations.** In the intrapulmonary and mediastinal lesions, there are special locations where the thoracoscopic instrumentation is quite difficult: Lesions located at mediastinal aspect of the lung, and those close to hilum. Mediastinal mass (swollen lymph nodes) adjacent to

the vital structures such as great vessels is also least suitable for this technique because of danger of massive bleeding.

Keywords: Surgery, VATS, Risk

MTE16 WHAT IS CHANGING IN THE MANAGEMENT OF PULMONARY NEUROENDOCRINE TUMOURS? (TICKETED SESSION)
TUESDAY, SEPTEMBER 25, 2018 - 07:00-08:00

MTE16.01 PROPER TREATMENT OF LCNEC; CHEMOTHERAPY OR TARGETED THERAPY

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Neuroendocrine Tumors of the Lung consisted of two subtypes which is small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC). Both subtypes represent around 15% of all Lung Cancer. The incidence of LCNEC was quite low as compare to SCLC. However both are aggressive and poor prognosis. The treatment of LCNEC was usually followed the SCLC. In early stages (I-II-III), surgery is recommended but does not seem to be sufficient. Platinum-based adjuvant chemotherapy may be useful while the role of neoadjuvant chemotherapy is still not well defined. In patients with advanced stage LCNEC, the chemotherapy regimens used in SCLC which is cisplatin plus etoposide remain the standard of treatment, but results are not satisfactory. Due to their peculiar clinical and biological features and the lack of literature data, there is an emerging need for a consensus on the best treatment strategy for LCNEC and for the identification of new therapeutic options. In this review, we will discuss the key aspects of LCNEC management and the possibility of using the gene sequencing to clarify the selection of chemotherapy regimen.

Keywords: large cell neuroendocrine carcinoma, lung

MTE16 WHAT IS CHANGING IN THE MANAGEMENT OF PULMONARY NEUROENDOCRINE TUMOURS? (TICKETED SESSION)
TUESDAY, SEPTEMBER 25, 2018 - 07:00-08:00

MTE16.02 THE MANAGEMENT OF SMALL CELL LUNG CANCER FOLLOWING FIRST LINE TREATMENT FAILURE

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SCLC remains a clinical challenge that has not benefited from the same medical advances in recent years as non-small cell lung cancer (NSCLC). Beyond first line chemotherapy, there are few approved therapies for recurrent small cell lung cancer (SCLC). A multitude of agents have been tested over the past decades, yet little improvement has been made in survival rates. This talk will review previous efforts in treating SCLC upon progression after first-line therapy, the current science that is changing our understanding of the biology of SCLC and will discuss the evidence for new agents in this indication, by reviewing recent and current clinical trials. The addition of platinum agents to first-line chemotherapy regimens in the 1980's improved overall response (OR) and complete response (CR) rates, and thus platinum doublet chemotherapy, most commonly in combination with etoposide, is the current standard of care.[1] SCLC is initially very chemosensitive, OR rates to platinum-etoposide chemotherapy in the first line setting for limited disease (LD) are between 60-90% with CR rates of 40-70%[2], and one third of patients will survive 5 years and be considered cured. The prognosis is far less optimistic for the two thirds of patients with SCLC who are diagnosed with extensive-stage (ES) disease. OR rates for ES SCLC are 40-70%[2], and CR rates are 10-20%.[3,4] The median progression-free survival (PFS) in the first-line setting is in the order of 15 months for LD[5] and 6 months for ES.[6] Unfortunately, the high response rate seen in the first line setting is not maintained when patients are retreated. Patients can be classified into three groups based on their response to initial chemotherapy: sensitive (tumor response ≥ 90 days), resistant (recurrence within 90 days of completing primary therapy) and refractory (non-responders and progression on treatment).[2] Therapeutic options therefore include re-challenge for those patients with sensitive disease or a change of regimen. Topotecan has been approved by the FDA since 1996 for the second-line treatment of SCLC following first-line relapse.[7] There are additionally several guideline-recommended therapies that are not FDA/EMA approved, such as cyclophosphamide/doxorubicin/vincristine (CAV), irinotecan (Japan), docetaxel, paclitaxel, gemcitabine, temozolomide and nivolumab with ipilimumab.[8] Response rates to second line therapy are 27% at best and less than 15% in chemo-refractory cases[9], with a median time to progression of only 13 weeks.[10] Despite decades of testing with multiple agents, there have been no new drug approvals in over 20 years and **improved therapy is urgently needed.** With the advent of targeted therapies over the past decades, there has been no shortage of early phase clinical trials in SCLC. However, these agents have yet to demonstrate success in phase II-III evaluation. The lack of progress in improving survival rates for SCLC led to its inclusion in the U.S. Congress' Recalcitrant Cancer Research Act in 2012. Subsequent comprehensive molecular characterization of the disease has led to a better understanding of known molecular vulnerabilities and has pointed to new areas requiring therapeutic interrogation. Examples include developmental regulatory pathway abnormalities, DNA damage repair aberrations, and the manipulation of the immune response. Fundamental to further therapeutic progress remains the challenge of understanding the mechanisms that underlie the rapid emergence of chemo-resistance in SCLC. Recent reports of early phase clinical trials with immune checkpoint inhibitors documenting important response and survival rates, provide tangible hope for the approval of new treatment options. However, immune strategies should exclude the empiric testing of new monotherapies and combinations in the absence of strong pre-clinical science. This will necessitate the development of next generation pre-clinical models, that are biologically representative of the human immune system and disease. Finally, improved translational research will inform more rational clinical trial design, and concentrate resources towards the most promising therapeutic avenues. References: 1. Sundstrøm S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: Results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol*. 2002;20(24):4665-4672. doi:10.1200/JCO.2002.12.111. 2. Cheng S, Evans WK, Stys-Norman D, Shepherd FA. Chemotherapy for relapsed small cell lung cancer: A systematic review and practice guideline. *J Thorac Oncol*. 2007;2(4):348-354. doi:10.1097/01.JTO.0000263720.15062.51. 3. Alvarado-Luna G, Morales-Espinosa D. 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Keywords: Recurrent disease, small cell lung cancer, new strategies

MTE17 LIVING WITH AND BEYOND LUNG CANCER: AN EDUCATION FOR ADVOCATES (TICKETED SESSION)
TUESDAY, SEPTEMBER 25, 2018 - 07:00-08:00

MTE17.01 LIVING WITH AND BEYOND LUNG CANCER: AN EDUCATION FOR ADVOCATES

A. McNamara[1], W. Boerckel[2], M. Rigney[3]
[1]Information Development, Irish Cancer Society, Dublin/IE, [2]Social Service, Cancercare, Syosset/US, [3]Lung Cancer Alliance, Washington/DC/US

Who is this session for? This session is aimed at lung cancer advocates, including members of healthcare teams and advocacy organisations. The session will be an interactive discussion on living with and beyond lung cancer. Key topics include an introduction to survivorship, issues for lung cancer survivors, interventions and a global discussion on how advocates can address the needs of lung cancer survivors in their country. The session will be jointly presented by both authors. **Background:** Lung cancer has been the most common cancer in the world for several decades with an estimated 1.8 million new cases in 2012 (IARC, 2018). Sadly lung cancer is the leading cause of cancer deaths worldwide. Every year, lung cancer causes more than 1.6 million deaths; more than breast, colon and prostate cancers combined (IASLC, 2015).

However there are lung cancer survivors. According to the Concord study (2015) 5-year net survival from lung cancer is typically low, in the range of 10–20% for most geographical areas. This study is the most comprehensive international comparison of cancer survival to date, covering countries that are home to two-thirds of the world's population and shows extremely wide differences in survival between countries. Anyone who has been diagnosed with cancer is a survivor – from the time of diagnosis to the end of life. Caregivers and family members are also cancer survivors (National Coalition for Cancer Survivorship, 1986). For the purpose of this session, we will focus on lung cancer patients who are post treatment. **Unmet needs:** The impact of a cancer diagnosis can evoke a range of emotions, anything from fear, anxiety, anger or denial. There is no right or wrong way to feel and patients often describe it as being on 'an emotional rollercoaster.' A study performed by Zabora et al. in 2001 examined the prevalence of psychological distress by cancer site and found considerable variation. Of the patients surveyed, 43% of lung cancer patients experienced elevated levels of distress in comparison to 32% of breast cancer patients, 31% of bowel cancer patients and 30% of prostate cancer patients. Numerous studies have since replicated these results. And being off treatment does not imply less distress for lung cancer survivors (Eichler, 2018). Lung cancer survivors' health related quality of life is generally low; therefore, management is crucial during the posttreatment period. The experience of having unmet supportive care needs is most strongly associated with intrusive cancer-related thoughts, limitations in physical functioning, distress associated with physical symptoms, and health-care satisfaction (Sanders et al., 2010). **Issues for post treatment survivors:** The concept of quality of life has become a core concern for many healthcare professionals (Brennan, 2004). Surviving cancer does not always result in a return to 'normal life'. The impact of a diagnosis can affect the overall quality of life of a survivor, including physically, psychologically and socially (Ivers, M. et al., 2009). For the purpose of this presentation, we will focus on post-treatment survivors and outline concerns real lung cancer survivors have expressed, including: Expectations Avoiding Triggers Anxiety Volume Guilt The Meaning of My Lung Cancer Experience Who/What Am I Social Disconnections Vulnerability **Interventions:** Psychosocial interventions with cancer patients usually focus on adaption and adjustment to diagnosis and treatment, helping the patient to engage in behaviours that are more conducive to better health (Neuz & Neuz, 2007). We will outline a variety of interventions that are successfully used to support lung cancer patients, including: CBT Focusing on Current Facts Staying In the Moment Talk Therapy Managing and Creating New Expectations Lowering the Anxiety Volume Re/Building Self-Esteem Socialization Exercises **Global variations:** There are wide variations in survival rates globally and this in turn impacts the work priorities of advocates. Both authors will present on lung cancer survival in their own country, demonstrating different unmet needs and priorities. The audience will then be invited to discuss key survivorship concerns within their organisations and given an opportunity to share their own survivorship initiatives and projects. **Conclusion:** Following group discussion, the authors will present some top tips on advocating for lung cancer survivors and direct the audience to useful resources. **References:** IARC (2018) Globocan 2012: *Estimated Cancer Incidence, Mortality and Prevalence Worldwide.* Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx IASLC (2015) *2015 Lung Cancer Factsheet.* Available at: https://www.iaslc.org/lung-cancer-fact-sheet-2015-europe Allemani, C. et al. (2015) Global surveillance of cancer survival 1995 – 2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). *The Lancet,* 385, March 14, 2015. 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Keywords: Global variations, survivorship, interventions

MTE18 CASE-BASED MANAGEMENT OF PATIENTS WITH INADEQUATE TISSUE FOR MOLECULAR TESTS (TICKETED SESSION)
TUESDAY, SEPTEMBER 25, 2018 - 07:00-08:00

MTE18.01 CASE-BASED MANAGEMENT OF PATIENTS WITH INADEQUATE TISSUE FOR MOLECULAR TESTS

B. Levy[1], A. Sacher[2]

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Plasma genotyping has rapidly evolved from an investigational technology into a standard-of-care tool with the potential to direct therapy in metastatic non-small cell lung cancer (NSCLC). Tissue genotyping has historically been considered the gold standard for genotyping in NSCLC both at initial diagnosis and acquired resistance to therapy. However, plasma genotyping is increasingly useful as a rapid alternative to tissue genotyping in certain clinical contexts. This technology is particularly applicable in patients with insufficient tissue available for genotyping at initial diagnosis as well as at the development of acquired resistance. The optimal use and interpretation of plasma genotyping requires understanding of cell-free DNA (cfDNA) biology, assay characteristics and the application of testing in different clinical scenarios. In newly diagnosed metastatic NSCLC, plasma genotyping is useful for the detection of targetable genomic alterations or non-targetable driver alterations (eg, *KRAS*) that are mutually exclusive with targetable alterations. The potential utility of plasma genotyping in newly diagnosed patients is particularly pronounced in patients with insufficient tissue from their diagnostic biopsies for genotyping, those with inaccessible or difficult to biopsy lesions and patients in which rapid initiation of treatment is needed due to clinical deterioration. The high positive predictive value of most modern plasma genotyping platforms for the detection of targetable genomic alterations means that positive results can be used to rapidly guide initial targeted therapy in metastatic NSCLC patients. However, the modest sensitivity of these assays requires that negative results be confirmed by tissue genotyping with repeat biopsy, if necessary. In patients with acquired resistance to targeted therapy, plasma genotyping can be utilized to detect resistance mutations at the time of progression. Furthermore, plasma genotyping may detect resistance mutations missed by standard tissue genotyping in this context due to tumor heterogeneity. Plasma T790M testing in patients with acquired resistance to first- and second-generation EGFR kinase inhibitors has been utilized extensively for selecting patients for treatment with second-line osimertinib. However, the utility of this technology in acquired resistance to EGFR therapy is likely to decrease as more patients are treated with front-line osimertinib without a targeted therapy option at development of acquired resistance. The recent explosion of multiple treatments for ALK acquired resistance has opened a new opportunity to apply plasma genotyping technology for the selection of second-line targeted therapy in these patients. While cfDNA technology has aided in the detection of actionable mutations, there remain challenges at present related to modest assay sensitivity, standardization of both analytic and clinical validation across testing platforms and adapting this technology to the ever-changing treatment landscape of metastatic NSCLC. In addition, DNA captured in plasma may be from multiple sources other than tumor, including germline, fetal, post-organ transplantation and clonal hematopoiesis of indeterminate potential (CHiP). These mixed sources have been routinely detected in commercial-based assays and can affect the interpretability of assay results. Despite potential limitations, cfDNA platforms offer immense promise in serving as an accurate molecular proxy for tumor biology. There is considerable potential for plasma genotyping in the detection of early-stage disease and for patients at risk for disease recurrence post curative intent therapy. In addition, there may be future utility with these assays in the detection of tumor mutational burden (TMB) and other predictive biomarkers of immunotherapy. Future prospective efforts that mandate plasma interrogation both as a static and dynamic biomarker will enable a firmer understanding of how best to utilize this unique technology.

Keywords: NSCLC, Genomics, plasma genotyping

MTE19 HOW I TREAT ADVANCED STAGE THYMIC MALIGNANCY PATIENTS (TICKETED SESSION)
WEDNESDAY, SEPTEMBER 26, 2018 - 07:00-08:00

MTE19.01 HOW I TREAT ADVANCED STAGE THYMIC MALIGNANCY PATIENTS

H. Wakelee
Medicine (Oncology), Stanford Cancer Intitute/stanford University, Stanford/CA/US

Given the rarity of thymic epithelial tumors (thymoma and thymic carcinoma) accumulation of clinical trial data to guide management has been challenging, yet the chemo-sensitivity of these malignancies is clearly established. As with most solid tumors it is important to fully assess for any chance of locally aggressive therapy with surgery or radiation for a curative intent. Thymic malignancies are often very radiation sensitive as well and I am quick to refer to radiation oncology for localized disease progression or any symptomatic areas. The high rates of paraneoplastic syndromes and autoimmunity adds to the complexity of management of this disease, especially thymoma.[1]I am grateful for the support of neurology colleagues and immunology colleagues to help with myasthenia gravis and immunotherapy/rheumatology management of these complex patients. Once the disease has spread extensively in the pleural or metastases have developed, systemic therapy will be essential. I tend to start with a platinum based regimen initially. For young and fit patients the three drug CAP regimen of cyclophosphamide, doxorubicin and cisplatin has a very high response rate.[2] Given the cumulative cardiotoxicity of the anthracycline in the regimen, I usually stop at 4 and no more than 6 cycles. Most patients are then able to enjoy a chemotherapy holiday for several months, and even up to a year or longer. I will consider cisplatin/etoposide[3]if anthracyclines are contraindicated, and especially if any concurrent radiation is under consideration. Carboplatin/paclitaxel was also studied prospectively and remains the most studied regimen for thymic carcinoma.[4]The response rates with all of these regimens are approximately 50%, somewhat higher with the platinum/anthracycline combinations, though given low numbers in trials the precise response rates are difficult to state with certainty. None of these regimens include a maintenance component, yet the PFS can be 1-2 years. I will also consider giving platinum/pemetrexed as a first line regimen given the improved tolerability, despite limited data. This is primarily focused in thymoma patients, though activity in a limited number of thymic carcinoma patients has been noted despite the usual squamous histology.[5] Once a patient has progressed on first line treatment one may choose between a number of single chemotherapeutic agents with activity including 5-FU and derivatives, gemcitabine, pemetrexed, taxanes and others. I choose between these based on toxicity profiles and prior regimens for the patient and do not have a single standard approach. For younger and fit patients, especially if they have a high disease burden, I will consider combination regimens. There is also growing evidence for activity of agents with mechanisms of action that differ from those of traditional cytotoxic drugs. One of the first of these was octreotide with or without prednisione.[6]I have used this regimen rarely and in the setting of a positive octreotide scan, or a patient with autoimmune diarrhea where the octreotide was also effective in controlling symptoms of disease. More recently I have begun to use the mTOR inhibitor everolimus in my thymic malignancy patients based on a 51 patient trial with the compound.[7]At 10 mg/day oral dosing the drug had a disease control rate of 88%, which was slightly higher for the thymoma subgroup. There was a complete response in a thymic carcinoma patient and partial responses observed in a minority of both thymoma and thymic carcinoma patients. Median PFS exceeded a year in the thymoma patients. However, significant toxicity was seen with serious drug related adverse events in 14 of the 51 patients including 3 events of fatal pneumonitis. In my practice I have found that most patient do require a dose reduction to 7.5 or 5 mg daily. Pneumonitis remains a risk with this agent, but can be managed if discovered early. More specifically for thymic carcinoma emerging data with sunitinib has been very encouraging. In a trial that included 23 evaluable thymic carcinoma patients (as well as 16 with thymoma) the partial response rate was 26% for the thymic carcinoma patients with a further 65% with stable disease. Again toxicity is a concern with 13% rate of cardiac toxicity (reduction in ejection fraction).[8] Detailed molecular analysis of a large group of thymic malignancies was published by the TCGA study group and confirmed GTF2I as the most common mutation in thymoma, as well as revealing 4 distinct categories in the primarily early stage thymoma samples analyzed. Unfortunately no obvious new therapeutic options emerged from this work, but this deeper understanding of the molecular underpinnings of the disease will hopefully allow us to improve our therapeutic options.[9]The low tumor mutation burden of thymomas was also confirmed in the TCGA effort. Thymic malignancies, however, are known to have high PD-L1 expression as shown by multiple groups and that led to the first trials of immunotherapy in thymic malignancy patients. A phase II trial with pembrolizumab, restricted to thymic carcinoma patients without any evidence of autoimmunity, enrolled 41 patients.[10] The overall response rate was 22.5% including a complete response, however 15% of patients had severe autoimmune toxicity, which involved grade 4 myocarditis in 2 of the patients and myositis (elevated CPK) in an additional 3 patients. Taken together I am still very cautious in considering PD-(L)1 inhibitors in thymic carcinoma patients as the risk/benefit ratio (23% response and 15% severe autoimmune toxicity) is much closer than we have with many other therapeutic options. The risks in patients with thymoma or any underlying paraneoplastic autoimmunity limits our utility of these drugs at this time. Thymic malignancy patients have multiple treatment options and many can have long periods of disease control with the traditional cytotoxic options available and a growing number of targeted therapeutics. REFERENCES: 1. Padda SK *J Thorac Oncol*13(3):436-446;2017 2. Loehrer PJ*J Clin Oncol* 12:1164-1168;1994 3. Giaccone G*J Clin Oncol* 14: 814-820;1996 4. Lemma GL*J Clin Oncol* 29:2060-2065;2011 5. Liang Y *Lung Cancer*87(1):34-8;2015 6. Loehrer PJ *J Clin Oncol*22:293-299;2004 7. Zucali PA *J Clin Oncol*36 (4); 342-349;2018 8. Thomas A *Lancet Oncol*16(2):177-186;2015 9. Radovich M *Cancer Cell*33:244-258;2018 10. 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Keywords: Thymoma, Thymic Carcinoma

MTE20 MOLECULAR TESTING IN SMALL SAMPLES (TICKETED SESSION)
WEDNESDAY, SEPTEMBER 26, 2018 - 07:00-08:00

MTE20.01 MOLECULAR TESTING IN SMALL SAMPLES

J. Longshore
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Recent advances over the past decade in canger genomics allows the rapid identification of patients with driver mutations or immune phenotypes that are eligible for targeted, rather than systemic, therapy. In many centers worldwide, biopsy material obtained from lung cancer patients is limited to core needle biopsy or fine needle aspirate samples. After a histologic diagnosis is rendered on these samples, often a limited amount of tissue remains for biomarker testing. To further complicate matters, the number of biomarkers required to profile patients is increasing with the number of new therapeutics available for treatment. During this educational session, techniques for proper tissue stewardship when working with small biopsy samples as well as utilizing tissue sparing biomarker testing methods will be presented.

Keywords: Tissue stewardship, Small biopsy samples, Biomarker testing methods

MTE20 MOLECULAR TESTING IN SMALL SAMPLES (TICKETED SESSION)
WEDNESDAY, SEPTEMBER 26, 2018 - 07:00-08:00

MTE20.02 MOLECULAR TESTING IN SMALL SAMPLES

J. Chung
Pathology, Seoul National University Bundang Hospital, Seoul/KR

Molecular targeted therapies have become a standard treatment for patients with lung cancer. Driver genetic alterations such as *EGFR* mutations, *ALK* rearrangements and *ROS1* rearrangements are currently used as predictive biomarkers for EGFR tyrosine kinase inhibitors (TKIs), ALK inhibitors, and ROS1 inhibitors, respectively. In addition, antibodies blocking the PD-1 ligand PD-L1 have shown prominent antitumor activities and durable clinical response. Molecular analyses of these predictive biomarkers in tumor tissue or cytology specimens are the first prerequisite laboratory tests for the clinical management of lung cancers. Despite the increasing number of targets to be tested, most patients harboring non-small cell lung carcinoma (NSCLC) presents with advanced stage at the time of diagnosis, so the amount of tissue that can be acquired is very small. Small biopsy and cytology samples obtained from a variety of methods are acceptable for molecular testing, including transbronchial lung biopsy, endobronchial ultrasound– guided transbronchial needle aspiration, bronchial brushing or washing, computed tomography–guided gun biopsy or needle aspiration, and pleural fluid sampling. The molecular testing results using cytology samples are highly concordant with those of the corresponding tissue samples, especially with more sensitive methods. Routinely prepared cytology samples such as alcohol-fixed smears or cell block samples are also suitable for mutation testing. As targetable genetic alterations are increasingly identified, individual genotyping or molecular test seemed to be relatively inefficient and expensive. Thus, next-generation sequencing (NGS) technology with DNA or RNA is reported to be useful method for multiplexed and deep targeted sequencing. In this situation, each pathology laboratory needs to make a strategic approach to use these small samples in considerations of the important priorities for the management of the patients. In this MET session, I will introduce our experience of strategic approach to obtain the most useful information while reducing the loss of tissue using a small amount of samples.

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Keywords: small samples, Lung neoplasms, molecular testing

MTE22 INCORPORATION OF SMOKING CESSATION IN CLINICAL CARE (TICKETED SESSION)
WEDNESDAY, SEPTEMBER 26, 2018 - 07:00-08:00

MTE22.01 INTEGRATION OF CESSATION AND LUNG CANCER SCREENING

M. Steliga

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Lung cancer screening with low dose computed tomography (LDCT) has been studied extensively and is recommended for individuals who are deemed to be at increased risk, typically with a smoking history of 30 pack-years or more. The National Lung Screening Trial (NLST) demonstrated that with a screening program, there was a 20% reduction in lung cancer mortality. The overall incidence of lung cancer in the NLST was around 2%. Unfortunately, an often overlooked, yet treatable condition in any lung cancer screening program is continued tobacco use. In the NLST, 48% of participants were actively smoking at the time of the screening, and in our institutional program 71% are actively smoking. Cessation in this group may be seen as a challenge, as many of these patients have a much greater than 30 pack-year history and have not quit despite being advised by their primary physician. However, the lung cancer screening program may interact with the patient in a 'teachable moment' and these patients receiving screening may have increased motivation and willingness to quit if given the right resources. External resources such as quitlines or referrals to external tobacco cessation programs require action and increased motivation on the aprt of the patient, while integrating resources in the workflow of the screening program deliver the resources to the patient as a standard part of practice. Furthermore, the lung cancer screening program may be able to interact with the patient over time (through annual follow up at least) and may be an optimal way to deliver cessation resources to these patients. This session will explore different programmatic strategies to deliver cessation resources to patients in the construct of a LDCT Lung Cancer screening program. The coordinator of our screening program is a Advance Practice Registered Nurse (APRN) who sought out training and certification as a certified Tobacco Treatment Specialist (TTS). Referrals to the LDCT screening program are initially contacted by phone for a scheduling phone call, which also includes the initial elements of counseling these patients regarding tobacco cessation. An initial intake phone call determines appropriateness for screening and also can include elements of the 5A framework: ASK, ADVISE, ASSESS, ASSIST, ARRANGE. Then on the day of the scan, the APRN coordinator meets with the patient face-to-face at the point of the scan, and has already established rapport by telephone prior to the visit. The day of the scan, the patient recieves in person counseling as part of their visit, and a cessation strategy or "Quit Plan" is made which may include medications such as nicotine patches and/or gum. After the scan, telephone follow up is conducted to both discuss cessation and discuss scan results with a plan for follow up. Additionally, patients can be enrolled in a state Quitline program as a standard part of the workflow which provides them with ongoing support. Another option for patients is for the screening program to refer them to group counseling sessions. The American Lung Association's Freedom From Smoking is one such structured program. Patients may not independently seek these programs out, but as a lung screening program, developing ties to programs in the community with integrated referrals to group counseling programs can be another way to further the delivery of resources to these patients. As patients return for repeat scans to follow up indeterminate nodules, or return the following year for routine scans, further cessation support is delivered, and if they have quit, abstinence support is provided. Quitlines, group counseling, and nicotine replacement therapy have been shown to be cost effective strategies to help people who smoke to increase chances of quitting. A lung screening program may identify 2% of its participants with lung cancer, but if half (or in our case 71%) are smoking, and integrated cessation resources help those patients to reduce or quit smoking, the benefit of the lung screening program is greatly amplified, and patients can reduce risk for future cancers as well as cardiovascular and non-oncologic respiratory diseases.

Keywords: Smoking Cessation, Screening, tobacco

MTE23 SURGICAL CONSIDERATIONS FOLLOWING INDUCTION THERAPY FOR STAGE IIIA DISEASE (TICKETED SESSION)
WEDNESDAY, SEPTEMBER 26, 2018 - 07:00-08:00

MTE23.01 SURGICAL CONSIDERATIONS FOLLOWING INDUCTION THERAPY FOR STAGE IIIA DISEASE

E. Vallieres

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Considerations following Induction Therapy for Stage IIIA Disease Surgery after induction therapy can at times be very challenging. From my own observations, this may particularly be an issue when the patient had nodal involvement at presentation and experienced a good response to the induction treatment (induction chemoradiation (CRT) or induction chemotherapy (C) alone) where fibrosis of the responding lymph nodes may make the hilar vascular mobilization more difficult. (Induction immunotherapy as well in limited reported series) The following lines will describe some tips on how to minimize the risks of such resections. Preoperatively: One should always take advantage of the induction therapy period (12 weeks or more) to achieve absolute smoking cessation in these patients. After induction therapy, one should obtain a fresh set of PFTs including a DCO measurement as both radiation and some of the induction chemotherapy agents may have caused significant pneumonitis with resulting altered lung function. If there is a possibility that a pneumonectomy will be required, prepare yourself. (QVQ, stress echo). Radiation esophagitis may have brought some nutritional issues, consider an alimentary "boost" when a significant weight loss has occurred during the induction phase of therapy. If there may be a risk that the SVC will be clamped, repaired or replaced, discontinue the port-o-cath preoperatively. Finally, make sure to review all imaging, particularly the pre-induction therapy CT: the MTD is a good format for such review in our institution. Surgery Personally, I approach these cases via open thoracotomy, though some have reported successful resections on MIS platforms. All patients get an epidural catheter preop. If one anticipates, issues with the SVC with a R upper lobar resection, get infra diaphragmatic IV access preop. Emphasize w anesthesia, in the preoperative area, the absolute need to keep these patients dry: an irradiated mediastinum cannot handle excess fluid. At entry, I prepare/ harvest the intercostal muscle, without dividing it. (I now keep the omentum for later if needed to manage a complication, and spare the serratus anterior in all cases). If accessible, I usually clear zone 7 first, with frozen section read. (The frozen section information/ feedback during this type of surgery can be very useful to have when one gets into a tough surgical corner...) If one is attempting a lobectomy and anticipates possible difficulties in the hilum, one should consider obtaining early circumferential control of the main veins and main PA (if possible), and do so intrapericardially if needed. Similarly, early division of the azygos vein on the right, may help when one anticipates difficulties accessing the main R PA and surrounding structures. One may have to alter their usual sequence of dividing the central structures. With both upper lobes, when bulky fibrotic changes are present in the suprahilar areas, proceeding retrograde, from the fissures up is often very helpful. As well, dividing open the upper lobe bronchi from the back can help access and control the often fibrosed and foreshortened proximal lobar PA upper lobar branches. On the left, I will identify the vagus nerve low down, away from the fibrotic field and follow it up into the AP window to minimize the risks of inadvertently injuring the recurrent nerve. During the case, I constantly remind anesthesia to keep these patients dry. For pneumonectomies, we give a steroid bolus before dividing the main PA, similarly we initiate amiodorone prophylaxis by infusion during surgery. In high R pneumonectomies, when we have stapled the bronchial stump and a portion of the tracheal wall, I add an additional non resorbable monofilament stitch to reinforce both ends of the bronchial stapled line. Finally, we cover all of our bronchial stumps after induction CRT, and selectively after induction C alone, with the intercostal muscle flap. POSTOP AND DC Remember to keep the patient dry. Consider maintaining amiodorone prophylaxis for 72 hours after pneumonectomies or with other patients deemed at elevated risk of going into atrial fibrillation post op. Beware of a possible left vocal cord palsy after L pneumonectomy and difficult left upper lobectomy: we keep these patients NPO until we are confident that their cords are OK. If there are any concerns, we get an immediate laryngoscopy. If the left cord is found to be paretic, we immediately get VC medicalization. (not negotiable) In addition to having a high Caprini DVT Risk Score by virtue of their diagnosis, age and magnitude of surgery, patients who have received induction C or CRT may potentially be at higher risk of post op TBE as some of the C agents are thrombogenic. Unless contraindicated, we will discharge them home on continued TBE chemical prophylaxis for one month after surgery, longer if the recovery lags.

Keywords: surgery, induction therapy

MTE23 SURGICAL CONSIDERATIONS FOLLOWING INDUCTION THERAPY FOR STAGE IIIA DISEASE (TICKETED SESSION)
WEDNESDAY, SEPTEMBER 26, 2018 - 07:00-08:00

MTE23.02 SURGICAL CONSIDERATIONS FOLLOWING INDUCTION THERAPY FOR STAGE IIIA DISEASE

J. Spicer
Division of Thoracic Surgery, Mcgill University, Montreal/QC/CA

Seeking new solutions through the windows of opportunity offered by induction therapy for locoregional disease. The predominant model of care for locally advanced solid organ malignancies involves a shotgun approach. Indeed, the full range of "omic" strategies are currently insufficiently exploited when assigning treatment regimens to patients with IIIA non-small cell lung cancer (NSCLC). Despite the advent of precision oncology, management strategies for stage IIIA NSCLC remain relatively untargeted despite such successes as those described in the PACIFIC trial [1]. Indeed, the workhorses of curative intent therapy for IIIA NSCLC and their various permutations (surgery, radiation and chemotherapy) remain essentially unchanged over the last 25 years since the first trials of induction chemotherapy were performed in the early 1990s [2-3]. The paradigm of multimodality therapy combining local and systemic treatments holds true today and offers the best available oncological outcomes recorded to date. After decades of debate, emerging data seem to conclude that induction therapy with chemotherapy alone or concurrent chemoradiation offer essentially identical results when planned prior to surgery [4]. However, these data remain largely retrospective with few randomized head to head comparisons in this most heterogeneous of stage groupings. Hence, not only has stage IIIA remained a highly heterogenous cohort with a wide spectrum of disease burden, but its relative rarity has hampered the execution of innovative randomized trials. Thus, most centers have adopted a preferred institutional approach based on expert readings of the available literature. These variations in care have led to heated debates over what is essentially a game of musical chairs, arranging various permutations of conventional therapeutics for which the outcomes are largely identical. In this respect, the old debate of whether to give induction chemotherapy or concurrent chemoradiation misses the point and overlooks a tremendous opportunity for discovery. Years of clinical trials have taught us that approximately 15 to 20% of patients will experience a major pathological response after induction chemotherapy [5] and approximately one third will have a pathological complete response after concurrent chemoradiation [6]. Yet, we are no closer to selecting those patients most likely to benefit most from these conventional therapeutics. The windows of opportunity offered by induction therapy in surgically resectable IIIA NSCLC are numerous and vastly powerful. Properly exploited, these opportunities make IIIA NSCLC the perfect pivot point for discovery that will inform both the metastatic setting and novel approaches to early stage disease. As NSCLC patients are offered more therapeutic options, the ability to tailor induction therapeutics based on predictive analyses up-front remains under-exploited in IIIA disease. Current trials exploring the value of checkpoint inhibition prior to surgical resection for locally advanced NSCLC assign patients randomly to the available combinations. This again is a key moment to provide improved selection through the extensive correlative science pipelines offered by these window of opportunity trials [7]. The surrogate measure of major pathological response and its close association with long term survival outcomes provides a powerful incentive to rapidly adopt new regimens into the corpus of available therapeutic options. Our program capitalizes on the availability of large tissue samples offered by patients treated with multimodality therapy in surgically resectable IIIA NSCLC, to establish lab-based patient avatars. These living and highly personalized biobanks provide the necessary materials to profile and generate a lab-proven first line therapeutic regimen. While such programs would be highly inefficient in early stage disease where cure rates are much higher, patients with stage IIIA have high rates of recurrence and generally benefit from a sufficiently long disease-free interval. This luxury of time offers yet another window of opportunity where patient-derived xenograft models and organoids are generated from the surgical specimen to create the necessary patient avatar to execute a predictive analysis and establish the optimal next step for the significant number of patients who will experience progressive disease. Moreover, the sensitivity of liquid biopsy protocols is easily tested in this setting where a significant proportion of patients are placed into remission with no radiological evidence of disease [8]. Such opportunities provide the ideal setting to revisit our surveillance strategies which have become so resource intensive, yet offering so little measurable benefit [9]. Finally, a dedicated research program centred on locally advanced NSCLC provides a desirable clinical entity to rapidly establish predictors of response and failure to conventional and emerging biologicals by leveraging all "omic" platforms, from clinical to radiological and from pathological to deep sequencing, metabolomics, immunoprofiles and beyond. Such research provides the pipeline to generate the true essence of personalized medicine in NSCLC, which can easily be translated to both early and late stage disease. References

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Keywords: Stage IIIA, neoadjuvant, locally advanced non-small cell lung cancer

MTE24 MULTIPLE LUNG NODULES; RESECT, RADIATE OR WATCH? (TICKETED SESSION)
WEDNESDAY, SEPTEMBER 26, 2018 - 07:00-08:00

MTE24.02 SMALL LUNG TUMOURS: HIGH RISK LESIONS AND CONTRAINDICATIONS TO STEREOTACTIC ABLATIVE BODY RADIOTHERAPY (SABR)

D. Ball
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The development of SABR has revolutionised the non-surgical treatment of small, node negative lung tumors, both primary and metastatic. SABR is a convenient, painless, inexpensive outpatient procedure and there is now randomized evidence that it not only results in better local control than conventionally fractionated radiotherapy in patients with inoperable peripheral stage I non-small cell lung cancer, but increases survival as well. The impressive local control rates of over 80% have tempted some investigators to expand the indications for high dose hypofractionated SABR beyond small peripheral tumors. Perhaps the most controversial extended indication is the use of SABR for "central" lung tumours. There is no agreed definition of what constitutes a central tumor, although in the absence of consensus, the "no-fly zone" described by Timmerman is widely used even though it was based on a very small number of events.[1] Phase II trials have been interpreted as indicating that SABR of central tumors has acceptable toxicity (RTOG 0813), even though there was a 3% mortality likely resulting from treatment; or conversely as unsafe, with the Nordic HILUS trial reporting around 10% mortality after SABR of tumours close to the main or a lobar bronchus. The European Lung Tech trial should throw more light on the safety of treating central tumors with a "risk-adapted" approach using a more fractionated schedule of 60 Gy in 8 fractions.[2] Many patients referred for SABR have poor respiratory or cardiac function making them unsuitable for surgical resection. Does this make them unsuitable for high dose SABR as well? The available evidence suggests not,[3] but extreme caution should be taken in patients who have underlying interstitial lung disease.[4] The relationship between SABR and cardiac injury, especially in the era of combined immunotherapy and SABR, remains under investigation. This high risk group of patients are currently eligible for the Stablemates trial, which is comparing sublobar resection with SABR. Eligibility includes FEV1 or DLCO < 50% predicted. A patient's suitability for SABR will also depend on the dose constraints on nearby organs at risk. The chest wall is less concerning than previously, but is it the dose to the neurovascular bundle, rib or the whole musculoskeletal structure that most accurately predicts risk of chest wall pain? The brachial plexus tolerates hypofractionation poorly, and as with other scenarios where there is doubt about the safety of SABR, it is well to recognise that less effective but safer fully fractionated schedules are available. Other considerations, not in terms of risk, but of practical delivery of the treatment include synchronous multiple tumors, large tumors (>5 cm), and visibility for image guidance: Well defined? Too small? Image degraded by implanted fiducials? 1. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer. J Clin Oncol 2006;24:4833-9. 2. Adebahr S, Collette S, Shash E, et al. LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a

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Keywords: Stereotactic ablative radiotherapy, contraindications

MTE25 ENHANCING THE CARE OF YOUR OLDER ADULT POPULATION WITH LUNG CANCER (TICKETED SESSION)
WEDNESDAY, SEPTEMBER 26, 2018 - 07:00-08:00

MTE25.01 ENHANCING THE CARE OF YOUR OLDER ADULT POPULATION WITH LUNG CANCER

M. Puts
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Lung cancer is the most common cancer around the world and it affects many older adults (1). With older age, the risk of treatment complications may rise. However, there is a lack of evidence on how to best treat older adults with cancer as this population has been severely under-represented in clinical trials. As patients age, their health and function can vary significantly, resulting in an increasingly heterogeneous population Lung cancer is the most common cancer around the world and it affects many older adults (1). With older age, the risk of treatment complications may rise. However, there is a lack of evidence on how to best treat older adults with cancer as this population has been severely under-represented in clinical trials. As patients age, their health and function can vary significantly, resulting in an increasingly heterogeneous population (3). Many older adults have other health and functional status impairments that may impact cancer treatment benefits and treatment risks. Several professional societies and organizations have recommended that for older adults with cancer for whom treatment is considered (3,4,5), comprehensive geriatric assessment (CGA) (consisting of the domains comorbidity, medication use, functional status, cognition, psychosocial wellbeing, social support, mobility/fall risk) should be conducted to help clinicians with the treatment selection and care during the treatment. Implementing a comprehensive geriatric assessment in the oncology setting can help the oncology team with 1) detecting additional health conditions, 2) the assessment data can be used to predict life expectancy; 3) the assessment data can be used to predict chemotherapy toxicity; 4) the assessment data can result in changing treatment plans; and 5) the assessment data can be used to potentially reducing toxicity (3,4,5). The randomized trial of Dr. Corre and his team showed that treatment selection for older adults with Non Small Cell Lung cancer (NSCLC) based on the CGA was associated with decreased treatment toxicity (6). This assessment should be followed up with a care plan to address the health and functional status issues identified. In this session we will review how to enhance the clinical care for your older adult with lung cancer. **The learning objectives for this session are:** 1. To review the currently available evidence with regard to comprehensive geriatric assessment and management for your older adult with lung cancer patients including the Corre study. 2. To review how you can improve the clinical care of your older adult with lung cancer (the who/what/how of CGA including which tools, domains, who does what as well as the top 10 clinical pearls). Reference list. 1. Ferlay, J. et al. GLOBOCAN 2012v1.0, Cancer Incidence and Mortality Worldwide. IARC Cancer Base No. 11. Lyon, France: International Agency for Research on Cancer (2013). 2. Santoni G, Angleman S, Welmer AK, Mangialasche F, Marengoni A, Fratiglioni L. Age-related variation in health status after age 60. PLoS One 2015;10(3):e0120077. 3. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014 August 20;32(24):2595-603. 4. Mohile SG, Dale W, Somerfield MR, Hurria A et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology Summary. J Oncol Pract. 2018 Jun 22:JOP1800180. doi: 10.1200/JOP.18.00180. [Epub ahead of print] 5. Hurria A, Wildes T, Baumgartner J et al. NCCN Clinical Practice Guidelines in Oncology. Older Adult Oncology. Version 1.2018. NCCN; 2018. 6. Corre R, Greillier L, Le Caër H, et al. Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC-GECP 08-02 Study. J Clin Oncol. 2016 May 1;34(13):1476-83.

Keywords: Geriatric Oncology, functional status, comprehensive geriatric assessment

MTE26 NEW PARADIGMS IN SYMPTOM MANAGEMENT IN LUNG CANCER (TICKETED SESSION)
WEDNESDAY, SEPTEMBER 26, 2018 - 07:00-08:00

MTE26.01 ONCO-PULMONOLOGIST

P. Rivera
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The majority of patients with lung cancer are diagnosed with advanced disease where the 5-year survival rate remains low. Improving survival, quality of life (QOL) and control of symptoms are pivotal goals for health care professionals caring for patients with lung cancer. Several studies have shown that symptom burden and distress are higher among patients with lung cancer [1,2]. Despite advances in treatment of advanced lung cancer including targeted oral therapies which have resulted in improved survival and QOL[3], and early palliative care intervention which results in improvement in symptom control and quality of life[4], a recent study showed persistent significant symptom burden, distress and unmet needs in patients with advanced lung cancer[5]. The most common symptom in lung cancer is fatigue, reported in about 40% of patients, followed by pain (30%)[5]. Organ specific symptoms and complications include cough and dyspnea (20%), airway obstruction, hemoptysis, pleural effusions and tracheoesophageal fistula[5,6]. Providers caring for lung cancer patients need to be aware of common symptoms and interventions available, particularly non-drug interventions, and work together in multidisciplinary teams to ensure lung cancer patients are receiving the best therapeutic and non-therapeutic interventions in their cancer care in order to improve survival and QOL. **Interventions: -Fatigue:** Cancer-related fatigue, sometimes referred as cancer fatigue syndrome may be related to both the disease process and treatments, including surgery, chemotherapy and radiation therapy. Other factors that may contribute to fatigue include anemia, dyspnea, decreased nutrition, decreased exercise, pain, depression, and insomnia.Pulmonary rehabilitation (PH)/physiotherapy, shown to be very effective in patients with COPD, is an underappreciated intervention in patients with lung cancer due to lack of randomized data and low rates of referral (<25%). Although limited, existing, evidence supports PH/physiotherapy in lung cancer patients before and after surgery and that in patients receiving therapy other than surgery, may result in both ability to maintain and improve physical function, muscle strength and quality of life [7,8]. **-Pain:** Acute and chronic pain in the lung cancer patient may be multifactorial and influenced by physical, psychosocial and spiritual factors[6]. Pain-assessment tools and targeted imaging as required are as first essential steps in evaluating a patient's pain symptom[6]. Healthcare providers should understand the WHO analgesic ladder which recommends use of analgesics (acetaminophen and NSAIDs) for mild pain, addition of weaker opioids (codeine or dihydrocodeine) for mild to moderate pain and stronger opioids (morphine, hydromorphone, oxycodone)for severe pain[6]. Psychologic factors contribute to increased pain and suffering among cancer patients and non-drug interventions including hypnosis, cognitive behavioral coping mechanisms, meditation and relaxation exercises have been shown to reduce pain in patients and long term survivors[9]. **-Dyspnea:** The symptom of dyspnea is complex , often multifactorial and results in worsening QOL in patients with lung cancer. Dyspnea may be due underlying COPD or cardiac disease, complications of the tumor such as airway obstruction or pleural effusion, and side effects of treatment such as anemia, muscle fatigue, infection, pneumonitis and decreased nutrition. Careful and thorough assessment is paramount in order to manage dyspnea effectively. **-Airway Obstruction:** Patients with symptomatic endobronchial and extrinsic airway obstruction can benefit significantly from therapeutic bronchoscopy. Therapeutic bronchoscopic interventions, often used in combination, include debulking of airway tumors mechanically, using laser, electrocautery, cryotherapy, argon plasma coagulation. Balloon dilatation and insertion of silicone or metallic airway stents may be performed to treat extrinsic stenosis or endobronchial strictures due to radiation and covered metallic airway stents are effective in the management of tracheoesophageal fistulas[6]. **-Hemoptysis:** Hemoptysis, occurring in about 7-10% of lung cancer patients, is most commonly due to endobronchial tumor involvement. Rare causes include airway-vascular fistula formation, tumor necrosis with cavity formation, and complications from treatment (bevacizumab). Hemoptysis can be minor or severe/massive, the later defined as more than 200 mL of blood in a 24-hour period and commonly requires intervention. Securing the airway with a single-lumen endotracheal tube is paramount. Bronchoscopy is an excellent tool for both diagnosis and therapeutic intervention when endobronchial disease is found as the cause of the hemoptysis and includes laser, electrocautery, and argon plasma coagulation. External beam radiation therapy may also be used for endobronchial tumors causing hemoptysis[6]. When hemoptysis is due to parenchymal lesion such cavitary lung lesions due to cancer or due to complications of therapy, external bean radiation therapy or bronchial artery embolization is recommended. **References:** 1. Cooley ME. Symptoms in adults with lung cancer. A systematic research review. *J Pain Symptom Manage 2000;19:137-53* 2. Graves KD, Arnold SM, Love CL, et al. Distress screening in a multidisciplinary lung cancer clinic

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Keywords: lung cancer symptoms, hemoptysis, dyspnea

MTE27 CONTROVERSIES IN RADIOTHERAPY FOR SCLC (TICKETED SESSION)
WEDNESDAY, SEPTEMBER 26, 2018 - 07:00-08:00

MTE27.01 RADIOTHERAPY IN ES-SCLC

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Introduction Primary therapy for ED-SCLC is 4-6 cycles of platinum-based chemotherapy followed by PCI in select patients. Although response rates to chemotherapy 60-70%, time-to-progression and median survival are modest (4-6 months and < 10 months, respectively).[1] Response and improvement in survival is limited for second-line chemotherapy, particularly if progression is within 30-90 days.[2] PCI decreases brain metastases [3] and improve 1-year OS in patients that respond to chemotherapy.[4] Consolidative thoracic radiation (TRT) for ED-SCLC has been shown to improve survival and locoregional control in both prospective trials [5,6,7,8] and retrospective reviews.[7] Additionally, radiation therapy to extra-thoracic disease as part of primary management changes failure patterns.[7] It is difficult to interpret these trials and apply this information on a patient-to-patient basis. The patient population is diverse and patient selection, timing and dose of radiation varies significantly from study-to-study. *Thoracic Radiation* The trial published by Jeremic et al in 1999 supported TRT for ED-SLC in patients with at least a PR to locoregional disease and a CR to extrathoracic sites with chemotherapy.[6] After chemotherapy patients were randomized to two cycles of carboplatin and etoposide +/- concurrent hyperfractionated RT to the thorax (54Gy/36 fractions). Median Survival (17 months versus 11 months, p=0.041), five-year survival (9.1% versus 3.7%, p=0.041). The CREST trial included 495 patients with ED-SCLC randomly assigned to PCI or PCI and TRT (30Gy/10 fractions) after response to chemotherapy. Two-year OS favored the TRT arm, 13% (95% CI 9–19) versus 3% (95% CI 2–8; p=0.004).[5] Additional analysis showed that TRT led to a significant difference in overall and progression-free survival in patients who had residual intrathoracic disease after chemotherapy.[9] NRG 0937 randomized patients with ED-SCLC to radiation versus observation after response to chemotherapy. All patients randomized to treatment had TRT (45 GY in 15 fractions). Patients received consolidative RT to metastatic lesions if they had residual metastases after induction chemotherapy. Patients randomized to radiation had lower rates of local progression.[7] Yee et al prospectively evaluated the use of TRT in 32 patients with good response to chemotherapy (40 Gy in 15 fractions) resulting in only 5 thoracic recurrences.[8] Radiation dose, fractionation and timing were different in each of these trials although each has demonstrated the effectiveness of TRT. These trials have not established a standard of care although provide important information for individualizing treatment. *Failure Patterns* It is intuitive that the most likely site of failure after chemotherapy for ED-SCLC is in areas of measurable disease at diagnosis, particularly sites without at CR to chemotherapy. In the PCI trial for EDSCLC, 90% of patients had intrathoracic progression in the first year.[4] Likewise, patients on 0937 were more likely to fail in in sites of disease present at diagnosis (intrathoracic and metastatic). With proper patient selection and improved systemic therapy to address microscopic metastatic disease, radiation therapy to the chest and oligmetastases is may improve overall survival. *Prophylactic Cranial Irradiation* PCI remains controversial for ED-SCLC despite a survival advantage at 1 year demonstrated by Slotman et al[4] and advantages of PCI in early trials with subset analysis of patients with extensive disease.[10] A Japanese prospective trial did not show a survival benefit with PCI, although demonstrated a decrease in brain failures with PCI.[3] Although PCI is generally well tolerated, toxicity remains and concern. Improving the toxicity profile of PCI is being evaluated with use of hippocampal sparing in patients with LD SCLC. *Conclusion* Patients with ED-SCLC represent a diverse patient population with a wide range of anticipated outcomes. Radiation is effective for local control and prophylaxis of brain failures although patient selection, timing of radiation, dose and fractionation must be individualized. Patients should enrolled on trials. **Reference** 1. Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patientswith previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol. 2006 May 1;24(13):2038-43. PubMed PMID: 16648503. 2. Hurwitz JL, McCoy F, Scullin P, et al. New advances in the second-line treatment of small cell lung cancer. Oncologist. 2009 Oct;14(10):986-94. doi:10.1634/theoncologist.2009-0026. PubMed PMID: 19819917. 3. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2017 May;18(5):663-671. doi: 10.1016/S1470-2045(17)30230-9. 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Keywords: ED-SCLC, Radiation Therapy, Oligometastases

MTE28 LESSONS FROM THE PAST-WHAT I WOULD NOT DO AGAIN IN DIAGNOSTIC AND THERAPEUTIC IP (TICKETED SESSION)
WEDNESDAY, SEPTEMBER 26, 2018 - 07:00-08:00

MTE28.01 LESSONS FROM THE PAST-WHAT I WOULD NOT DO AGAIN IN DIAGNOSTIC AND THERAPEUTIC IP

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Lung cancer and pulmonology are inseparable – as lung cancer patients are invariably first seen by pulmonologists, often undergo diagnostic and staging procedures performed by pulmonologists, get evaluated by pulmonologists for fitness for surgical resection (in early stage disease), are treated by pulmonologists at certain geographical regions of the world, undergo follow up with pulmonologists for treatment related complications and/or symptom palliation related to either the disease or associated pulmonary co-morbid conditions. The current focus of this abstract is the role of diagnostic and therapeutic interventional pulmonology (IP) in the context of lung cancer. The growing armamentarium of IP includes several procedures as listed in Table 1 below

	PROCEDURE	ROLE
1.	Flexible bronchoscopy	
a)	Endobronchial biopsy (EBBx)	Diagnosis
b)	Transbronchial lung biopsy (TBLB)	Diagnosis
c)	Conventional TBNA (c-TBNA)	Diagnosis, Staging

	PROCEDURE	ROLE
2.	Endobronchial ultrasound (EBUS)	
a)	Convex probe EBUS	Staging, Diagnosis
b)	Radial probe EBUS	Diagnosis
3.	Medical Thoracoscopy	
a)	Flexi-rigid	Diagnosis, Palliation
b)	Rigid	Diagnosis, Palliation
4.	Rigid bronchoscopy	
a)	Mechanical coring	Palliation, Diagnosis
b)	Stent placement	Palliation
c)	Argon plasma coagulation	Palliation
d)	Electrocautery	Palliation
e)	Laser	Palliation
f)	Cryotherapy	Palliation

Endobronchial biopsy (EBBx): This is the most frequently performed bronchoscopic procedure for diagnosis of lung cancer. Its relatively safe with a high diagnostic yield (76%-97%). As airway bleeding is one of the commonly encountered problems, the learning points include: 1)Hot (electrocautery enabled) biopsy from vascular lesions 2)Avoid biopsy from cavity 3)Avoid biopsy from an excavating ulcer with vascular supply 4)Avoid biopsy from tracheal tumor or tumor at the tracheal carina Importantly, biopsy with electrocautery enabled forceps does not affect the tissue quality or the diagnostic yield. **Transbronchial lung biopsy (TBLB):** In certain situations TBLB is needed for diagnosing diffuse infiltrative lung disease in the setting of lung cancer including but not limited to lymphangitis, drug-induced interstitial lung disease, radiation pneumonitis and secondary infection. As pneumothorax, airway bleeding and crush artefacts are the commonly encountered problems, the important learning point is: 1)Do not use cup forceps for doing TBLB. Alligator forceps is preferred. It is likely that the cup forceps cuts through the blood vessels, whereas the alligator forceps crushes the blood vessels, thus leading to higher bleeding with the former method. In addition, the cup forceps has a smaller diameter (4 mm) compared with the alligator forceps (7 mm) in the open position; thus,it possibly reaches the lung segments more distally compared with the alligator forceps, leading to more pneumothoraces. **Bronchoscopic staging procedures:** EBUS-TBNA is an accurate, safe and cost-effective tool for lung cancer staging. It has been shown to have a pooled sensitivity and specificity of 93% and 100% respectively. The subgroup of patients who were selected on the basis of CT or PET positive results had higher pooled sensitivity than those without any selection (94% vs. 76%; $p<0.05$). EBUS-TBNA and EUS-FNA have been shown to have similar yield but lower complication rates as compared to mediastinoscopy in the initial mediastinal staging of non-small cell lung cancer. These endosonographic procedures are also safe and highly specific (99%) for mediastinal restaging of lung cancer The important learning points are: 1)Use of EBUS-TBNA results in significantly shorter time to treatment decision compared to conventional techniques 2)Do not use conventional TBNA for staging of lung cancer. EBUS-TBNA is preferred for both diagnosis and staging 3)Upfront mediastinoscopy for lung cancer staging in untreated patients and for restaging in patients after neoadjuvant chemotherapy (or neoadjuvant chemoradiation) is not needed as endoscopic procedures (EBUS-TBNA, EUS-FNA or their combination) are preferred for both of these **Medical thoracoscopy:** Medical thoracoscopy is a very useful procedure for both diagnosis of malignant pleural effusions as well as performing pleurodesis. Most patients present late at our center with extensive pleural adhesions and fibrosis. In such cases, flexi-rigid thoracoscopy has a lower yield in such cases (73% vs. 98%). The important learning point is: 1) Do not use flexi-rigid thoracoscopy for diagnosis of malignant pleural effusions **Rigid bronchoscopic procedures:** These are often undertaken as part of intervention for airway obstruction/stenosis. The important learning points are: 1) Avoid complex intervention procedures using flexible bronchoscope - prefer doing them using a rigid bronchoscope 2) Avoid placing stents when the distal airways are involved 3) When in doubt, place a silicon stent. Silicon stents are easy to extract, work even in malignant disorders, can always be replaced by metallic stents. Sometimes, what appears malignant may not be so and in tuberculosis endemic countries, endobronchial tuberculosis is a great mimicker of malignancy 4) Never place uncovered metallic stent for malignant disorders 5) Do not place metallic Y-stents using flexible bronchoscopy as this can be associated with criss-crossing of guidewires, loss of airway control (and immediate conversion to rigid bronchoscopy) and need for fluoroscopic guidance 6) Do not place silicone stents using flexible bronchoscopy **In summary**, each bronchoscopic procedure has inherent risks and potential for unintended complications. Therefore, each procedure teaches us something. The crux of safety in the context of diagnostic and therapeutic IP in lung cancer is to avoid performing biopsy during flexible bronchoscopy in tracheal tumors associated with airway obstruction, to use EBUS-TBNA for diagnosing/staging lung cancer, performing all complex interventions with a rigid bronchoscope and avoiding stent placements in patients with distal airway involvement. The most important principle for IP and practice of medicine, in general, is Primum non nocere (first do no harm).

Keywords: Staging, palliation, diagnosis

GR01 THYMIC MALIGNANCIES TUMOR BOARD
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

GR01.01 PATHOLOGY

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The pathologist is an integral member of the thymic malignancies tumor board team as he/she provides information on diagnosis, tumor stage, completeness of resection, and potential performance of biomarkers which is necessary for the team to decide on the optimal treatment for each individual patient. Information that will be expected from the pathologist differs dependent on whether a preoperative biopsy, a resection specimen or a specimen from a recurrence/metastasis is discussed (Table 1). For preoperative biopsies it is important to establish a histologic diagnosis including thymoma, thymic carcinoma, thymic neuroendocrine tumor, or benign thymic gland. Morphologic mimickers of thymic epithelial tumors (TET) such as lymphoma or germ cell tumors also need to be considered. Thymoma are not further subtyped on biopsies given the potential heterogeneity of these tumors. Moreover, the subtype of a thymoma in general does not play a role for treatment decisions. In contrast, the subtype of a thymic carcinoma might be of value at the time of biopsy as some subtypes behave in a very aggressive manner and might be treated differently from a squamous cell carcinoma, the most common subtype of thymic carcinomas. For instance NUT carcinoma commonly have already metastasized at time of diagnosis(1). Similarly, *SMARCA4*-deficient tumors (even though not included in the current WHO) are highly aggressive tumors(2). Lymphoepithelioma-like carcinoma can also behave more aggressively(3). Although these subtypes of thymic carcinoma are quite rare, they should be kept in mind and the threshold of ordering ancillary tests such as immunohistochemical stains for NUT and/or BRG1 or an EBV in situ hybridization should be low. As some TET are unresectable, suggestions for biomarker testing might also be expected from the pathologist. If a resection specimen of a TET is discussed stage and resection status are critical as they are the most important prognostic parameters and guide additional treatment decisions. To stage TET the recently introduced 8th edition of the UICC/AJCC TNM should be used. Currently, in many centers, both, Masaoka-Koga stage(4) and TNM stage(5) are reported simultaneously as some treatment protocols are still based on the Masaoka-Koga stage. The histologic classification also plays a role especially if the TET was not previously biopsied (which is the most common scenario in thymoma). In resection specimens the histologic classification should include the distinction between thymoma, thymic carcinoma and thymic neuroendocrine tumor vs benign thymic gland (i.e., thymic follicular hyperplasia, true thymic hyperplasia) vs mimickers of TET. In resection specimens the thymoma should be further subtyped, which is usually performed according to the 2015 WHO classification. (6) If the patient underwent neoadjuvant therapy, a comment on treatment effect of the resection specimen might be made(7). Although uncommon, biopsies or resections of recurrences or metastases of TET are performed and are discussed during tumor board. Based on the type of specimen (biopsy vs resection specimen) similar issues as described above will be discussed. In addition, especially in resection specimens, the WHO subtype of the TET should be mentioned as it might differ from the original specimen. In conclusion, the pathologist will contribute important information in regards to histologic diagnosis, stage, completeness of resection and biomarker testing of TET to the tumor board discussion which will be crucial for further treatment decision.

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Table 1: Pathology discussion points at thymic malignancies tumor boards

Time / type of specimen	Important information from pathology
Presurgical / initial biopsy	Histologic subtype of thymic epithelial tumor Subtype of thymic carcinoma Mimicker of thymic epithelial tumor Biomarker testing
Resection specimen	Stage Resection status Thymic epithelial tumor histologic subtype including thymoma subtype Treatment effect Biomarker testing
Recurrence / metastasis	Histologic subtype of thymic epithelial tumor including thymoma subtype (especially if resection) Resection status if excision Biomarker testing

Keywords: thymic epithelial tumor, stage, biomarker testing

GR01 THYMIC MALIGNANCIES TUMOR BOARD
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

GR01.02 SURGICAL ONCOLOGY

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The treatment strategy for Thymic Epithelial Tumors (TETs) is based first on the tumour resectability. If complete resection is deemed feasible upfront, as it is the case in Masaoka-Koga stage I/II as well as for some stage III tumours, surgery represents the first step of the treatment, sometimes followed by postoperative radiotherapy and, less frequently, chemotherapy. Pretreatment biopsy is not always required, if the diagnosis of thymic tumour is highly probable and upfront surgical resection is achievable. Biopsy is therefore required in all other clinical situations: approaches may consist of percutaneous core-needle biopsy or incisional surgical biopsy through mediastinotomy or mini-thoracotomy. Pleural spaces should be respected to avoid tumour cell seeding. Fine-needle aspiration is generally not recommended. The standard approach is median sternotomy, which allows the complete opening of the mediastinum and both pleural cavities, and the evaluation of tumour macroscopic capsular invasion, infiltration of perithymic and mediastinal fat, peritumoural and pleural adherences and possible involvement of surrounding anatomical structures. Generally, complete thymectomy including the tumour, the residual thymus gland and perithymic fat is preferred because local recurrences have been sometimes observed after partial thymectomy, when a part of the thymus gland is left behind. However, thymomectomy alone is an option in stage I tumours and in non-myasthenic patients. If the tumour is widely invasive (stage III/IV), en bloc removal of all affected structures, including lung parenchyma (usually through limited resection), pericardium, great vessels, nerves and pleural implants, should be carried out. Resection of venous vascular structures (innominate vein(s) and superior vena cava) includes partial resection with suturing or complete resection and vessel reconstruction using vascular prosthesis. Areas of uncertain resection margins are marked with clips to allow a precise postoperative radiotherapy delivery. Phrenic nerve preservation does not affect survival, but increases the risk of local recurrence, and should be balanced with the achievement of a complete resection, especially in patients with severe and uncompensated myasthenia gravis. Frozen sections to assess tumour involvement of resection margins are not always recommended, since the risk of false-negative results is high. Minimally invasive surgery is an option for presumed stage I and possibly stage II tumours in the hands of appropriately trained thoracic surgeons. This includes transcervical, extended transcervical, video-assisted thoracoscopy (VATS) and robotic approaches (right or left, right and left, right and cervical, left and cervical, subxiphoid and right and left, cervical and subxiphoid); furthermore, robotic surgery may allow a better visualisation of the tumour when compared with VATS. The choice for minimally invasive resection should not jeopardise or change the principles that are deemed appropriate for an open approach, especially the achievement of complete resection that may ultimately require switching to an open procedure. Minimally invasive surgery is not recommended for stage III tumours, because the lack of long-term follow-up. Lymphadenectomy has historically rarely performed after resection of thymic tumours. The new IASLC/ITMIG TNM staging system of thymic tumours, however, leads to the recommendation that locoregional lymphoadenectomy should be carried out during resection of all types of thymic tumours. A proposed nodal map is available from ITMIG. Routine removal of anterior mediastinal nodes and anterior cervical nodes is also recommended. Systematic sampling of other intrathoracic sites is encouraged (i.e.

paratracheal, aortopulmonary window and subcarinal areas, depending on tumour location) in stage III/IV tumours. Systematic lymphadenectomy (N1 + N2) is strongly recommended in case of thymic carcinoma due to the high rate of lymphatic spread (20% versus 3% in thymomas) If complete resection is deemed not to be achievable upfront on the basis of imaging studies, as it is frequently the case in Masaoka-Koga stage III/IVA tumours, a biopsy should be carried out, followed by primary/induction chemotherapy as part of a curative-intent sequential strategy that integrates subsequent surgery or radiotherapy. Patients not eligible for local treatment should receive palliative chemotherapy only. Recurrences of thymic epithelial tumours are not uncommon (10%–15% of all-stage resected tumours) and should be managed according to the same strategy as newly diagnosed tumours. Complete resection of recurrent lesions represents a major predictor of favourable outcome, and surgery is then recommended in case of resectable lesions.

Keywords: Thymus, Tumour, Surgery

GR01 THYMIC MALIGNANCIES TUMOR BOARD
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

GR01.03 SURGICAL ONCOLOGY

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In this section we will address the controversial areas of surgical management in the more advanced stages of thymoma. Using case-based discussion we will debate the following clinical scenarios: **Stage III Thymic tumours** (with invasion of great vessels) *Is there a role for primary surgical debulking leaving an intentional R2 resection?* There is little survival evidence to support intentional debulking but such procedures may reduce the dose and extent of radiotherapy subsequently required and therefore the associated morbidity [1]. However, there is a lack of supportive evidence for debulking surgery in thymic carcinoma. [2,3] *Should primary treatment be chemoradiotherapy followed by consolidation surgery?* Induction therapy is feasible in locally advanced thymic tumours and has been reported to achieve around a 50% partial response. A complete pathological response has not been seen but such treatment can facilitate a high rate (over75%) of R0 resection.[4] **Stage IVa Thymic tumours** – pleural/pericardial deposits *Is there a role for radical surgery?* The International Thymic Malignancies Interest Group have recommended that in locally-advanced Stage IVa patients with pleural involvement, major pleural resections, including pleurectomy/decortication or extrapleural pneumonectomy are indicated, provided a complete resection of the pleural deposits is anticipated, usually in a multidisciplinary setting [5] *Should this be extrapleural pneumonectomy or thymectomy and extended pleurectomy/decortication?* As in other disease, extrapleural pneumonectomy (EPP) is associated with a high 30 day mortality of up to 17% (6). Providing a complete resection can be achieved there is no difference between EPP and extended pleurectomy decortication (EPD) (7) and median survival may exceed 4 years. The contribution of occult nodal metastases must be recognized and radical resection must include lymph node dissection. Stage migration due to lymph node metastases, WHO-classification type C, and T3/4-status are associated with inferior survival but extended surgery has been found to be the only independent significant prognosticator in multivariate analysis [8,9]. *Which surgical incision is best?* Radical resections can be facilitated by extended approaches which are well tolerated and adequate exposure is necessary to ensure a complete resection **Recurrent thymic tumour** – after previous resection *Is there evidence that extending local control prolongs overall survival over systemic therapy alone?* Survival is acceptable and superior to non surgical treatment if complete resection of recurrence is achieved. There is no evidence to support debulking of recurrent thymoma [10] A significant poorer prognosis is associated with multiple versus single relapses, Masaoka stage III primary tumour versus Masaoka stage I-II primary tumour, distant versus loco-regional relapses and B3 histotype versus other. On multivariate analysis, completeness of resection, number of metastases, Masaoka stage of primary tumour and site of relapse were identified as the only independent predictors of prognosis [10] **Conclusions** The relative rarity of thymic neoplasms has contributed to the lack of high grade evidence from randomized controlled trials of large numbers of patients. Most supportive evidence for radical surgery in advanced thymic malignancies has therefore been provided by relatively small selected case series. However, the formation of larger collaborative groups with cumulative databases has provided more robust support for extended surgical procedures that many have avoided previously. The superiority of resection as part of multimodality treatment over non-surgical treatment alone seems to be justified provided high quality surgical standards are maintained. **References** 1. Ried M et al. Extended surgical resections of advanced thymoma Masaoka stages III and IVa facilitate outcome. Thorac Cardiovasc Surg. (2014) 2. Hamaji M et al A meta-analysis of debulking surgery versus surgical biopsy for unresectable thymoma. Eur J Cardiothorac Surg. (2015) 3. Attaran S et al , Does surgical debulking for advanced stages of thymoma improve survival? Interact Cardiovasc Thorac Surg. 2012 Sep;15(3):494-7 4. Korst RJ, et a. lNeoadjuvant chemoradiotherapy for locally advanced thymic tumours: a phase II, multi-institutional clinical trial. J Thorac Cardiovasc Surg. 2014 Jan;147(1):36- 44 5. Ruffini E et al, Optimal surgical approach to thymic malignancies: New trends challenging old dogmas. Lung Cancer. 2018 Apr;118:161-170. 6. 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Keywords: Thymoma, Surgery

GR01 THYMIC MALIGNANCIES TUMOR BOARD
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

GR01.04 MEDICAL ONCOLOGY

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Thymic malignancies represent a heterogeneous group of cancers, which are classified according to the World Health Organization (WHO) histopathologic classification, that distinguishes thymomas from thymic carcinomas; thymomas are further subdivided into different types (so-called A, AB, B1, B2, and B3) based upon the relative proportion of the non-tumoral lymphocytic component, and the resemblance to normal thymic architecture. Thymic carcinomas are similar to their extra-thymic counterpart, the most frequent subtype being squamous cell carcinoma. Neuroendocrine tumors may occur in the thymus, for which the management is similar to that of advanced neuroendocrine tumors originating from other anatomic locations. The management of thymic epithelial tumors is a paradigm of cooperation between clinicians, surgeons, and pathologists from establishing the diagnosis to organizing the multimodal therapeutic strategy. Data related to the systemic treatment of thymic malignancies are mostly based on non-randomized studies, retrospective data, and recommendations rely on expert opinion; this is related to the rarity of the disease, precluding large clinical trials to be developed. Systemic treatment may be delivered in a curative-intent approach, for patients presenting with locally-advanced tumor at time of diagnosis, with invasion of intra-thoracic neighboring structures, and/or dissemination to the pleura and the pericardium, precluding upfront complete resection to be achieved. In such cases, chemotherapy has been used both to reduce the tumor burden - possibly allowing subsequent surgery and/or radiotherapy- and to achieve prolonged disease control. In this setting, cisplatin-based combination regimens should be administered; combinations of cisplatin, adriamycin, and cyclophosphamide, and cisplatin and etoposide have been recommended, based on historical studies. When the patient is not deemed to be a surgical candidate - either because R0 resection is not thought to be achievable, or because of poor performance status or co-existent medical condition, definitive radiotherapy is recommended part of a sequential chemoradiotherapy strategy. Combination with chemotherapy may be considered as well. Chemotherapy is also a palliative-intent treatment of unresectable, metastatic, and recurrent tumors, which are more frequently thymic carcinomas than thymomas. Again, cisplatin-based combination regimens with anthracyclins and/or etoposide are standard. No randomized studies have been conducted, and it is unclear which regimens are best; multi-agent combination regimens and anthracycline-based regimens appear to have improved response rates compared to others, especially the etoposide, ifosfamide and cisplatin combination; however, the effect of corticosteroids to deplete the lymphocytic component of thymomas, without any antitumor effect, may significantly impact radiologic response assessment, and hamper comparisons between chemotherapy regimens. Combination of carboplatin and paclitaxel is an option for thymic carcinoma, based on results of recent phase II trials. Recurrences of thymic epithelial tumors should be managed according to the same strategy as newly diagnosed tumors. In non-resectable recurrences, several consecutive lines of chemotherapy may be administered when the patient presents with tumor progression. The re-administration of a previously effective regimen has to be considered, especially in case of previous response, late occurring recurrence. Preferred regimens for second-line treatment include carboplatin plus paclitaxel, and platin plus etoposide; capecitabine plus gemcitabine is an option. These regimens were evaluated in dedicated

phase II trials. Options for subsequent lines include pemetrexed, oral etoposide. Sunitinib is an off-label option in the second-line setting, based on its antiangiogenic activity. Everolimus may be another option for refractory disease. Several trials assessing the efficacy of PD-1 checkpoint inhibitors are currently ongoing. Phase II studies of pembrolizumab were recently reported, collectively enrolling 63 patients, showing response rates of 24%, but occurrence of serious, autoimmune adverse events in 20% to 30% of patients. The off-label use of checkpoint inhibitors is currently not recommended. The management of patients requires continuous multidisciplinary expertise at any step of the disease. A dramatic improvement in our knowledge has occurred in the last few years, through the development of databases, translational research programs, and clinical trials. While access to innovative strategies represents a major challenge, as the rarity of the tumor precludes specific approval of drugs to be obtained, patient-centered initiatives, such as the establishment of dedicated networks to provide expertise for the actual management of patients, are warranted. In France, RYTHMIC (Réseau tumeurs THYMiques et Cancer; www.rythmic.org) is a nationwide network for thymic malignancies, which was appointed in 2012 by the French National Cancer Institute, as part of its rare cancer program. Since then, the management of all patients diagnosed with thymic tumors has been discussed on a real-time basis at a national multidisciplinary tumor board (MTB), which is organized twice a month basis using a web-based conferencing system. Decision-making is based on consensual recommendations, that were originally established based on available evidence, and are updated and approved each year by all members of the network. A prospective database of all patients is hosted by the French Thoracic Cancer Intergroup. Overall, more than 2,500 patients have been enrolled, demonstrating the feasibility of a national MTB for thymic malignancies, that, besides ensuring patients an equal access to highly specialized management, provides with a comprehensive tool to monitor dedicated actions to improve the management of patients, and enroll patients in clinical trials. Similar thymoma-dedicated and mesothelioma-dedicated networks are now being implemented in France and in other European countries, such as Spain and Italy (the TYME collaborative group). Within the European Reference Network EURACAN, the rare thoracic tumor domain – referred as to G8 domain - handles a network of 20+ healthcare providers; the objectives of EURACAN include the updating and the assessment of current guidelines, the development of educational programs, dissemination and communication with patients groups, and the establishment of research projects, from the diagnosis workup of the disease to the therapeutic strategies. Achieving the highest quality of patient care is the main objective of EURACAN, and the RYTHMIC model provides some practical tools to be implemented at the European level, including Clinical Patient Management System. The European network also provides an infrastructure for collaboration with diagnosis and pharmaceutical companies; one example may be the opening of dedicated cohorts in basket studies assessing new drugs, for which the network allows a better identification of patients and facilitates the recruitment in the trials.

Keywords: Network, multidisciplinary board, Thymoma

GR02 MANAGEMENT OF N2 NSCLC - A CASE BASED DISCUSSION
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

GR02.01 CASE 1: SINGLE ZONE N2 (NO PNEUMONECTOMY NECESSARY)

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Lung cancers invading ipsilateral mediastinal lymph nodes (stage IIIA/N2) account for 30-50% of the locally advanced NSCLC cases [1]. The optimal treatment strategy for potentially resectable stage IIIA/N2 remains challenging and controversial. Interpretation of literature data is complicated by inconsistent evaluation of N2 disease (pathological confirmation vs. imaging-based), heterogeneity of N2 disease spectrum (ranging from single-station microscopic to bulky, multilevel nodal involvement) and pooled analysis of N2 patients with other stage III patients. Results of primary surgery or radiotherapy used as single modality are disappointing. To improve the outcomes combinations of chemotherapy+/-radiotherapy and surgery are being explored. Treatment strategies for patients presenting with non-bulky N2 disease include: (1) induction chemotherapy followed by surgery and postoperative radiotherapy if indicated; (2) induction chemoradiotherapy followed by surgery and postoperative chemotherapy if indicated; (3) definitive chemoradiation. Preoperative chemotherapy offers the possibility of tumor downstaging, may increase operability and assists in early eradication of micrometastases. Latest meta-analysis of 15 randomized clinical trials showed a significant survival benefit of preoperative chemotherapy (hazard ratio [HR] 0.87, 95% CI 0.78-0.96, p=0.007) [2]. It was consistent with an absolute survival improvement of 5% at 5 years, from 40 to 45%. The tumor downstaging effect is dependent on chemotherapy regimen and number of administered cycles. Cisplatin as compared to carboplatin is found to be more effective in inducing tumor response, that is most pronounced after three cycles of chemotherapy [3]. Adding radiotherapy to preoperative chemotherapy can increase pathological complete response (pCR) and mediastinal downstaging. Preoperative chemoradiotherapy, as compared to induction chemotherapy alone, is associated with comparable peri-intervention mortality and higher R0 resection [4]. However, based on the negative results of the Intergroup 0139 trial, designed to address the role of surgery after neoadjuvant chemoradiotherapy, level 1 evidence exists for definitive chemoradiation alone [5]. Additionally, in the three published meta-analyses, the use of preoperative chemoradiotherapy did not translate into better overall and progression-free survival of resectable stage IIIA/N2 NSCLC [4, 6, 7]. Furthermore, delivering doses of ≥45Gy in combination with chemotherapy is predictive of postoperative complications [8]. However, in case of a substantial risk of positive resection margins the use of preoperative radiotherapy in combination with chemotherapy, in expert hands, should be considered for carefully selected, fit patients. After induction chemo(radio)therapy lobectomy is the preferred surgical approach, as pneumonectomy, especially right-sided, may carry the risk of unacceptable perioperative mortality (14-26%) [5, 9]. To conclude, neoadjuvant chemoradiotherapy or chemotherapy alone followed by surgery seem both acceptable in selected stage IIIA/N2 NSCLC clinical scenarios. Those approaches present an alternative to definitive chemoradiation strategy for clinically fit patients with potentially resectable N2 NSCLC. In the context of the available data a real-life single zone N2 NSCLC case will be presented and discussed. The importance of careful patients' selection and rigorous staging procedures (PET/CT, brain MR, invasive evaluation of mediastinal lymph nodes with pathologic confirmation) will be highlighted. The PET/CT of our 72-year old lung adenocarcinoma patient revealed a primary tumor in the right upper lobe (13x10mm, SUVmax=9,6) accompanied by higher FDG uptake in right hilar lymph nodes (15x13mm, SUVmax=9,5) and lymph nodes located in front of the carina (15x9mm, SUVmax=6,4). To determine the optimal treatment strategy in stage IIIA NSCLC the precise evaluation of the mediastinum is required. As imaging-based evaluation of mediastinal lymph nodes is not sufficient, pathologic confirmation of involvement is obligatory. Our patient underwent EBUS that confirmed the involvement of 4R and 10R lymph node stations. The brain CT ruled out the distant spread into the CNS. The optimal treatment strategy of lung cancer patients should be achieved on the basis of multidisciplinary tumor board (MTB) consensus. During the MTB meeting our patient with T1N2 NSCLC was qualified to three cycles of preoperative chemotherapy based on gemcitabine (900mg/m2) and cisplatin (75mg/m2) combination and subsequent upper right lobectomy with mediastinal lymphadenectomy. After the completion of chemotherapy, chest CT and mediastinoscopy were performed, as the adequate post induction re-staging is of paramount importance. The partial response of the primary tumor and the persistent N2 disease were confirmed. The patient underwent right upper lobectomy with mediastinal lymphadenectomy. In the pathological report stage ypT1aN2,R0 was documented. The patient refused the offered adjuvant treatment and is now in watchful follow-up. 1. 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Keywords: single zone N2 NSCLC, preoperative chemo(radio)therapy, surgery

PC01 CONTROVERSIES IN MESOTHELIOMA
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

PC01.01 PRO INTRAPLEURAL CHEMOTHERAPY IS IT THE FUTURE?

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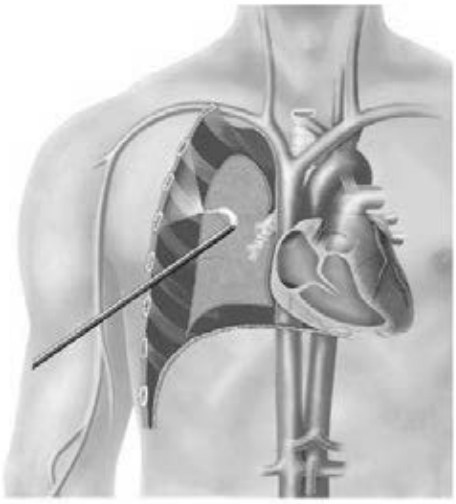
Considerable progress was achieved in the field of mesothelioma (MPM) research and treatment over the last decades. However, high local recurrence rates – even after aggressive treatment - remain an unresolved problem. Based on anatomic constraints, it is impossible to leave adequate safety margins - usually required for oncological surgery - when resecting mesothelioma, therefore leading to only macroscopic – but not microscopic - complete resection (MCR). The remaining microscopically small tumor residuals are most probably the origin of later recurrence. Intracavitary local treatment modalities target this hypothesis. Substances can be applied locally in desired high doses, while side effects can be reduced by decreased systemic absorption. Several intracavitary approaches have been evaluated to try to reduce local recurrence and were mostly applied after MCR, either lung sparing (extended) pleurectomy / decortication ((e)P/D) or extrapleural pneumonectomy (EPP). Intracavitary chemotherapy has been successfully applied in peritoneal carcinomatosis[1-4] and the knowledge gained transferred to MPM because of certain similarities of both tumors. Adding hyperthermia to the concept is based on the principle that hypothermia leads to increased penetration depth of the chemotherapeutic agent into the tissue and therefore a maximized cytotoxic effect on tumor cells. Looking at current guidelines, intracavitary treatments have not yet entered routine treatment regimens for mesothelioma patients. The recommendation of the American Society of Clinical Oncology Clinical Practice Guideline (ASCO)[5] summarizes: Intracavitary therapies (chemotherapy or photodynamic therapy) may be administered safely in experienced centers of excellence, preferably in the context of a clinical trial. Their role in improving outcome is indeterminate (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak). Hyperthermic intraoperative chemotherapy (HIOC) with cisplatin has demonstrated safety and some efficacy in two phase I or II prospective clinical trials in patients undergoing EPP and P/D immediately after surgery[6, 7]. A safe maximally tolerated dose and the methodology to reduce associated complications have been established (table 1). Another technique to reduce systemic side effects and simultaneously increase the local concentration of the drug is to combine cisplatin with a fibrin glue. Cisplatin-fibrin can be sprayed on the resection surface of the chest wall and the lung after surgery (figure 1)[8].The pharmacokinetic advantages and efficacy to reduce tumor recurrence have been demonstrated in several preclinical studies[9-11]. In a phase I dose escalation trial (INFLuenCe-Meso) safety was confirmed, and currently further tested in a phase II clinical trial (NCT01644994). Addionally to intracavitary applied chemotherapeutics which are mainly platinum based other substances were tested. Tada et al recently published the results of a phase I clinical trial using zoledronic acid[12]. This intrapleuraly applied drug is a third generation bisphosphonate and was used in patients with inoperable MPM. Prior to this, the efficacy was equally demonstrated in preclinical studies[12, 13].



	n	Histology	N2 or Nx	IMIG stage	intraoperative regimen	HIPEC	Surgery type	Peri-op Mortality	Morbidity / Toxicity	Adjuvant systemic CTX	Adjuvant RT	Median OS (months)	Median PFS (months)
Opitz 2016	12	8 epithelioid 4 biphasic	3	I-II: 3 III-IV: 9	Cisplatin + fibrin	no	P/D	0%	33%	None	None	21	8
Sugarbaker 2013	72	63 epithelioid 9 biphasic	46	I-II: 14 III-IV: 60	cisplatin	yes	P/D or EPP	4.2%	NR	57%	57%	35.3	27.1
Tilleman 2009	92	53 epithelioid 39 non-epithelioid	NR	I-II: 14 III-IV: 78	cisplatin	Yes	EPP	4.3%	49%	NR	NR	13.1	15.3
Zellos 2009	29	24 epithelioid 5 non-epithelioid	9	I-II: 18 III: 11	cisplatin	Yes	NR	7%	NR	NR	NR	20	16
Richards 2006	44	24 epithelioid 17 biphasic 3 sarcomatoid	33	I-II: 27 II-III: 17	cisplatin	Yes	P/D	11%	25%	None	None	13	7.2
Lu 2005	33	23 epithelioid 2 biphasic 3 sarcomatoid 5 unspecified	NR	I-II: 11 III-IV: 17	Liposomal entrapped cisplatin analogue	No	NA	9%	NR	None	None	13.2	5

	n	Histology	N2 or Nx	IMIG stage	intraoperative regimen	HIPEC	Surgery type	Peri-op Mortality	Morbidity / Toxicity	Adjuvant systemic CTX	Adjuvant RT	Median OS (months)	Median PFS (months)
Chang 2004	50	NR	31	I-II: 19 III: 31	cisplatin	Yes	EPP	2%	60%	Unknown	Unknown	NR	NR
Monneuse 2003	17	NR	NR	I-II: 10 III-IV: 7	mitomycin C and/or cisplatin	Yes	P/D or pleurectomy	6%	29%	NR	NR	18	NR
Van Ruth 2003	20	16 epithelioid 4 biphasic	0	NR	cisplatin + doxorubicin	Yes	12 P/D 8 EPP	0%	65%	None	Thoracotomy scar and drainage ducts	11	8
Ratto 1999	10	4 epithelioid 6 biphasic	0	I-II: 10	cisplatin	Yes	P/D or EPP	0%	20%	None	55 Gy to chest wall incision	NR	NR
Colleoni 1996	20	10 epithelioid 7 biphasic 3 sarcomatoid	2	NR	cisplatin + cytarabine	No	P/D	0%	NR	Epirubicin, mitomycin	None	11.5	7.4
Colleoni 1996	14	NR	NR	NR	Cisplatin + interferon α	No	pleurectomy	0%	7%	29% carboplatin + interferon α	None	NR	NR
Sauter 1995	13	NR	NR	NR	cisplatin + cytosine arabinoside	No	Subtotal pleurectomy	8%	23%	Cisplatin + mitomycin C		9	6
Lee 1995	15	7 epithelioid 4 biphasic 4 sarcomatoid	0	NR	cisplatin + cytosine arabinoside	No	P/D	0%	13%	46%	73%	11.5	NR
Rusch 1994	27	19 epithelioid 6 biphasic 2 sarcomatoid	16	I-II: 9 III-IV: 18	cisplatin + mitomycin	No	P/D	3.7%	None	Cisplatin, mitomycin	None	18.3	13.6
Rice 1994	19	10 epithelioid 7 biphasic 2 sarcomatoid	5	I: 13 III: 6	cisplatin + mitomycin C	No	P/D or EPP	5%	32%	Cisplatin	None	13	11

Figure 1: Application of cisplatin-fibrin after MCR Table 1: intracavitary chemotherapy

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Keywords: Mesothelioma, intrapleural chemotherapy

PC01.03 PRO IO IN MESOTHELIOMA SHOULD ONLY BE GIVEN ON CLINICAL TRIALS

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It is 15 years since the pivotal study of pemetrexed and cisplatin versus cisplatin in inoperable pleural mesothelioma was reported, demonstrating a median overall survival (OS) improvement for the combination (pemetrexed/cisplatin 12.1 months vs. cisplatin 9.3 months) [1]. Since that time the only trial to demonstrate a further improvement in OS has been with the addition of bevacizumab to standard chemotherapy (median OS 18.8 months vs. 16.1 (hazard ratio [HR] 0·77 [0·62–0·95]; p=0·0167) [2]. IO is showing promise in mesothelioma. The PD-1 inhibitors, pembrolizumab and nivolumab as single agents have response rates ranging from 18-29% (Table), with prolonged duration of responses reported. In combination, nivolumab and ipilimumab has a disease control rate (DCR) at 12 weeks of 50%, and the combination of durvalumab and tremelimumab had response rate of 28%. In combination with chemotherapy durvalumab, pemetrexed and cisplatin had a 65% 6 month progression free survival and 55% response rate (Table). While these results are encouraging, the majority of reported trials are small, single arm, with response or disease control rates as the primary endpoints. The only randomized control trial to have been completed so far, evaluated tremelimumab as a single agent in patients with previously treated mesothelioma following encouraging results from two single arm single institution studies of tremelimumab (9). Unfortunately, the primary endpoint of OS was not met (tremelimumab vs. placebo median OS 7.7 months vs. 7.3 months (0·92 [95% CI 0·76–1·12], p=0·41). It is notable that the DCR on the placebo arm (defined as CR, PR or SD of at least 12 weeks) was 21·7% (16·0–28·3) highlighting some patients have indolent disease and the need for randomized trials comparing with standard of care. There are a number of randomized trials currently accruing, which will address the role of checkpoint inhibitors for the treatment of mesothelioma and may establish a new standard of care in the future. 1. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. Vogelzang NJ, Rusthoven JJ, Symanowski J et al. J Clin Oncol. 2003 Jul 15;21(14):2636-44. 2.Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Zalcman G, Mazieres J, Margery J et al. French Cooperative Thoracic Intergroup (IFCT). Lancet. 2016 Apr 2;387(10026):1405-1414. 3. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. Alley EW, Lopez J, Santoro A et al. Lancet Oncol. 2017 May;18(5):623-630 4. A Phase II Study of Nivolumab: A Multicenter, Open-Label, Single Arm Study in Malignant Pleural Mesothelioma (MERIT). Goto Y, Okada M, Kijima T et al. WCLC 2017 MA 19.01 5.Avelumab (MSB0010718C; anti-PD-L1) in patients with advanced unresectable mesothelioma from the JAVELIN solid tumor phase Ib trial: Safety, clinical activity, and PD-L1 expression. Hassan R, Thomas A, Patel MR. et al. J Clin Oncol 34, 2016 (suppl; abstr 8503) 6. Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2 study. Calabrò L, Morra A, Giannarelli D et al. Lancet Respir Med. 2018 Jun;6(6):451-460. doi: 10.1016/S2213-2600(18)30151-6. Epub 2018 May 15. 7. Second- or third-line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Results of the IFCT-1501 MAPS2 randomized phase II trial. Scherpereel A, Mazieres J, Greillier L et al. French Cooperative Thoracic Intergroup (IFCT). J Clin Oncol 35, 2017 (suppl; abstr LBA8507) 8. DREAM: A phase II study of durvalumab with first line chemotherapy in mesothelioma—First results. Nowak AK, Lesterhuis WJ, Maxwell Hughes BG et al. J Clin Oncol 36, 2018 (suppl; abstr 8503) 9. Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. Calabrò L, Morra A, Fonsatti E et al. Lancet Respir Med 2015;3: 301–09 10. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. Maio M, Scherpereel A, Calabrò L et al. Lancet Oncol 2017; 18: 1261–73

Trial	Drug	Trial design	Patient population (patient number)	Endpoint	Efficacy
KeyNote 0-28 Alley et al. [3]	Pembrolizumab	1B, single arm	Post chemotherapy or unable to receive (N=25)	Safety/tolerability ORR	PR=20%; SD 52% Clinical Benefit 40% (95% CI 21·1–61·3) Median PFS 5.4 months (3.4-7.5)
MERIT Goto et al. [4]	Nivolumab	Single arm	2nd or 3rd line (N=34)	ORR	ORR 29% (16.8-46.2) DCR 67.6% (50.8-80.9%) PFS 6.1 (95%CI: 2.9, NR)
JAVELIN Hassan et al. [5]	Avelumab	Single Arm	2nd Line (N=53)	ORR	ORR 9.4% (42.3-3.1-20.7) DCR 56.6% (42.3-70.2)
NIBIT-MESO1 Luana Calabrò et al. [6]	Tremelimumab/ Durvalumab	Single arm	2nd line or first line N=40	Immune OR	28% [95% CI 15–44]) Median duration of immune response 16.1 months (IQR 11·5–20·5).
MAPS-2 A Scherpereel et al. [7]	Nivolumab Nivolumab/ Ipilimumab	Non-comparative randomized	2nd or 3rd Line (N=129)	DCR at 12 weeks	44.4% (31.2-57.7) 50% (36.7-67.3)
DREAM Nowak et al. [8]	Pemetrexed/ cisplatin/ durvalumab	Single arm	First line, inoperable (N=31)	PFS at 6 months	65% PFS at 6 months Confirmed ORR 55%
Tremelimumab Intensified schedule. Luana Calabrò et al. [9]	Tremelimumab	Single arm	2nd Line (N=29)	iORR	4 PR (13·8%; 3·9–31·7) DCR 52%. median duration 10·9 months (95% CI 8·2–13·6).
DETERMINE Michele Maio et al. [10]	Tremelimumab vs. placebo	Phase IIB randomized	2nd or 3rd line (N=571)	OS	median OS 7.7 vs. 7.3 months (0·92 [95% CI 0·76–1·12], p=0·41) DCR (CR, PR or SD of at least 12 weeks). (27·7%, 23·3–32·5 versus 21·7%, 16·0–28·3)

Keywords: Mesothelioma, Checkpoint inhibitors

PC01.04 CON IN MESOTHELIOMA SHOULD ONLY BE GIVEN ON CLINICAL TRIALS

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Malignant pleural mesothelioma (MPM) is a relatively rare malignancy that is considered to be incurable despite advances in surgery, radiation, and chemotherapy. For patients with disease progression after primary platinum/pemetrexed-based therapy, there are limited options for treatment and no approved second-line agents. Recent data from several studies have demonstrated clinically meaningful, and sometimes remarkable activity of checkpoint inhibitors in patients with MPM that has failed first-line therapy. Although the data sets are relatively small, response and survival rates are consistent across studies and appear to be better than those seen in historical controls. Undoubtedly, larger trials with randomized cohorts would provide more robust data. However, access to clinical trials for rare diseases such as MPM is limited in many parts of the world. Therefore, the use of checkpoint inhibitor therapy is a reasonable and medically appropriate option for patients with MPM, especially when a clinical trial is unavailable.

Keywords: Mesothelioma, Checkpoint Inhibitor

PC01.05 PRO RADIATION OPTIONS: ARE WE SMART ENOUGH?

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Malignant pleural mesotheliomas (MPM) are rare but aggressive tumours involving the pleura associated with prior asbestos exposure. Although asbestos use has been significantly curtailed, the latency period between asbestos exposure and development of MPM is long, ranging up to 40 years [1]. The incidence of MPM is still increasing and expected to peak by the 2020s. The prognosis of MPM is grim with disappointing treatment outcomes. The median survival is 4 to 12 months without treatment [2] and the 2-year overall survival is 0 to 12% [3]. Its management is controversial without consensus as to what constitutes the best treatment. There is still debate as to the type of resection these patients should receive. Previous enthusiasm for aggressive debulking resection using extra-pleural pneumonectomy (EPP) has been tempered by lack of benefit and the considerable toxicity seen [4]. Several features unique to MPM has conspired to hamper the discovery of its optimal management. First, MPM is rare (with annual incidence of approximately 1 in 100, 000). Rare tumours are often left orphaned by pharmaceuticals due to the difficulty justifying the cost of drug development for such a small patient population. Furthermore, it is challenging to mount large scale clinical trials due to poor accrual rates. Outside of specialized MPM clinics, most clinicians see MPMs infrequently, greatly limiting the accumulation of clinical expertise and experience in its management. Second, MPM involves the entire hemithorax (pleural envelope). Large volume disease is, in general, more difficult to manage, both surgically and radiotherapeutically. EPP is a major surgical procedure associated with significant perioperative morbidity and mortality. Hemithoracic radiation therapy (RT) needs to be planned carefully in order to avoid the risk of fatal radiation pneumonitis is the contralateral lung [5]. Patients must be carefully selected to ensure the disease is still resectable and patients must be sufficiently fit enough to tolerate and complete their treatment. As a result, only 20% of MPM patients are suitable for aggressive management at the time of assessment. Third, MPM is heterogeneous disease entity with heterogeneous management approaches, varying from best supportive care to aggressive trimodality treatment. Clinical heterogeneity introduces clinical variance and "noise" into its management which, in turn, makes identification of any therapeutic "signal" more difficult. Normally, this limitation can be mitigated by increasing the sample size and, thus, the power of the study but in rare tumours, this is not easily achieved. Surgery, by itself, is generally considered to be a palliative option, not a curative one. Even with an EPP, one cannot achieve complete microscopic resection (R0) due to the presence of malignant pleural effusions contaminating the pleural space and surgical bed. As a result, without additional therapy, most patients fail locally in the thoracic cavity. Adjuvant therapy is, thus, a critical component in managing MPM. EPP followed by adjuvant hemithoracic RT was the first treatment approach that was able to show local control in the hemithorax was possible [6]. However, when their patterns of failure were analyzed more carefully, most of the recurrences were distant and usually involved the contralateral lung or abdomen. This suggested that a possible mechanism for distant failure could be from the tumour spillage into these compartments at the time of EPP during the removal of the diaphragm and pericardium. We hypothesized that altering the order of treatment to neoadjuvant hemithoracic RT followed by EPP would reduce the risk of distant metastases by preventing the irradiated clonogens from implanting and potentially improving survival. This provided the rationale for the Surgery for Mesothelioma After RT (SMART) study. This clinical trial is still on-going but our published interim results demonstrated a 3 year overall survival rate of 75% [7]. Other advantages to this approach are: the short accelerated treatment with an overall treatment time of 2 weeks from RT to EPP; excellent patient compliance with 100% completion rate; and acceptable treatment toxicity. As our understanding of the tumour microenvironment and the complex interaction between the tumour, host immune system, and therapy improves, we expect treatment outcomes will also improve. Newer targeted and immuno-oncologic agents show much promise and are an active topic of current research. In particular, we anticipate that the combination of immunotherapy agents and radiation will be an area of tremendous interest due to their synergistic effects and potentiation of the immune system [8]. References: 1. Bianchi C, Giarelli L, Grandi G, Brollo A, Ramani L, Zuch C. Latency periods in asbestos-related mesothelioma of the pleura. Eur J Cancer Prev. 1997;6(2):162-6. 2. Ruffie P, Feld R, Minkin S, Cormier Y, Boutan-Laroze A, Ginsberg R, et al. Diffuse malignant mesothelioma of the pleura in Ontario and Quebec: a retrospective study of 332 patients. J Clin Oncol. 1989;7(8):1157-68. 3. Curran D, Sahmoud T, Therasse P, van Meerbeeck J, Postmus PE, Giaccone G. Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. J Clin Oncol. 1998;16(1):145-52. 4. Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, et al. 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Keywords: radiation therapy, extra-pleural pneumonectomy, malignant pleural mesothelioma

PC02.01 SURGERY - PRO

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Surgery in the treatment of small cell lung cancer (SCLC) was commonplace up until the mid-1970's when the results of the medical research council (MRC) trial compared surgery to radiation and found no improvement with the addition of surgery. A later trial compared chemoradiation with adjuvant surgery to chemoradiation alone also failed to show an improvement with surgery. These two results have been used to justify nihilism amongst thoracic oncologists with respect to the use of surgery. However, modern screening, staging, minimally-invasive surgery and adjuvant therapy have changed the situation for the treatment of early SCLC. Modern evidence, albeit retrospective, supports a greater utility for surgery in the treatment of early SCLC than what may have been suggested by older randomized trials that are no longer applicable in the modern era. Surgery has much to offer in the treatment of early SCLC and this lecture will outline the potential utility of surgery - in particular anatomic resection and systematic lymph node dissection - as part of a multimodality treatment regimen.

Keywords: small cell lung cancer, Thoracic Surgery

PC02.03 BID RADIATION - CON

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Thoracic radiotherapy for LS-SCLC: QD is just as good as BID?! Most of the advances in outcome of small cell lung cancer (SCLC) in the past few decades can be attributed to improvements in radiotherapy, including better imaging and target selection, better treatment planning, better integration with chemotherapy, and use of prophylactic cranial irradiation. Thoracic radiotherapy plays an important role in the treatment of limited disease SCLC (LS-SCLC). Best results are obtained with twice daily (BID) radiotherapy, starting early and given concurrently with chemotherapy [1]. In addition, it was shown that a shorter time from start of chemotherapy to completion of radiotherapy was associated with longer survival [2]. Two meta-analyses demonstrated that use of thoracic radiotherapy led to improved local control and an absolute survival benefit at 3 years of 5% [3,4]. Turrisi et al. [5] demonstrated in the Intergroup 0096 study that 45 Gy given BID in 30 fractions in 3 weeks was superior compared to the same dose delivered once-daily (QD) in 25 fractions over a 5 week period. Overall survival at 5 years was improved (26% vs 16%), but at the expense of more G3-4 oesophagitis (32 vs 16%). In spite of these results, BID radiotherapy is still used in a only a minority of SCLC patients [6,7]. In The Netherlands, early concurrent BID rasdiotherapy is given in about a quarter of the patients [7]. The radiotherapy dose in the QD arm of the Intergroup trial [5] was relatively low and some argued that a higher QD radiotherapy dose might be equivalent to or even better than the 45 Gy BID scheme. In the ongoing CALGB 30610 / RTOG 0538 study (NCT00632853) a dose of 70 Gy once-daily in 35 fractions in 7 weeks is compared with the 45Gy BD scheme. In this trial, radiotherapy starts with the first course of chemotherapy and includes elective nodal irradiation. Accrual is expected to continue for several years. In the recently published CONVERT trial (ISRCTN91927162), patients were randomized between 45 Gy BID in 3 weeks and 66 Gy QD in 33 fractions in 6.6 weeks starting with the second course of chemotherapy [8]. Treatment did not include elective nodal irradiation. The study was designed to investigate whether the higher QD regimen would lead to improved survival. Median overall survival was 30 months for the BID and 25 months for the QD arm. There were no statistically significant differences in the rates of local and metastatic progression. Survival in the control arm (BID) was 12% higher than expected when designing the study, possibly due to improvements in radiotherapy techniques. Based on the study, it can be concluded that a higher dose given QD does not lead to improved survival or better local control. There were no significant differences in acute toxicity, except for more G4 or higher neutropenia in the BID arm (49% vs 38%). The risk of Grade 3-4 oesophagitis was 19% with no significant differences between the two study arms. Based on the results of this trial, 45 Gy given BID in 3 weeks should remain the reference standard. This regimen leads to the best results in the shortest time with the fewest number of fractions. The CONVERT study also indicates that where delivery of a BED scheme is not feasible, a higher dose once-daily schedule does not compromise clinical outcomes. However, it Is surprising that the significantly higher biologically equivalent radiotherapy dose of the QD scheme in the CONVERT study did not translate into better outcome.Does the early distant dissemination of the disease preclude further improvements in local control and survival by local treatment? Or is the influence of the repopulation may greater than calculated in our radiobiological models? The possible benefit of shortened treatment time was evaluated in a phase II study from Norway in which 45 Gy BID in 3 weeks was compared with 42 Gy in 15 fractions in 3 weeks given QD. There was no significant difference in progression free survival at 1 year, the primary endpoint of this study in which 157 patients were enrolled (49% vs 45%). Although overall response rates were similar (88% and 92%), more complete responses were seen in the BID arm (33 vs 13%). In addition, although not statistically significant, overall survival was 25 months for the BID vs 19 months for the QD arm. In the BID scheme, treatment is completed in 3 weeks and a BED10 of 52 Gy is delivered, whereas the same BED10 is reached after about 22 fractions of 2 Gy delivered once-daily. The delivered BED during the last third of the QD treatment does not seem to contribute to outcome. This suggest that repopulation starts very early and that tumor doubling times may be much shorter than generally assumed and a shorter QD scheme may be preferable if treatmenti is not deliverded BID. . **References** 1. Fried DB. S J Clin Oncol 2004;22:4837–45. 2. De Ruysscher D.et al., J Clin Oncol 2006;24:1057–63. 3. Pignon JP, et al. N Engl J Med 1992;327:1618–24. 4. Warde P, Payne D. J Clin Oncol 1992;10:890–5. 5. Turrisi AT, ert al. et al. N Engl J Med 1999;340:265–71. 6. Komaki R, et al. Int J Radiat Oncol Biol Phys 2013;85:1082-9. 7. Damhuis R, et al. Clin Oncol 2018;30:17-22. 8. Faivre-Finn C. et al. Lancet Oncol 2017;18:1116-25. 9. Gronberg BH, Acta Oncol 2016;55:591-7.

Keywords: LS-SCLC, SCLC, Radiotherapy

PC02 DEBATE ON LOCAL THERAPIES FOR LIMITED SMALL CELL LUNG CANCER? SURGERY PRO/CON AND BID RADIATION PRO/CON
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

PC02.04 BID RADIATION - PRO

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The optimal thoracic radiotherapy dose for treating limited stage small cell lung cancer remains to be defined. Given the radiosensitivity of small cell lung cancer cell lines in preclinical studies in the 1980's it was postulated that twice daily radiotherapy would result in improved efficacy. Subsequent clinical experience included the landmark Intergroup 0096 trial, which demonstrated improved overall survival for patients assigned to twice daily radiotherapy (45 Gy) compared with once daily radiotherapy to the same total dose. Despite being one of the few randomized trials showing that changing the radiotherapy regimen impacts overall survival, the twice-daily regimen was slow to be adopted in clinical practice and many NCI cooperative group studies continued to use once-daily radiotherapy. Reluctance to routinely use the twice-daily regimen likely relate to concerns with acute toxicity, logistic issues, and use of a modest radiotherapy dose of only 45 Gy on the standard arm. In addition, a contemporaneous study from NCCTG did not show an advantage to twice-daily radiotherapy, although a planned treatment break was included such that radiotherapy was not accelerated. Alternate strategies to improve the efficacy of thoracic radiotherapy have included the development of high dose once-daily regimens with a 70 Gy regimen utilized in several phase II trials from the Cancer and Leukemia Group B. These trials are somewhat difficult to interpret, as radiotherapy was not initiated until the 3rd cycle of chemotherapy and novel induction chemotherapy regimens were included. The RTOG has also studied a concomitant boost regimen, though overall survival was lower than expected in the phase II experience. Results from the CONVERT trial, comparing 45 Gy twice-daily and 66 Gy once-daily radiotherapy, were recently published. The trial was powered to show superiority of high dose daily radiotherapy and failed to do so, and thus the authors concluded that 45 Gy twice-daily remain the standard of care. The CALGB 30610 trial, which uses 70 Gy in the once-daily arm, is near completion and will provide further data regarding the therapeutic ratio of these regimens. For the time being it should be kept in mind that the long held assumption that increasing radiotherapy dose with conventional fractionation will result in improved outcomes may not be justified – particularly in the setting of concurrent chemotherapy. For example, increasing the radiotherapy dose from 50.4 Gy to 64.8 Gy, with cisplatin and 5-FU, did not improve outcomes for patients with esophageal cancer on the phase 3 Intergroup 0123 trial. Perhaps even more suprising are the results of RTOG 0617, where even in the era of advanced radiotherapy treatment planning raising the radiotherapy dose resulted in worse outcomes.

Keywords: accelerated, thoracic radiotherapy, twice daily

PC03.01 POST-OPERATIVE RADIATION THERAPY OR NOT: PRO

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Thymic epithelial tumors are rare tumors which has been an obstacle to performing prospective randomized studies. There is definite evidence that these tumors are radio-responsive but the exact role of radiation remains unclear. An additional confounding factor is that until the proposed standardization of classification and staging by the International Thymic Malignancy Interest Group (ITMIG) there has been significant inconsistency of interpretation of both histology and staging leading to inconsistency in recommendation for post-operative radiation. Radiation fields, techniques and doses have also been very variable. Literature informing about post-operative radiation is largely reliant on single institution data and mostly retrospective work which introduces inherent bias. More recently consortiums (such as JART and ChART) were formed to try and combine data. Unfortunately most of these databases were primarily surgical based and indications for radiation and radiation techniques are not well defined. The largest data base of thymic tumors is the one established by ITMIG which has facilitated international collaboration and establishing of large retrospective and prospective databases. In this debate we will review the literature supporting the role of radiation in the post-operative setting after thymectomy. Recent studies from different institutions have produced very different results for post-operative radiotherapy and we will compare these to try to define why the results are different. The patient must have sufficient risk to justify radiation It has clearly been demonstrated that complete surgical resection is the most important prognostic factor. Improved

outcomes with postoperative radiation will depend on appropriate patient selection. We will try to define the patient population that might benefit from treatment. We will also try to answer the question of routine postoperative treatment in more advanced stage disease, or only if resection is incomplete? We will explore how histology impacts on the decision to offer post-operative radiation? We will also try to define what fields would be appropriate, what techniques would be optimal and what doses should be delivered. The thymus resides in the mediastinum adjacent o heart, lungs and great vessels. Despite improved conformal techniques of radiation these organs still receive radiation and the potential damage from the radiation is not well quantified. International collaboration with standardization of definitions and complete radiation data is ultimately the only way we will achieve knowledge to advise the exact role of post operative radiation.

Keywords: Thymic epithelial tumors, post-operative radiation thymoma

PC03 CONTROVERSIES IN MANAGEMENT OF RESECTABLE THYMOMA
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

PC03.02 POST-OPERATIVE RADIATION THERAPY OR NOT: CON

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The role of postoperative radiation therapy in the context of resectable thymoma remains controversial. Indeed, data is conflicting, with some historical studies demonstrating an advantage to this approach, and others failing to show a benefit over surgery +/- systemic therapy. In the absence of randomized studies, it is difficult to draw conclusions regarding the appropriate approach. However, available data do not support the routine use of postoperative radiation therapy in this context. Decisions regarding management after resection should be made with the input from the multidisciplinary team, with discussions focusing on margin status, histology, extent of disease, and intraoperative concerns.

PC03 CONTROVERSIES IN MANAGEMENT OF RESECTABLE THYMOMA
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

PC03.05 DEBATE ON STANDARD SURGICAL APPROACHES - OPEN THYMECTOMY

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The first case of total thymectomy for myasthenia gravis was done by Sauerbruch in 1911, which was through cervical incision. The first case of thymoma resection through median sternotomy was done by Blalock in 1934. Before video-assisted thoracoscopic surgery (VATS) was introduced to thymectomy by Yim et al in 1993, median sternotomy had been the main approach for resection of the thymus and thymic tumors. Approach through median sternotomy holds several variations, such as, partial sternotomy, full sternotomy, full sternotomy with lateral thoracotomy, and hemi-clam shell approach. Partial sternotomy usually splits the two thirds to three fourths of the caudal side of the sternum, resulting in difficulty in resecting the lesions near diaphragm. In case of thymectomy, however, for non-thymomatous myasthenia gravis, resection of peri-thymic fat tissue around the upper poles of the thymus is more important than the lower poles because of ontogeny of the thymus. Partial sternotomy requires skin incision of less than 10cm, and therefore, is less invasive compared to full sternotomy. Thus, it is reasonable to choose partial sternotomy in thymectomy for non-thymomatous myasthenia gravis. Actually, Masaoka adopted partial sternotomy for their original extended thymectomy, and Maggi also chose partial sternotomy for thymectomy for myasthenia gravis. In addition, partial sternotomy is sufficient for resection of a small non-invasive thymoma if not located near diaphragm. The advantage of sternotomy compared with unilateral or bilateral VATS approach is no need to access to the thoracic cavity, because the mediastinal pleura can be dissected from the fat tissue of the anterior mediastinum, which can reduce the possibility of intraoperative pleural implantation of tumor cells. Full sternotomy is the most commonly selected approach for resection of anterior mediastinal tumors, and especially, useful in resecting a large or invasive thymic tumor. Thymoma and thymic carcinoma often involve the superior vena cava or brachiocephalic vein, and cardio-pulmonary bypass is required in reconstruction of the great vessels. In these cases, median sternotomy is the most appropriate approach. While simple full sternotomy is sufficient for partial resection of the lung when involved by a tumor, lateral thoracotomy at the 4th intercostal space is sometimes added when concomitant upper lobectomy is required. When extrapleural pneumonectomy for stage 4A thymoma is intended, posterolateral thoracotomy is added in addition to full sternotomy by changing the patient's position from the prone to the decubitus position. Hemi-clam shell approach is another variation of median sternotomy when combined resection of the involved organs is required. In this approach, sternum is split from the sternal notch to the level of 4th intercostal space, and there, lateral thoracotomy is added. This approach enables the procedures of various kinds of lung resection. Japanese Association for Thoracic Surgery (JATS) has conducted nation-wide survey of the general thoracic surgery in Japan annually since 1986. According to JATS survey, the number of VATS in surgery for thymic epithelial tumors has increased gradually since late 1990's. In 2013, surgical resection of thymic epithelial tumor was done in 2230 cases in Japan. Approach through VATS or thoracotomy with VATS procedure was selected in 843 patients, indicating that the proportion of VATS rose up to 38% during 20 years. The remaining 1387 patients are presumed to experience median sternotomy, indicating that median sternotomy was chosen in 62% of operations of thymic epithelial tumors. In thymoma, median sternotomy was chosen in 1139 (60%) out of 1904 cases. On the other hand, in thymic carcinoma or neuroendocrine tumors, median sternotomy was chosen in 248 (76%) out of 326 cases, suggesting that invasive or aggressive tumors are resected using median sternotomy. Japanese Association for Research of the Thymus (JART) conducted Japanese nation-wide database study in 2013, and collected the clinical data of 2835 patients undergoing surgical treatment between 1991 and 2010. Because VATS thymectomy was introduced in the middle 1990's in Japan, the patients treated from 2001 to 2010 were focused in this review. 1978 cases were treated during those 10 years among the JART database. 1542 patients experienced median sternotomy with or without addition of lateral thoracotomy, indicating that 78% of the entire cases were operated by median sternotomy-based surgery. Lateral thoracotomy was chosen in 92 patients, which corresponds to only 4.7% of the entire cases. The proportion of median sternotomy according to TNM-based pathological stage was 74% in stage I, 87% in stage II, 91% in stage IIIA, and 91% in stage IIIB, suggesting that VATS is likely to be indicated to less invasive tumors. Although a study using JART retrospective database revealed that the long-term outcome of VATS for thymic epithelial tumors is compatible with that by open procedure, recurrence after VATS resection for thymoma larger than 5cm was reported, suggesting limited indication of VATS thymectomy. Thus, further experience of VATS or RATS procedure is required to determine the definitive indication of thoracoscopic approach, and open surgery using median sternotomy has still its role as one of the standard procedures.

Keywords: Thymoma, Thymic carcinoma, VATS

PC03 CONTROVERSIES IN MANAGEMENT OF RESECTABLE THYMOMA
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

PC03.07 ADJUVANT CHEMOTHERAPY FOR THYMIC CARCINOMA - YES

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The role of postoperative treatment in thymic carcinoma is still a controversial issue, because of the low level evidence supporting clinical management of this cancer, made of cohort studies, retrospective studies and case reports, but no randomized clinical trials. Stage is not the only factor we should consider when the choice of postoperative chemotherapy is discussed; completeness of resection and histologic subtype have their own relevance. Thymic carcinoma accounts for about 20% of all thymic cancers, most cases diagnosed as Masaoka-Koga stage III. In this scenario, about 60% of the cases relapses at 10 years. Time of relapse and sites of disease progression should be carefully reviewed when we consider potential benefit of postoperative systemic treatment; thymic carcinomas relapse earlier and commonly at distant sites compared with thymoma, with significantly different 5 years overall survival and progression free survival. Histology preserves its association with progression free survival as radicality of resection. One reason for the controversies about the prognostic role of histology itself may be found in the difficult diagnosis of the specific subtypes as defined by WHO. Across series a complete Interobserver agreement was reported in 10 to 50% of the cases. Most difficulties seem to be the differential diagnosis among B tumors, and a better agreement was achieved when B2-B3 thymoma were grouped together with carcinoma, suggesting overlapping features among them and supporting evidence that type B3 thymomas and thymic carcinomas form a biologically different group. Complete resection of thymic carcinoma is possible in 60%-70% of the cases, achieving 5-Y and 10Y survival of 60% and 40% respectively. Type of resection and Masaoka stage seem to be correlated with survival and cumulative incidence of recurrences. However, a prognostic role of adjuvant treatment, particularly radiotherapy, is shown with possible effect not only in overall survival but also in relapse free survival. On the basis of the available data, it would be tempting to suggest a possible

role for chemotherapy in R1-R2, independently by stage, preferably associated with radiation. On the other hand guidelines suggest a role for adjuvant chemotherapt in resectable thymic carcinoma R1 and, in R0 cases, in stage III or in those cases become resectable after induction chemo, independently by stage e type of resection, especially if not received before. The upcoming IASLC/ITMIG staging system, which re-defines Masaoka-Koga stage III downstaging some situations to stage I and II (as mediastinal pleural or pericardial involvement) could potentially influence adjuvant chemo in stage III thymic cancer. Stage III will be distinguished into T3, potentially resectable upfront, and T4, which might need induction chemo. Adjuvant chemoregimens may be chosen on the basis of drugs combinations effective in the palliative setting; platinum-based doublet plus etoposide or taxanes, or multiple drug regimens including anthracycles are the most used, no data favoring one regimen over the others. Response rates among 60 to 100% in main phase II trials are reported, with primary chemotherapy alone or plus concomitant radiotherapy, in all thymic malignancies. Higher response rates with anthracycles in thymoma and cisplatin in thymic carcinoma are suggested by literature evidence.

Keywords: Adjuvant; thymic carcinoma; stage

PC03 CONTROVERSIES IN MANAGEMENT OF RESECTABLE THYMOMA
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

PC03.08 ADJUVANT CHEMOTHERAPY FOR THYMIC CARCINOMA - NO

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Thymic carcinoma is a more aggressive neoplasm than its more common counterpart thymoma, with a higher cumulative incidence of recurrence and worse overall survival when matched by stage and complete resection status.[1] Large retrospective database studies provide support for adjuvant radiation for completely resected thymic carcinoma. Therefore, the Thymic Carcinoma Working Group of the International Thymic Malignancy Interest Group (ITMIG) has recommended adjuvant radiation for completely resected Masaoka stage II and III thymic carcinoma.[2] In a recent survey of thymic carcinoma management patterns among 100 ITMIG physicians, the role of adjuvant chemotherapy was highlighted as an area of controversy.[2] The survey responders provided the following recommendations after completely resected stage II and III thymic carcinoma, respectively: 51% and 14% observation, 25% and 42% adjuvant radiation alone, 13% and 34% adjuvant radiation and chemotherapy, and 11% and 10% adjuvant chemotherapy alone. There is data that neoadjuvant chemotherapy may be useful for locally advanced thymic carcinoma, as it may facilitate surgical resection and improve the chances of a complete resection, a known strong prognostic factor.[3] However, data supporting the use of adjuvant chemotherapy for thymic carcinoma is limited and its potential to decrease local recurrence and distant metastases after achievement of a complete resection is controversial. In one of the largest known datasets of thymic carcinoma, including 1042 cases pooled from the ITMIG and European Society of Thoracic Surgeons (ESTS) retrospective databases, 764 cases had available chemotherapy information. Sixty-one percent (n=463) of patients received neoadjuvant or adjuvant chemotherapy, with 22% receiving chemotherapy in the neoadjuvant setting, 31% in the adjuvant setting, and 8% in both the neoadjuvant and adjuvant setting.[4] Chemotherapy was more frequently given to patients with Masaoka stage III-IV disease. The most common adjuvant treatment strategies included adjuvant chemotherapy and radiation (26%) and adjuvant radiation alone (22%), although 10% of patients received both neoadjuvant chemotherapy and adjuvant radiation. In a univariate analysis, chemotherapy was associated with an improved overall survival but was not associated with recurrence-free survival. Because of the limited sample size, it was unclear which multimodality treatment strategy improved overall survival such as delivery of chemotherapy in the neoadjuvant or adjuvant setting. However, chemotherapy was not a significant factor for clinical outcomes in a multivariate analysis. There are other smaller database studies investigating adjuvant chemotherapy for thymic carcinoma. Due to both the retrospective nature of the studies and small sample sizes, it is difficult to evaluate the independent impact of adjuvant chemotherapy on clinical outcomes, as chemotherapy was often given in conjunction with radiation. Across these studies, there is no clear indication of benefit of adjuvant chemotherapy for resected thymic carcinoma. In the Japanese Association for Research on the Thymus (JART) database report on 155 patients with stage II and III thymic carcinoma, adjuvant chemotherapy was not a significant factor for relapse-free survival in a multivariate model that also included adjuvant radiation, stage, and resection status.[5] In the Chinese Alliance for Research of Thymoma Database (ChART) report on 329 patients with thymic carcinoma, there was no difference in overall survival between patients who received adjuvant chemotherapy and those who did not in the overall cohort and in Masaoka-Koga stage subsets and resection status categories.[6] However, of the 148 patients who received adjuvant chemotherapy, 127 received sequential chemotherapy and radiation. In a study from the National Cancer Database, there were 468 patients with thymic carcinoma who underwent surgery alone and 557 who underwent surgery and adjuvant radiation, with 28% and 56% also receiving adjuvant chemotherapy, respectively.[7] Chemotherapy was not associated with overall survival in both univariate and multivariate analyses. Finally, in a meta-analysis of 973 patients with thymic carcinoma, the rate of adjuvant chemotherapy was 21.2-61.5% among those who received adjuvant radiation and 6.7-50% among those who did not, with four of the studies demonstrating no significant association between adjuvant chemotherapy and survival in both univariate and multivariate analyses.[8] Several retrospective database studies have shown no clear benefit of adjuvant chemotherapy for patients with resected thymic carcinoma, although these datasets have their limitations. Many additional questions remain about adjuvant chemotherapy including the indications for recommending adjuvant chemotherapy; the details of the chemotherapy such as the regimen and number of cycles; and the timing of initiation of chemotherapy after surgery and how it should be integrated with perioperative radiation. In summary, there is lack of data to support the routine use of adjuvant chemotherapy after complete resection of thymic carcinoma and further study is required. References: 1. Detterbeck FC, Stratton K, Giroux D, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. *J Thorac Oncol* 2014;9:S65-72. 2. Shepherd A, Riely G, Detterbeck F, et al. 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Keywords: chemotherapy, ADJUVANT, Thymic carcinoma

PC04 TARGETED THERAPY FOR NSCLC
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

PC04.01 OPTIMAL SEQUENCING OF EGFR TKI THERAPY (GEFITINIB/ ERLOTINIB/AFATINIB FIRST VERSUS OSIMERTINIB FIRST)

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Patients with advanced non-small cell lung cancer harboring epidermal growth factor receptor(EGFR) mutations should be treated with EGFR tyrosine kinase inhibitor as first line treatment based on several large randomized phase III studies comparing first/second generation EGFR TKI vs. chemotherapy. The standard of care of using gefitinb/erlotinib/ afatinib as first line treatment has been challenged recently from a few progress made from recent reports. First challenge is the selection of first generation gefitnib/erlotinib versus second generation afatinib or recent reported dacomitinib as first line treatment. Two randomized studies comparing afatinib versus gefitinib (Lux-Lung-7) or dacomitinib versus gefitinib (ARCHER1050) demonstrate progression survival improvement for 2nd generation EGFR TKI versus 1st generation EGFR TKI in patients with common EGFR mutations. In addition ARCHER1050 showed a statistical difference in overall survival (OS) for dacomitinib. The advantage of 2nd generation EGFR TKI as first line treatment are the coverage of HER2 inhibition, and probably deeper response due to irreversible inhibition of EGFR pathways. The higher duration of response should be balanced with higher side effect due to potent wild type EGFR inhibition in normal cells that caused severe side effects. The second improvement of first line therapy was shown in two Japanese studies randomizing erlotinib versus erlotinib and bevacizumab. Bevacizumab seemed to improve PFS substantially in both phase II and phase III studies. However, OS difference has not been observed, for reason not clearly understood. A 3rd approach using first generation EGFR TKI upfront was the success of combination of gefitinib and pemetrexed and carboplatin

over gefitinib in a Japanese study resulted in PFS and OS improvement. These three approach need to be further studied for universal application. However, the PFS of these three approach seemed to be close or higher than first line osimertinib (approximately 19 months) achieved by the phase III randomized study FLAURA or phase II AURA expansion cohorts. Since the salvage strategy of osimertinib failure is still under intensive investigation due to heterogeneous resistance that can be caused by osimertinib prolonged use, the use of osimertinib as first line treatment should be considered only as an option rather than standard, pending the above mentioned PFS and OS improvement in these novel strategies to be compared to osimertinib in the future (if there will be studies). In conclusion, we had made substantial advanced for the treatment of EGFR mutation positive NSCLC patients. Yet the best sequence of treatment should be further studied since long term control close to cure is always our ultimate goal for treatment of these patients.

Keywords: EGFR TKI, osimertinib, Sequence

PC04 TARGETED THERAPY FOR NSCLC
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

PC04.02 OPTIMAL SEQUENCING OF EGFR TKI THERAPY - 3RD GENERATION FIRST

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Lung cancer is a heterogeneous genomic disease defined by molecular pathways that mediate oncogenesis which are often driven by genetic alterations and targeted therapies are available to modulate these pathways and improve patient outcomes.[1] Non-small cell lung cancer (NSCLC) has been at the forefront of expanding knowledge of genomic alterations to inform therapeutic options that improve cancer patient outcomes. Signaling through the epidermal growth factor receptor (EGFR) can modulate multiple intracellualar pathways, including mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)-AKT, and signal transducer and activator of transcription proteins (STATs). Activating mutations in the *epidermal growth factor receptor* (*EGFR)* gene have been associated with improved progression free survival when patients are treated with EGFR tyrosine kinase inhibitor (TKI) therapy.[1] Progress has been made in identifying these mutations and providing targeted therapy to improve outcomes for patients. Despite these advancements, tumors develop resistance and patients still succumb to the lung cancer, so overcoming the resistance became a priority. With the identification of third-generation EGFR TKIs, such as osimertinib,[2] clinical benefit was maintained after tumor progression on first-generation EGFR TKIs, and questions regarding the optimal sequencing of EGFR TKIs emerged. Mutations in the TK domain of the *EGFR* gene demonstrate increase sensitivity to EGFR TKI in NSCLC.[3,4] Gefitinib was the first EGFR TKI to demonstrate PFS benefit over chemotherapy as front line treatment of patients with EGFR mutant NSCLC.[1] This was the first study to definitively identify mutation status as an important predictive marker for EGFR-TKI therapy and support molecular selection for patients with metastatic NSCLC. Multiple subsequent trials with gefitinib, erlotinib and afatinib confirmed enhanced PFS for front line EGFR TKI therapy. Developing appropriate therapies for EGFR-TKI-resistant disease requires a detailed understanding of mechanisms of resistance. Secondary mutations have been described that may arise that render initially sensitive tumors that harbor *EGFR* mutations, resistant to EGFR therapy. Multiple mechanisms of resistance have been identified, but approximately 50-60% of *EGFR* mutant NSCLC develops a T790M resistance mutation.[5-7] Osimertinib was developed to overcome T790M resistance and block mutant *EGFR* while sparing wild type *EGFR*. Treatment following the development of T790M resistance led to improved objective response rates (ORR) and PFS for patients with *EGFR* mutant NSCLC.[8] Early evidence suggested that osimertinib could be effective as first-line treatment,[9] and had the potential benefit to prevent the most common cause of resistance. In the phase III FLAURA trial, 556 patients were randomized to osimertinib or standard, first generation EGFR TKI (erlotinib or gefitinib).[10] The primary endpoint was progression free survival (PFS), and demonstrated an improvement for osimertinib at 18.9 months (95% CI, 15.2-21.4) compared to standard EGFR TKI at 10.2 months (95% CI, 9.6-11.1) with a hazard ratio (HR) 0.45 (95% CI, 0.37-0.57) and p< 0.001. The PFS for patients with central nervous system metastases remained higher for osimertinib at 15.2 months (95% CI, 12.1-21.4) compared to standard EGFR TKI at 9.6 months (95% CI, 7.0-12.4) with a hazard ratio (HR) 0.47 (95% CI, 0.30-0.74) and p< 0.001. The improvement of PFS in patients with brain metastases augments the clinical benefit to patients who may avoid or defer radiation treatments to the brain. Overall survival (OS) was immature with a trend toward improvement with osimertinib. ORR was similar in both arms, 80% (95% CI, 75-85) for osimertinib and 76% (95% CI, 70-81) for standard EGFR TKI therapy (95% CI, 70-81). These results have led to the US Food and Drug Administration approval of osimertinib as front line therapy for patients with advanced EGFR mutant NSCLC. Providing a drug with less toxicity and increased efficacy as a first-line option improves quality of life and outcomes for patients. New mechanisms of resistance will develop and must be overcome, but third-generation EGFR TKI therapy is now the new standard of care for front line therapy in metastatic *EGFR* mutation positive NSCLC. **References** 1. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57. 2. Wakelee HA, Gettinger S, Engelman J, et al. A phase Ib/II study of cabozantinib (XL184) with or without erlotinib in patients with non-small cell lung cancer. Cancer chemotherapy and pharmacology 2017;79:923-32. 3. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39. 4. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500. 5. Yu HA, Arcila ME, Rekhtman N, et al. 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Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.

Keywords: osimertinib, tyrosine kinase inhibitor, EGFR

PC04 TARGETED THERAPY FOR NSCLC
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

PC04.03 ADJUVANT TARGETED THERAPY FOR PTS WITH GENOMIC ALTERATIONS - YES

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1. Introduction: In recent years, the discovery of targetable gene alterations such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements has revolutionized the therapeutic approach to advanced NSCLC. The outstanding activity shown by EGFR-and ALK- tyrosine kinase inhibitors (TKIs) in advanced NSCLC patients with EGFR mutations or ALK rearrangements, respectively, leads to the logical question of what role these agents may have if used in the adjuvant setting. **2. Rationale for adjuvant targeted therapy** At the present time there is no evidence suggesting a worse prognosis for EGFR-mutated NSCLC in early stage disease [1]. Similarly, retrospective studies exploring the impact of ALK rearrangements in early stage NSCLC suggested that ALK status lacks a prognostic role, as no significant difference in DFS was found between ALK-rearranged and ALK-negative patients [2-3]. Nevertheless, EGFR mutations and ALK rearrangements are both highly predictive of response to selected targeted therapy in advanced NSCLC. **3. Prospective trials**

(See next page)

Prospective trials of an EGFR-TKI as adjuvant treatment					
Author, phase	**Stage, biomarker selection**	**No. of pts, design**	**Length of exposure to EGFR-TKI**	**Primary end-point**	**Results for primary end-point**
Goss et al., 3 (NCIC CTG BR.19) [4]	IB–IIIA, unselected	503, gefitinib vs. placebo	2 years	OS	HR =1.24, P=0.14
Kelly et al., 3 (RADIANT) [5]	IB→IIIA, EGFR + by IHC and/or FISH	973, erlotinib vs. placebo (2:1)	2 years	DFS	HR =0.90, P=0.324
Pennel et al., 2 (SELECT) [6]	IA→IIIA	100, erlotinib	2 years	DFS	2-year DFS rate =90%
Li et al., 2, randomized [7]	IIIA (N2), EGFR mutation	60, CBDCA/PEM → gefitinib vs. carboplatin/pemetrexed	6 months	DFS	HR =0.37, P=0.014
Feng et al., 2, randomized [8]	IB (high risk)*→IIIA, EGFR mutation	41, platinum-based chemotherapy → icotinib vs. platinum-based chemotherapy	4–8 months	DFS	2-year DFS 90.5% vs. 66.7%, P=0.066
Wu et al., 3 (CTONG 1104) [9]	II–IIIA (N1,N2), EGFR mutation	222, gefitinib ×2 years vs. cisplatin/vinorelbine	2 years	DFS	28.7 vs. 18.0 months, HR =0.60, P=0.05
EVAN	IIIA (N2), EGFR mutation	222, erlotinib ×2 years vs. cisplatin/vinorelbine	2 years	2 years -DFSR	81.35% vs. 44.62%, P<0.001
Ongoing randomized phase 3 trials of an EGFR-TKI as adjuvant treatment for patients with EGFR mutant NSCLC					
Clinical trial	Region	Stage, planned accrual, EGFR mutation	Study design	Primary end-point	
NCT02125240 (ICWIP)	China	II→IIIA, 300, ex19del and L858R	Rand. to icotinib ×2 years vs. placebo ×2 years (platinum-based chemotherapy ×4 cycles)	DFS	
NCT01996098 (ICTAN)	China	II→IIIA, 477, ex19del and L858R	Rand. to icotinib ×12 months vs. icotinib ×6 months vs. observation (platinum-based chemotherapy ×4 cycles)	DFS	
NCT02193282 (ALCHEMIST)	U.S.	IB (≥4 cm)-IIIA, 450, ex19del and L858R without T790M	Rand. to erlotinib ×2 years vs. placebo ×2 years (after standard adjuvant chemotherapy)	OS	
NCT02201992 (ALCHEMIST)	U.S.	IB (≥4 cm)-IIIA, 378, ALK-positive	Rand. to crizotinib ×2 years vs. placebo for 2 years (after standard adjuvant chemotherapy)	OS	
WJOG6401L	Japan	II→IIIA, 230, ex19del and L858R without T790M	Rand. to gefitinib ×2 years vs. cisplatin/vinorelbine ×4 cycles	5-year DFS	
NCT02448797 (EVIDENCE)	China	II→IIIA, 320, ex19del and L858R	Rand. to icotinib ×2 years vs. cisplatin/vinorelbine ×4 cycles	DFS	
NCT02518802	China	II→IIIA (N1, N2), 220, ex19del and L858R	Rand. to cisplatin/pemetrexed ×4 cycles + gefitinib ×2 years vs. cisplatin/pemetrexed ×4 cycles	DFS	
NCT01996098 (ICTAN)	China	II→IIIA, 477, ex19del and L858R	Rand. to icotinib ×12 months vs. icotinib ×6 months vs. observation (platinum-based chemotherapy ×4 cycles)	DFS	
NCT02511106 (ADAURA)	International	IB→IIIA, 700, ex19del and L858R ± other EGFR mutation	Rand. to osimertinib ×2 years vs. placebo ×2 years (standard adjuvant chemotherapy allowed)	DFS	

4. Conclusions and future directions A critical issue is how to select the patients who may need adjuvant targeted therapy. Measurement of residual disease by circulating tumor cells and/or DNA could help identify the high-risk population. However, for these patients it should be clarified whether targeted therapy should be used sequentially after platinum-based chemotherapy or as stand-alone treatment; therefore, better understanding of the biology at recurrence and novel testing strategies for residual disease are crucial in order to help select those patients who could benefit the most from adjuvant targeted therapy. **5. Reference:** (1) Liang W, He Q, Wang W, et al. The impact of EGFR mutations on the prognosis of resected non-small cell lung cancer: a meta-analysis of literature. Ann Oncol 2017;28:abstr ii20-3. (2) Paik JH, Choi CM, Kim H, et al. Clinicopathologic implication of ALK rearrangement in surgically resected lung cancer: a proposal of diagnostic algorithm for ALK-rearranged adenocarcinoma. Lung Cancer 2012;76:403-9. (3) Pan Y, Zhang Y, Li Y, et al. ALK, ROS1 and RET fusions in 1139 lung adenocarcinomas: a comprehensive study of common and fusion pattern-specific clinicopathologic, histologic and cytologic features. Lung Cancer 2014;84:121-6. (4) Goss GD, O'Callaghan C, Lorimer I, et al. Gefitinib versus placebo in completely resected non-small-cell lung cancer: results of the NCIC CTG BR19 study. J Clin Oncol 2013;31:3320-6. (5) Kelly K, Altorki NK, Eberhardt WE, et al. Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non-Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial. J Clin Oncol 2015;33:4007-14. (6) Pennell NA, Neal JW, Chaft JE, et al. SELECT: A multicenter phase II trial of adjuvant erlotinib in resected early-stage EGFR mutation-positive NSCLC. J Clin Oncol 2014;32:abstr 7514. (7) Li N, Ou W, Ye X, et al. Pemetrexed-carboplatin adjuvant

chemotherapy with or without gefitinib in resected stage IIIA-N2 non-small cell lung cancer harbouring EGFR mutations: a randomized, phase II study. Ann Surg Oncol 2014;21:2091-6. (8) Feng S, Wang Y, Cai K, et al. Randomized Adjuvant Chemotherapy of EGFR-Mutated Non-Small Cell Lung Cancer Patients with or without Icotinib Consolidation Therapy. PLoS One 2015;10:e0140794. (9) Zhong WZ, Wang Q, Mao WM, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol. 2018 Jan;19(1):139-148.

Keywords: Targeted therapy, ADJUVANT

PC05 OPTIMIZING CLINICAL TRIAL DESIGN IN NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

PC05.01 DEBATE 1: WHICH IS MOST IMPORTANT EFFICACY ENDPOINT IN FIRST LINE TRIALS IN ADVANCED NSCLC PFS OR OS - POINT OF VIEW: PFS

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Royal Marsden Hospital, Sutton/GB

This is an old chestnut. The debate has gone on for years and for first line trials in advanced NSCLC it is always OS that wins. So why do I think I will win this time? Well maybe it is because (I was given the task and I like a challenge) we are in a new era of medicine and we are in such a hurry to get new drugs to our patients to prolong our lives and cure them. A PFS (DFS) endpoint in a clinical trial is all about the activity of that drug or intervention, it is reported at a point when crossover to other treatments has not happened. It is the standard endpoint for treatments for advanced breast cancer and other disease where there are many treatment options and in general patients will live to get all those treatments options. An OS endpoint in advanced lung cancer in the past has been quite similar to PFS – both of them short ie. less than one year. An OS endpoint suggests that a treatment has truly modified the natural history of a disease and therefore this new treatment should be given as early as possible. In this era of new treatments it is gratifying to see that an improved PFS has predicted an improved OS e.g. Keynote 024 and it is a gratifying to see that the trial did not report until PFS and OS were available at the same time as in coprimary endpoints. So in these trials of very active treatment PFS reported one year earlier than OS could have cut down the expense of the trial and got the drug to patients earlier. Looking at drugs that target the EGFR mutation gefitinib, erlotinib and Afatinib – all positive for PFS and all negative for OS because of crossover. If OS had been the only endpoint, all these drugs would still not be on our pharmacy shelves. So I believe if you have a great treatment that should activity very early on then PFS should be the endpoint. However if the benefit is small but still significant then OS must be the endpoint. But surely at this point in time we only want very active treatments that give us big differences in PFS as we know that these will be the treatments that can change lives.

Keywords: PFS OS debate

PC05 OPTIMIZING CLINICAL TRIAL DESIGN IN NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

PC05.04 DEBATE 2: PATIENT REPORTED OUTCOMES SHOULD BE THE MOST IMPORTANT ENDPOINT IN TRIALS IN THE PALLIATIVE SETTING - YES

M. Pérol
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The aim of an anticancer treatment in palliative setting, i.e. when there is no curative intent, is to improve the quantity and the quality of life. The evaluation of a treatment effect is mainly based on randomized clinical trials which are meant to provide a correct assessment of the effect size. Therefore, the selection of the primary endpoint is critical not only for the sample size calculation but mainly to judge the relevance and the meaning of the treatment results which define the treatment utility from both the patient perspective and the healthcare system in terms of cost-effectiveness. Two categories of endpoints are used in clinical trials: some are patient-centered, clinical endpoints including overall survival (OS), health-related quality of life (HRQoL) assessment and tolerance profile whereas other are tumor-centered as progression-free survival (PFS), response rate, disease control rate. OS is a universally accepted measure of the treatment benefit in oncology, directly reflecting the quantity of life gained and is still the preferred endpoint of Phase III clinical trials. However, OS as a primary endpoint has some limitations: it usually requires a longer follow-up and a large sample size leading to an increase in the cost of trials. Moreover, especially in cancer with an improved prognosis as for lung cancer depending on an oncogenic driver, OS can be confounded by the effect of crossover and subsequent treatments with small expected OS differences between treatment sequences. These reasons make increasingly difficult to demonstrate an OS benefit especially for first-line therapy. These limitations have led to consider tumor-centered endpoints, mainly PFS, as surrogate endpoints for patient benefit in a clinical trial. PFS provides results earlier than OS and is not influenced by subsequent treatments. However, selecting PFS as primary endpoint assumes that there is a statistical validation of PFS as a surrogate endpoint for OS, which is not the case in advanced NSCLC, especially in palliative setting: many trials have demonstrated a PFS benefit without improvement of OS. Furthermore, there is a lack of consensus for PFS definition or tumor progression (i.e. taking or not into consideration symptomatic progressions), blinding or independent review is required to provide more robust evidence of a PFS benefit and its assessment is dependent on the schedule of tumor evaluations. In this context, HRQoL may constitute an alternative endpoint, which ensures earlier assessment of direct clinical benefit for the patient and takes into account the impact of potential treatment-related toxicities; HRQoL is therefore more recognized as a component endpoint for assessment of the benefit coming from cancer therapy by the American Society of Clinical Oncology and the European Society of Medical Oncology and for drug approval by Regulatory Agencies. It appears obvious that a delay in the time to symptom deterioration, or improvements in symptoms and in HRQoL might be more meaningful to the patient with an advanced lung cancer than the RECIST criteria or PFS, not necessarily reflecting a clinically meaningful benefit. HRQOL is a multidimensional concept representing the patient's perception of the effect of illness and treatment on physical, psychological, and social aspects of life. QoL measurement in clinical trials is based upon patient reported outcome (PROs) which are reports of the status of a patient's health condition coming directly from the patient, without any interpretation by a clinician. Many validated self-completion QoL questionnaires for cancer patients are available, taking into consideration the multidomain aspect of QoL; the EORTC QLQ-C30 with its specific module for lung cancer (LC-13), the FACT-L are the most frequently used for assessment of patients HRQL, physical functioning, or tumor related symptoms in lung cancer. HRQoL evaluated with PROs has been shown to be an independent prognostic factor in advanced lung cancer. However, the complexity and heterogeneity of QoL data reports and numerous methodological issues for QoL analyses make the PROs difficult to understand for clinicians and limit their utility to help for therapeutic decisions. Indeed, HRQoL is challenging to assess and raises many methodological issues, including missing data and patient drop-out rate, multiplicity, longitudinal analysis and lack of standardization making impossible to perform cross trials comparisons. These issues as well as the usual deferred publication of QoL results after tumor-centered endpoints communication have led the scientific community and the clinicians to give little attention to PROs. Nevertheless, there is a greater awareness that a similar degree of scientific rigor should be applied to the PRO strategy to make it a key component of treatment effect, likely more sensitive to assess therapy's effect on the disease and the patient than conventional measures. Different approaches have been underscored to improve the use of PROs in clinical trials. Recent extensions of the CONSORT have suggested recommendations for PROs analysis and report in clinical trials, with the need to define PROs as a primary or secondary endpoint with a specific statistical defined hypothesis, including approaches to deal with missing data; it is then possible to consider HRQoL as a co-primary endpoint. New statistical methods have also been suggested for longitudinal analyses of PROs as linear mixed model for repeated measures or time until definitive deterioration for symptoms or QoL score deterioration. Other approaches suggest focusing on three well-defined concepts: symptomatic adverse events, physical function, and disease-related symptoms which are easier to assess and are key components of a treatment effect. Information after the treatment and during subsequent treatment should also be collected to take into consideration the impact of a delayed disease progression on QoL or those of subsequent treatment or residual toxicities. As tremendous advances have been made in the field of lung cancer treatment, especially in advanced disease with its transformation into a chronic disease for some patients, the treatment focus has shifted to improve or preserve the patients QoL. It is therefore mandatory to develop new and validated endpoints that better indicate a clinical benefit rather than small variations in tumor size. PROs should not be viewed anymore as a surrogate endpoint, but regarded as an important patient-centered endpoint, needing an optimization of trials design and methods to analyze HRQoL.

Keywords: Patient-reported outcome, clinical trials, lung cancer

PC05.07 LET'S NOT FORGET CHEMO-REGRET

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Background: Although thousands of patients annually receive treatment for advanced non-small cell lung cancer (NSCLC), little is known about their views on the decision to receive that treatment. Even with encouraging newer treatments, survival rates continue to be low in NSCLC. With potential treatment toxicities and with modest response rates, there are many risks for regret by both patients and their supporters. The highly symptomatic nature of NSCLC, coupled with pressures to decide rapidly on therapy, creates challenges that affect quality decision making. In a recent review of 59 studies dealing with regret (Becerra Perez et al, *Med Decis Making*; 2016;36:777-790), no study focused on lung cancer, even with 66% of the studies in oncology settings, none reported reduced regret over time during the study, and only 2 studies reported delayed regret several months after the decision. In this review, risk factors for regret seemed to be able to be affected by clinicians, according to the opinion of the authors of this systematic review. In a large survey (Morse et al, *J Psychosocial Oncol*, 2014;32:112-123) results including more than 3500 patients with cancer. More than 90% of these individuals rated "making decisions about care" as being important to them, out of 26 issues. The patients with lung cancer, ranked decision making as the third most important issue of the 26 surveyed. In a recent article in the New England Journal of Medicine (Groopman and Hartzband 2017;377:1507-1509), the authors state that the risk of regret is in almost every medical decision a patient makes and the impact of regret is underestimated in patient decision making. They observe that regret and its impacts are not sufficiently considered by physicians as part of the decision-making process. A profile of the extent of regret, and factors contributing to that regret, is lacking for those undergoing systemic therapy for lung cancer, and for their supporters. Identifying patients early and predicting patients at high risk for regret during treatment could assist in early intervention, which may decrease eventual regret. **Methods:** We sought to investigate prospectively the incidence, extent, and associated factors concerning regret in patients receiving systemic treatment for advanced NSCLC. All patients were enrolled into a phase III trial which included 164 patients. All patients were monitored using the LCSS PRO assessment questionnaire. Patients were randomized 1:1 to either usual care or to enhanced care. In the enhanced care group, all patients also completed the DecisionKEYS decision aid, and their oncologists were aware of the ongoing LCSS results. Also, in the enhanced care group, the results of the LCSS symptomatic and quality of life scores over time, and the results of the decision aid were discussed with the patient and supporter. The LCSS was completed every 3 weeks using the electronic LCSS (eLCSS-QL). The LCSS analysis included using the 3-Item Global Index ("3-IGI," assessing: distress, activities, and quality of life). All patients, in both arms of the study, completed the Decision Regret Scale (Brehaut et al, *Med Decis Making* 2003;23:281-292) at 3 months after starting treatment, and at the conclusion of treatment. **Results:** 164 patients signed consent and 160 received treatment (the modified intent to treat group). Patient characteristics included: 43% women; 92% Stage IV; median PS = 1; mean age 63, and 46% of patients represented minority groups. 86% of patients alive at 3 months completed the Decision Regret Scale. Results combined the 2 top categories indicating the greatest extent of regret. By this criterion, 13% of patients (95% CI: 7.4% - 19.2%) expressed regret at the 3-month timepoint after starting chemotherapy. Of note, nearly all patients expressing regret at this point could be identified at the 6-week LCSS evaluation. Of the patients expressing regret at the 6- week mark after starting treatment, nearly all of the patients had a 20% decline or greater by 6 weeks in the 3-IGI score compared with baseline. Specifically, when asked if they would make the same decision again, only 1% not having the 20% 3-IGI decline had regret, as contrasted to 15% with 20% or greater 3-IGI decline ($p = 0.01$). Results were similar in both randomization groups. Additionally, the supporters of these patients were also asked to complete the Decision Regret Scale. Only a subset of the supporters filled out the regret scale; of those 41 supporters, 3 (7%, 95% confidence interval: 1.5% to 19.9%) expressed regret. This indicates a similar extent of regret among both patients and their supporters. **Conclusions:** Regret is not common in patients receiving systemic therapy for NSCLC or their supporters. It is a positive finding that regret is found in only about one of eight patients undergoing systemic treatment or their supporters; however, it should be acknowledged that this regret is unfortunate for those individuals, and steps taken to modify this regret could contribute to enhanced care. Our findings clearly demonstrate that nearly all patients ultimately having regret could be identified much earlier using the 3-IGI of the LCSS measure. Identifying patients at high risk for regret allows for interventions which could address potential regret in patients and their supporters. Support: NIH/NCI R01 CA157409

Keywords: Systemic therapy, Decision regret, advanced lung cancer

PC06.02 LABORATORY DEVELOPED TEST - CON

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Blockade of immune checkpoints to reinstitute host antitumor immunity has been investigated extensively in the field of lung cancer, and a few anti-programmed cell death protein 1(PD-1) / programmed death-ligand 1 (PD-L1) agents have been approved in the US, Europe and Japan for treatments of advanced non-small cell lung cancer (NSCLC) as first line and/or second or further line therapy. In the clinical trials of anti PD-1/PD-L1 agents, PD-L1 immunohistochemistry (IHC) assays have been used for predictive biomarker testing, and positive results indicate the presence of an immunomodulatory molecule that can be impacted by the PD-1/PD-L1 blockade. There are five PD-L1 IHC assays (the Dako 28-8, Dako 22c3, Ventana SP142, Ventana SP263 and Dako 73-10) developed and validated as predictive biomarkers in the clinical trials.[1,2] Now, upon approval of an anti PD-1 agent as first line, PD-L1 IHC has become a mandatory diagnostic test in the treatment of advanced NSCLC patients. Therefore, thepathology laboratory needs to have at least one affordable, validated PD-L1 IHC assay, but it may not be practical to conduct several specific assays for one protein from a financial and regulatory perspective, and given the limited availability of tumor tissue for a number of tissue-based diagnostic tests required in the management of advanced NSCLC patients. However, selecting one assay among several available is challenging. While each of the five IHC assays recognizes PD-L1 protein, each antibody clone appears to be specific for a different epitope of the PD-L1 protein and may not have the same binding affinity for its epitope. In addition, different automated IHC platforms and detection systems are used in different assays, so the performance of these five assays may be different. Scoring systems to determine "positive" results are also quite different between the five assays, since these systems were determined based on a predictive value and clinical data obtained during the therapeutic/diagnostic test co-development process of individual anti PD-1/PD-L1 agents. For instance, not only tumor cell expression but also immune cell expression are taken into account with the Ventana SP142 assay, while expression on tumor cells only are scored with the other assays. Furthermore, each assay has a specific % of positive tumor cells as a cut-off, and the % may be different depending on first line vs. second or further line of treatment. Importantly, the outcomes for patients, when using these drugs in a cohort selected for "positive" PD-L1 expression, have only been evaluated in trials using the specific drug-assay combinations.[2] To answer the question as to whether one PD-L1 IHC assay could be used to select patients for the five anti PD-1/PD-L1 agents, several harmonization studies have been conducted to compare analytical performance between several PD-L1 IHC assays including laboratory developed tests (LDTs). These studies have shown high concordance among three of the five clinical trial-validated assays (the Dako 28-8, Dako 22C3 and Ventana SP263) when assessing PD-L1 expression on tumor cell membranes but not on immune cells; high inter-observer concordance among the five clinical trial-validated assays in tumor cell PD-L1 scoring but not in immune cell scoring.[3,4] Therefore, the three clinical trial-validated assays (the Dako 28-8, Dako 22C3 and Ventana SP263) may be interchangeable for tumor cell PD-L1 scoring provided that these assays are performed in specialized laboratories by trained pathologists. As for the LDTs, several studies compared various combinations of PD-L1 antibody clones (28-8, 22C3, SP142, SP263, E1L3N, QR1) and IHC platforms with a clinical trial-validated assay. The results of those studies were variable. In particular, two multi-institutional studies reported that only 50-55% of LDTs were compatible to a clinical trial-validated assay, and the remaining LDTs were less sensitive.[3,5,6] These differences may alter the outcome of the test, leading to alternative PD-L1 scoring around a given cut-off threshold. Therefore, rigorous optimization with a clinical trial-validated assay as the reference and standardization are warranted before LDTs can be recommended for routine clinical use. References 1. Tsao MS, Kerr KM, Dacic S, et al. IASLC Atlas of PD-L1 Immunohistochemistry Testing in Lung Cancer. COlorado: Editorial Rx Press; 2017. 2. Mino-Kenudson M. Programmed death-ligand 1 immunohistochemistry testing for non-small cell lung cancer in practice. *Cancer*. 2017. 3. Büttner R, Gosney JR, Skov BG, et al. Programmed Death-Ligand 1 Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2017. 4. 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Keywords: PD-L1 immunohistochemistry, laboratory developed test, clinical trial assay

PC06.03 TUMOR MUTATION BURDEN - PRO

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Immuno-oncology (IO) exploits the patient's immune system by blocking immune checkpoints (PD-1/PD-L1) to effect tumor cell killing and has shown superior response rates and survival outcomes relative to conventional chemotherapy in a variety of clinical contexts. IO has shown efficacy in solid tumors with a high burden of immunogenic neoantigens, including non-small cell lung cancer (NSCLC), and represents standard of care for a subset of patients. Not all patients benefit from IO, and efforts to enrich for responders have been confounded by the lack of a highly predictive biomarker. PD-L1 immunohistochemistry (IHC) has evolved with clinical trials of IO in the form of companion and complementary diagnostics and is the dominant biomarker for selecting patients for IO, however the PD-L1 has limitations as a biomarker. First, neither the sensitivity nor specificity of this biomarker is optimal. Over 10% of PD-L1 negative patients can show clinical responses to IO. Conversely, 40-50% or more of PD-L1 positive patients do not respond. Second, the diversity of commercially-available PD-L1 assays marketed for use with specific IO agents, some of which have different performance characteristics, has complicated practice in diagnostic laboratories. Third, tumoral PD-L1 is a dynamic biomarker that may be induced by the immune environment or exogenous stressors and may be expressed heterogeneously within the tumor. As a result, sampling bias can affect the proportion of cells showing PD-L1 expression. Finally, tumor genomics significantly influence response to IO, with certain driver alterations (in EGFR, ALK) predicting a lack of response irrespective of PD-L1 status. All of these features speak to a need for an alternative biomarker(s) that offers mores sensitive and specific prediction of response, is stable throughout the tumor, and can be can be standardized across laboratories and IO agents. In NSCLC, PD-L1 overexpression is thought to be driven predominantly via adaptive immune resistance, in which tumor mutations produce aberrant proteins (neoantigens) that can trigger cytokine-mediated PD-L1/PD-1 engagement, which in turn dampens the tumor-specific immune response. The tumor genome, therefore, appears to trigger the cascade of events leading to a phenotype associated with IO responsiveness. Neoantigenicity can only be assessed via costly approaches like whole exome sequencing and requires complex bioinformatics generally outside of the scope of available clinical practice. It appears, however, that higher tumor mutation burden (TMB) increases the likelihood of neoantigen-driven immune engagement. Hence, TMB, a genomic variable that can be assessed readily using targeted next generation sequencing (NGS) assays in clinical use today, may serve as a surrogate for adaptive immune resistance and predict response to checkpoint blockade. This correlation has been born out in retrospective analyses of outcomes data from IO clinical trials as well as from routine practice. Prospective clinical trials of combined IO agents have shown significantly longer progression free survival versus chemotherapy in patients with high TMB, irrespective of PD-L1 status. These agents show enhanced benefit in TMB-high small cell lung carcinoma patients as well- a tumor subtype where PD-L1 IHC appears to play no role as a biomarker. TMB calculated from NGS panels containing as few as ~150 genes may be predictive of IO response. Genomic profiling also permits simultaneous evaluation of biomarkers of response to tyrosine kinase inhibitors and identifies patients unlikely to benefit from IO. Widespread adoption will require standardization of inclusion and exclusion criteria for TMB; informatics solutions such as in silico downsampling may be required to further harmonize TMB across disparate sequencing panels. In contrast to PD-L1 expression, TMB status is likely relatively stable across a patient's tumor at any point in time, recognizing that subclonal evolution may lead to subtle differences across sampled sites of disease and that TMB may be less predictive at scores close to established "high" cutoffs. The optimal biomarker may not yet exist, however a holistic view of the tumor that takes into account tumor genomics, immune milieu, and checkpoint status is likely to offer the greatest hope for selecting patients most likely to benefit from IO. Taube JM, Galon J, Sholl LM et al. Implications of the tumor immune microenvironment for staging and therapeutics. Mod Pathol 2018; 31: 214-234. Gandhi L, Rodriguez-Abreu D, Gadgeel S et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018; 378: 2078-2092. Reck M, Rodriguez-Abreu D, Robinson AG et al. Pembrolizumab versus Chemotherapy fo PD-L1-Positive Non-Small-Cell Lung Cancer. 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PC07.01 DEBATE 1: CHEMOTHERAPY WILL BECOME A THING OF THE PAST IN THE MANAGEMENT OF ADVANCED NSCLC - FOR

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The advent of immune checkpoint inhibitors has been a major step forward in the management of non-small cell lung cancer. In recent years, agents that target the PD-1/PD-L1 pathway have been incorporated into the treatment of lung cancer in various settings. Initial studies compared the efficacy of immune checkpoint inhibitors against docetaxel monotherapy in the salvage treatment setting for both squamous and non-squamous histology. In these randomized trials, improvement in survival with hazard ratio of approximately 0.7 was observed across the trials. As a result, chemotherapy in the second-line setting was displaced by immune checkpoint inhibitors as the preferred treatment approach. Immune checkpoint inhibition in the second-line setting was also associated with a lower adverse events profile. More recently, immune checkpoint inhibition has entered the front-line treatment landscape for treatment of advanced non-small cell lung cancer. In patients with PD-L1 $\geq$ 50%, the use of pembrolizumab was superior to chemotherapy and pembrolizumab monotherapy is considered the standard of care for this patient subset. This approach has resulted in a four-year survival rate of approximately 48% as noted by a subset analysis from the KEYNOTE-001 study. The combination of chemotherapy with immune checkpoint inhibition has also shown successful results in recent times. This approach appears to be particularly suited for patients with low PD-L1 expression. The combination of platinum-based regimens with immune checkpoint inhibitors are associated with improvement in overall survival compared to chemotherapy alone in advanced stage non-small cell lung cancer. However, the efficacy of these combination approaches does not appear to be superior to pembrolizumab as monotherapy in patients with high PD-L1 expression. The combination of nivolumab and ipilimumab has also proven efficacious in patients with high tumor mutation burden. Consequently, both PD-L1 expression and tumor mutation burden are potentially predictive biomarkers for patient selection with immune checkpoint inhibition. As the landscape evolves, it is clear that the role of chemotherapy has changed substantially in patients with lung cancer. It is likely that the emergence of novel combination approaches and predictive biomarkers will lead to further reduction in the need for chemotherapy. There is limited knowledge on how various cytotoxic agents impact the immune system. This knowledge will enable the development of optimal chemotherapy-based combination approaches from the current use of empiric combinations. Ultimately, personalized immunotherapy will be required to maximize patient outcomes, and this will be enabled by novel combination approaches that build on predictive biomarkers.

Keywords: advanced NSCLC, immune checkpoint inhibition, PD-L1

PC07.04 DEBATE 2: FOR WILD-TYPE NSCLC, WHICH WILL BE THE PREFERRED STRATEGY: IO ALONE VERSUS CHEMO + IO - CHEMO + IO

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During the last decade, improvements in cancer biology and immune system knowledge led to a significant prolongation in overall survival for patients with metastatic non-small cell lung cancer (NSCLC). It is well

established thatimmune system plays a critical role in destroying cancer cells. Tumor cells, however, use different strategies to avoid recognition by the immune system, including "immune checkpoint" activation. Programmed death-1 (PD-1) immune checkpoint pathways have been the one most extensively studied. Several agents interfering with the PD-1 axes have been evaluated in clinical trials. Since these drugs directly target the patient's immune system, they have the potential for utility across multiple tumor types, including lung cancer. The PD-1 receptor is expressed on activated T-cells, and the key ligands for this receptor are programmed death-ligands 1 (PD-L1) and 2 (PD-L2). PD-L1 is up-regulated in many tumors and high levels of expression (^{3}50%) have been observed in approximately 30% of NSCLC. This overexpression helps tumor to evade immune responses. Binding of PD-L1 or PD-L2 to PD-1 receptors inhibits T-cell activation reducing antitumor immune responses. Therefore, PD-1 represents a logical target for cancer immunotherapy. At the present time, in first-line setting, immunotherapy as single agent or in combination with chemotherapy is the standard of care in PD-L1 expressing patients, target therapy is recommended in oncogene addicted and the proportion of patients still candidate for exclusive chemotherapy is gradually decreasing. Agents targeting PD-1 or PD-L1, such as pembrolizumab, nivolumab or atezolizumab, are now approved in clinical practice in first or in second-line setting. Results from several randomized clinical trials comparing immunotherapy as single agent or in combination with chemotherapy versus chemotherapy alone are rising the question on what is the best first-line treatment and whether platinum-based chemotherapy could be avoided in our patients. Three phase III studies compared immunotherapy as single agent versus platinum-based chemotherapy. The Keynote 024 study compared pembrolizumab monotherapy versus platinum-based doublets in NSCLC patients with high PD-L1 expression. The study demonstrated that pembrolizumab is superior to chemotherapy by doubling median overall survival (OS: 30.0 versus 14.2 months, p=0.002). Similar results were obtained in the Keynote 042 trial, a phase III study comparing pembrolizumab versus chemotherapy in patients with at least 1% of PD-L1 expression. This study, including a large percentage of patients with PD-L1 expression ≥50%, confirmed the superiority of pembrolizumab versus chemotherapy in terms of OS (20.0 versus 12.2 months, p=0.003). In contrast, the Checkmate 026 study, comparing nivolumab versus chemotherapy in patients with at least 1% of PD-L1 expression, showed no OS difference in both arms even in the subgroup of patients with PD-L1 expression ≥50%. Importantly, both Keynote 042 and Checkmate 026 showed no survival improvement in patients with low levels of PD-L1 expression (1-49%). Four different phase III trials, two in non-squamous (Keynote 189 and IMPOWER 150) and two in squamous histology (Keynote 407 and IMPOWER 131), compared standard chemotherapy plus a checkpoint inhibitor versus chemotherapy alone. The Keynote 189, evaluating pembrolizumab plus chemotherapy versus chemotherapy alone, showed a significant improvement in OS when pembrolizumab was added to chemotherapy in all patient subgroups, irrespective of PD-L1 expression. Interestingly, the OS Hazard Ratio (HR) was better than the HR obtained in studies with pembrolizumab monotherapy, suggesting that combination of immunotherapy and chemotherapy could be superior to chemotherapy alone even in patients with high levels of PD-L1 expression, with the cost of increased toxicity. The IMPOWER 150, a large 3 arms study (atezolizumab plus carboplatin-paclitaxel: Arm A; or atezolizumab carboplatin-paclitaxel-bevacizumab: Arm B; or carboplatin-paclitaxel-bevacizumab: Arm C), demonstrated a significant survival improvement for arm B versus C but not in arm A versus arm C, at least in at the initial survival analysis. The Keynote 407 compared pembrolizumab plus carboplatin-taxol (paclitaxel or nab-paclitaxel) versus the same chemotherapy regimens in patients with squamous histology. Similarly to Keynote 189, addition of pembrolizumab to chemotherapy yielded in a OS improvement in patients receiving immunotherapy, irrespective of PD-L1 expression. The IMPOWER 131 was a 3 arms study comparing atezolizumab plus carboplatin-paclitaxel (Arm A) or atezolizumab plus carboplatin-nab-paclitaxel (Arm B) versus carboplatin-nab-paclitaxel as initial therapy in patients with squamous histology. Although arm B was superior to arm C in terms of progression-free-survival (PFS), the first interim analysis showed that OS improvement was confined to individuals with PD-L1 expression ≥50%. Finally, of particular interest are the preliminary data from the PD-L1 negative cohort included in the Checkmate 227 study. In this trial, PD-L1 negative patients were randomized to nivolumab plus ipilimumab versus platinum-based chemotherapy versus platinum-based chemotherapy plus nivolumab. In patients with high Tumor Mutational Burden (high-TMB), defined as patients with ≥ 10 mutations/Mb, PFS at 12 months was almost 5 times higher with nivolumab-ipilimumab and 3 times higher with chemotherapy plus nivolumab than in individuals treated with chemotherapy alone. In patients with low TMB no difference in PFS was observed in the three arms. Overall these data support TMB and a relevant biomarker for refining selection of patients candidate to immunotherapy. Overall, all available data demonstrated that immunotherapy is the new standard of care as initial therapy in patients with NSCLC irrespective of histology. Current evidence support usage of immunotherapy single agent only in PD-L1 ≥50%. For patients with low or no PD-L1 expression immunotherapy plus chemotherapy is superior to chemotherapy alone. Combination of PD-L1 expression and TMB could better define in which patients chemotherapy can be avoided and in which patients immunotherapy is not effective.

Keywords: pembrolizumab, immunotherapy, NSCLC

PC08 THE GREAT OLIGOMETASTATIC DEBATES
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

PC08.01 DEBATE #1: LOCALLY ABLATIVE THERAPIES SHOULD BE STANDARD TREATMENT FOR PATIENTS WITH NSCLC OLIGOMETASTESE (PRO)

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The longstanding dogma that local therapies do not apply for metastatic cancers like non-small cell lung cancer (NSCLC) because "the horse is out of the barn" is predicated on two concepts that do not necessarily apply to a subset of patients with oligometastatic NSCLC. First, local ablative therapy (LAT) is assumed to be futile when the pace of the cancer is defined by a diffuse disease process. Second, LAT is presumed to incur challenging toxicities that limit its applicability. For patients with oligometastatic NSCLC, these limitations do not apply, making LATs a standard treatment strategy. Patients with a solitary brain or adrenal "precocious metastasis" have long been recognized as having a potential for prolonged survival after definitive treatment of both the primary tumor and the (usually) resected metastatic focus, with approximately 25% remaining alive and without evidence of recurrent cancer years later (1). This underscores that metastatic disease is not a binary variable that necessarily connotes a diffuse process and highlights that effective local therapy can render some patients in the spectrum of metastatic disease durably cancer-free. Patients with advanced NSCLC who are now strong candidates to benefit from LAT include those with oligometastatic disease, whether as their "de novo" presentation, induced oligometastatic disease after highly effective systemic therapy, "oligorecurrent" disease following prior treatment, or "oligoprogressing" disease after a prolonged duration of good disease control (2). The population of appropriate candidates has increased in recent years due to the growing range of systemic therapies that may induce deep and prolonged responses that becomes an oligometastatic state, or sustained disease control prior to oligoprogression. Along with the minority of patients with driver mutations who benefit dramatically from targeted therapies, a majority of patients with NSCLC who receive immunotherapy alone or in combination with chemotherapy can now achieve a good response to their first line systemic therapy. Along with a greater anticipated pool of strong candidates with oligometastatic NSCLC, LATs can now be pursued with markedly lower risk for the same or greater efficacy. Surgery to resect sites of metastatic/residual disease is typically feasible as a minimally invasive approach with good outcomes but fewer complications and easier recovery than the historical open surgeries required in the past (3). At the same time, stereotactic ablative body radiation (SABR) for primary or metastatic sites has now become widely established as an effective and generally very well tolerated option for patients (4), with a steadily growing body of evidence leading to wider availability of SABR. But are the theoretical benefits from LAT realized in this setting? Retrospective case series have consistent demonstrated that a subset of patients with oligometatatic NSCLC can achieve very favorable outcomes, particularly in terms of progression-free survival (PFS) as well as overall survival (OS) in some series (5). Of course, it is not possible to determine from a retrospective case series whether these patients do extremely well because of the intervention or the selection bias due to their candidacy for LAT. Prospective randomized trial results up to this point have been limited but highly supportive of significant benefits. An MD Anderson-led trial for patients with ≤3 sites of residual disease after three months of initial systemic therapy, testing LAT vs. maintenance therapy or surveillance alone, demonstrated a benefit in PFS so profound for LAT (median 11.9 vs. 3.9 mo, HR 0.35; LR p = 0.0054) that the trial was closed early by the Data Safety Monitoring Committee, with 49 patients randomized (6). Though the data from this trial were too immature to demonstrate a significant difference in OS, there was a significant improvement in the time to development of new metastatic sites. A similar trial from UT-Southwestern was also terminated after just 29 patients were enrolled, after demonstrating a similarly dramatic difference in PFS favoring the LAT arm (7). Notably, PFS interpretation in studies of LAT is limited by the fact that the most common site of progression is in the area(s) of known disease, but the fact that LAT extends the time to development of new and distant metastases illustrates that *local therapy can change the trajectory of systemic disease*. It is important to offer some caveats. First, LAT is an appropriate standard only for the subset of patients with very limited foci of disease that are amenable to eradication with LAT and without a more diffuse disease process. Whether the subset

of patients for whom LAT is a standard should be 1-2 or 3-5 lesions has yet to be clarified, but it is critical to apply LAT selectively, just as a molecularly targeted therapy or pembrolizumab monotherapy confers benefits only selectively. Broadening the treated population excessively will dilute the value compared to that in a more narrowly defined subset. Second, LAT cannot be presumed or insinuated to be curative in the setting of oligometastatic NSCLC, but like immunotherapy or targeted therapy, it should be considered as a standard based on it conferring a significant improvement in PFS without attendant significant toxicities, and/or time to new metastases, and potentially OS. Despite the limited prospective data, the NCCN recommends consideration of LAT for patients with oligometastatic NSCLC in the various clinical settings outlined above (8). Clinical trials of LAT for oligometastatic NSCLC are ongoing, but with such substantial potential benefits alongside such limited anticipated risks, LAT for appropriate patients is rightly considered a standard for appropriately selected patients. REFERENCES: 1) Congedo MT, Cesario A, Lococo F, et al. Surgery for oligometastatic non-small cell lung cancer: 137 long term results from a single center experience. *J Thorac Cardiovasc Surg* 2012; 144 (2): 444- 138 452. 2) Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995; 13 (1): 8-10. 3) Mutsaerts ELAR, Zoetmulder FAN, Meijer S, et al. Long term survival of thoracoscopic metastasectomy vs metastasectomy by thoracotomy in patients with a solitary pulmonary lesion. *Euro J Surg Onc* 2002; 28 (8): 864-868. 4) Shults DB, Filippi AR, Thariat J, et al. Stereotactic ablative radiotherapy for pulmonary oligometastases and oligometastatic lung cancer. *J Thorac Oncol* 2014; 9 (10): 1426-1433. 5) Griffloen GH, Toguri D, Dehele M, et al. Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors. *Lung Cancer* 2013; 82 (1): 95-102. 6) Gomez DR, Blumenschein Jr. GR, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled phase 2 study. *Lancet Oncol* 2016; 17 (12): 1672-1682. 7) Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol* 2018: 4(1): e173501. doi:10.1001/jamaoncol.2017.3501 8) NCCN clinical practice guidelines in oncology (NCCN guidelines): non-small cell lung cancer. Version 5.2018. Website: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf, accessed 6/29/2018.

Keywords: oligometastatic, LAT, SABR

PC08 THE GREAT OLIGOMETASTATIC DEBATES
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

PC08.02 DEBATE #1: LOCALLY ABLATIVE THERAPIES SHOULD BE STANDARD TREATMENT FOR PATIENTS WITH NSCLC OLIGOMETASTESE (CON)

P. Iyengar
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The evolution in the treatment of metastatic non-small cell lung cancer (NSCLC) with systemic therapies has historically been deliberate and rather sequential. With the refined use of genomics, however, a more rapid pace of advancement has been achieved with parallel development of biologic agents, including those targeting *EGFR* mutations and *ALK* rearrangements among others. Within just the last few years, immune checkpoint blockade has done even more to provide survival benefits to patients with stage IV NSCLC. As we continue to assess the impact of these new drug regimens, we are again asked to define and contextualize their true value. The concepts of overall survival (OS), progression free survival (PFS), and objective response rate as median values and/or values at certain time intervals (i.e. 6 months, 1, 3, or 5 years) are most often used to distinguish a successful vs unsuccessful treatment approach. Ultimately, many of us are simply applying these metrics as surrogates for durability of outcomes. The goal of our treatments, if curability is not currently achievable, is at least to drive metastatic NSCLC towards a chronic disease process. Just as diabetes and cardiovascular disease in its many forms can be treated over multiple decades with interventions that at least attempt to reduce progression of symptoms and disease severity, the same rationale could be applied to management of metastatic cancers. If we aim to convert stage IV NSCLC into a chronic disease state, the primary question is whether or not systemic therapies can suffice to reach this goal or if local therapies need to be added. Before we can answer this question fully, however, we must identify the biologic context in which long term durability of treatment-mediated disease control can be established. The most obvious environment to evaluate is patients with diffuse vs oligometastatic NSCLC, the latter originally defined by Hellman and Weichselbaum. Local therapies to date have only been used to treat widely metastatic NSCLC patients for palliation, though more recently as a means of enhancing the abscopal effect in trials. Due to the lack of significant prospective and/or randomized data assessing abscopal activity in metastatic NSCLC patients, we will not further discuss this local therapy treatment indication. Local therapies have been used in oligometastatic consolidation and for oligoprogression for NSCLC with surgery or/and radiation therapy (primarily stereotactic body radiation therapy). In this discussion, we argue that local ablative therapies should NOT be part of the standard treatment for oligometastatic NSCLC for several key reasons that are biologically and practically relevant. Our understanding of the natural history of oligometastatic NSCLC is still developing. No large systemic therapy clinical trial for NSCLC that provided survival data ever dichotomized patients between limited and widely metastatic disease. It is therefore still possible that oligometastatic disease in lung cancer patients has a different, perhaps more indolent course than diffuse disease, explaining why local therapies have suggested potential benefit in the former patient population. Even without local therapies, patients with oligometastatic NSCLC treated with any systemic therapy may have better disease or progression free intervals, a function of biologic differences. When further evaluating metastatic NSCLC, patterns of spread may also be relevant. Fundamentally, do new metastatic depositions develop from primary disease only, primary disease and older metastases, or are they present at the earliest stages of primary disease development? Preclinical data suggest that early metastatic spread and the presence of widespread microscopic disease may occur even when primary malignancies are in their infancy. If so, local treatment of gross, residual disease in consolidation or salvage for oligoprogression would not necessarily improve PFS outcomes. Hence, spread and development of new disease, perhaps the most critical driver of mortality, may be independent of local therapy if microscopic metastatic dissemination is an early event. Several other biologic implications should be worked out before incorporating local consolidation as part of standard therapy for oligometastatic NSCLC including – a) how many metastases represents the oligometastatic state, 1 vs 2 vs 3, vs 4 vs 5 vs >5, b) does anatomic distribution of metastases matter, and c) what is the best time to add local therapy, during consolidation vs salvage for oligoprogression vs in the abscopal setting. With uncertainty regarding all of these important parameters, local ablative therapy should not as yet be part of standard treatment for stage IV patients. Aside from the biologic concerns, there are more practical clinical-relevant issues with aggressively utilizing local therapy for oligometastatic NSCLC. No randomized study to date as shown an OS benefit to the use of local therapy. PFS benefits do not frequently translate into OS benefits. If this is the case, should we put patients through the local therapies if OS is not known to be altered to date? Furthermore, with the daily reports of new immunotherapy / chemotherapy combinations improving OS outcomes in subsets of NSCLC patients, including those with diffuse and limited metastatic disease, it may be that systemic therapy regimens on their own could enhance the chronicity of NSCLC. But it may be best to wait and determine the optimal systemic therapy combination before integrating with locally ablative therapy, another reason to not include local treatment as part of standard approaches for oligometastatic patients. Ultimately, the message of this talk is NOT that local ablative therapies should never be part of standard therapy for oligometastatic NSCLC. It's that local ablative therapies should not be part of standard approaches RIGHT NOW. With NRG LU 002, SARON, and CORE, randomized phase III efforts underway, we will learn if local therapies can improve OS in consolidation. NRG LU 002 will also permit immunotherapy, helping us understand the potential synergy between IO and radiation in oligometastatic NSCLC.

Keywords: Oligometastatic, consolidation, Ablative

PC08 THE GREAT OLIGOMETASTATIC DEBATES
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

PC08.05 DEBATE #2: KEEP CALM AND BEAM ON: THORACIC RADIATION OBVIATES THE NEED FOR SURGERY

M. Guckenberger
Department for Radiation Oncology, University Hospital Zurich, Zurich/CH

In this debate, it will become clear that radiotherapy in the form of stereotactic body radiotherapy (SBRT) is an evidence-based alternative to surgery, offering excellent local tumor and metastases control with simultaneously a highly favourable toxicity profile.

Keywords: Oligometastases, SBRT, Surgery

PC08.07 DEBATE #3: BRAIN METASTASES WITH A DRIVER MUTATION SHOULD BE TREATED WITH SYSTEMIC THERAPY FIRST (PRO)

M. Doherty
University of Toronto, Toronto/CA

Historically, brain metastases from non-small cell lung cancer (NSCLC) have been associated with short prognosis, with limited benefits from whole brain radiotherapy (WBRT) or cytotoxic chemotherapy.[1] The effectiveness of tyrosine kinase inhibitors (TKIs) in advanced EGFR- and ALK-driven NSCLC has translated into survival times far longer than chemotherapy in unselected patients.[2,3] Among these patients, brain metastases may occur in 20-40% at first presentation, and up to 50% over the course of their illness.[4,5] In spite of this, patients may live for several years following diagnosis of brain metastases and are accordingly at risk of longer-term toxicity from central nervous system (CNS)-directed treatments.[4,6,7] For patients diagnosed with brain metastases from EGFR- or ALK-driven NSCLC, initial treatment options range from TKI alone, through WBRT, stereotactic radiosurgery (SRS) to craniotomy and resection. All eligible patients will ultimately receive systemic therapy with TKI, and this is likely to be the most important component in preventing or delaying further CNS metastases. The utility of local radiotherapy is therefore worthy of debate in this patient population. Multiple retrospective series have attempted to examine this effect, the largest of which is a US multi-institution study, which reported longer overall survival (OS) for patients treated with SRS and TKI over TKI alone (median OS 46 vs 25 months, p<0.001).[7] Studies in Canada and China did not find a difference in survival, but all of these are largely subject to confounding and bias based on the selection of patients for local treatments, as well as potential bias in the follow-up of brain lesions.[6,8] In addition, most patients included in all of these studies were treated with 1st generation TKIs targeting EGFR or ALK. Within randomized trials including patients treated with modern TKIs, relatively few develop CNS progression, at least as their first evidence of progressive disease. This is evident among patients with brain metastases enrolled in the FLAURA trial in first-line EGFR mutation positive NSCLC, where CNS progression was seen in 12% of the osimertinib group and 30% of the control group, comprising of 1st and 2nd generation TKIs (p=0.01).[9] In ALK-rearranged NSCLC, results from the ALEX trial demonstrate much better CNS control with alectinib , with brain progression in 12% compared with 45% of those treated with crizotinib (p<0.001).[5] Among patients with measurable CNS metastases treated with alectinib, the objective response rate (ORR) was 81%, with complete responses seen in 45%, compared with an ORR of 59% for crizotinib and complete responses in 9%. Patients in both studies with CNS disease at entry were treated with SRS for control of brain metastases at study entry, but the high response rates and relatively low rates of progression speak to the efficacy of these TKIs in suppressing micrometastatic disease that would not be controlled by focal radiotherapy. With promising results like these, why would we wish to move away from radiotherapy? The purpose of palliative treatments for patients with advanced cancer is generally to preserve quality of life and function for as long as possible, with treatments that are not overly burdensome or toxic. The data from these trials of modern TKIs would suggest that for most patients, systemic therapy will effectively control their overt or subclinical brain metastases, and they can be spared the inconvenience and potential toxicity of locoregional treatments. Recently, there has been a move from WBRT towards SRS even for the treatment of multiple brain metastases, driven primarily by data reporting the neurocognitive toxicity of WBRT.[10] Although the rates of decline in neurocognition appear lower with SRS, in the setting of questionable clinical benefit and when patients are expected to live several years with CNS metastases, the risk of toxicity may not be justified. There are, however, patients where local therapy such as radiotherapy or surgery are indicated – those with major neurological symptoms, hydrocephalus, or in circumstances where molecular testing is delayed or where effective TKIs are unavailable or contraindicated. However, for most patients with oncogene-driven lung cancer who will receive TKI therapy, delaying upfront radiotherapy for brain metastases may not negatively affect patient outcomes. Data from randomized trials of targeted therapy alone or with radiotherapy will be required to definitively answer this question. References: 1. Chao JH, Phillips R, Nickson JJ: Roentgen-ray therapy of cerebral metastases. Cancer 7:682-9, 1954 2. Mok TS, Wu YL, Thongprasert S, et al: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947-57, 2009 3. Solomon BJ, Mok T, Kim D-W, et al: First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer. New England Journal of Medicine 371:2167-2177, 2014 4. Soria J-C, Ohe Y, Vansteenkiste J, et al: Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. New England Journal of Medicine 378:113-125, 2018 5. Peters S, Camidge DR, Shaw AT, et al: Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer. New England Journal of Medicine 377:829-838, 2017 6. 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Keywords: ALK, brain metastases, EGFR

PC08.08 DEBATE #3: BRAIN METASTASES WITH A DRIVER MUTATION SHOULD BE TREATED WITH SYSTEMIC THERAPY FIRST (CON)

M. Scorsetti
Humanitas University, Rozzano Milan/IT

Brain metastases (BM) are a common occurrence in non-small cell lung cancer (NSCLC), particularly in EGFR-mutated or ALK-rearranged tumors, with up to 50% of patients with advanced EGFR/ALK-driven NSCLC developing central nervous system (CNS) involvement[1]. With EGFR and ALK inhibitors, the expected patient survival is in the range of years, and long-term control of CNS disease with minimum long-term toxicity, rather than solely palliation, is an increasing priority. Many of these patients are young and active, making the preservation of cognitive function and quality of life the mainstay goal of treatment. Whole-brain radiotherapy (WBRT) has been for many years the standard treatment for patients with multiple BM, providing symptom palliation and survival improvement in selected cases. However, with longer patient survival, there has been growing concern for the well-known neurocognitive consequences of WBRT. On the other hand, targeting EGFR mutations and ALK rearrangements with small-molecule tyrosine kinase inhibitors (TKIs) has yielded high systemic response rates and improved survival outcome in first-line treatment of metastatic NSCLC. There are several reports of activity both in preventing or delaying the onset of CNS disease, and in leading to intracranial response for patients with preexisting BM. Therefore, there is general agreement in treating patients with asymptomatic multiple BM with a driver mutation with systemic therapy first, delaying the use of WBRT as longer as possible[2]. However, several drugs, including first- and second-generation EGFR TKIs (gefitinib, erlotinib, afatinib) and the ALK inhibitor crizotinib, have limited penetration in the CNS, due to poor blood-brain barrier permeability. Isolated CNS progression is common in patients on these targeted therapies. Current drug development is aimed at increasing CNS bio-availability, and new compound such as the third-generation EGFR TKI osimertinib and more recent ALK inhibitors (alectinib, lorlatinib) have shown preclinical and clinical evidence of greater penetration in the CNS[3]. The reduced penetration of targeted compounds in the CNS poses a clinical challenge, mainly in patients with symptomatic lesions and/or a single or a limited number of BM. In these patients, intracranial resistance to therapy is likely the greatest limitation to long-lasting disease control. Stereotactic radiosurgery (SRS) offers highly conformal radiation to metastases with limited dose to the remainder of the brain. A large amount of data has shown very high rates of symptomatic and radiological control with SRS, along with a favorable toxicity pattern[4]. Local ablative therapy (LAT), mainly by SRS, has recently emerged as a valid option in the setting of oligo-metastatic NSCLC[5]. In accurately staged patients with advanced EGFR/ALK-driven NSCLC progressing at a limited number of sites, including CNS, LAT plus continuation of first-line targeted therapy has been accepted as a valuable therapeutic strategy to provide additional clinical benefit, with limited side effects. More recently, a few studies have shown that stage IV NSCLC with oligo-metastases could benefit from LAT for consolidation during first-line TKIs. Data on molecular-driven NSCLC are still sparse, however there are reports showing in EGFR-mutated patients a progression-free survival (PFS) and overall survival (OS) improvement with consolidative LAT at all disease sites, as compared to consolidative LAT to partial sites or observation alone[6]. In these studies, consolidative SRS was associated with improved survival also in patients with synchronous brain oligo-metastatic disease. The timing of LAT remains controversial. Interestingly, a few recent retrospective analyses on EGFR-mutated

patients treated with first-line TKIs have shown that upfront SRS on BM resulted in longest survival compared with use of systemic therapy alone as first therapeutic strategy, suggesting that deferral of LAT on CNS disease may be associated with inferior PFS and OS[6,7]. In conclusion, use of advanced techniques in radiation therapy and development of new targeted approaches for BM have the potential to prolong life of lung cancer patients with a molecular driver. Importantly, most data refers to EGFR/ALK-driven NSCLC, while very few information is available for other drivers such as BRAF, MET and ROS1. Proper patient selection and staging is of paramount importance to choose a tailored therapeutic sequence and strategy. **References** 1. Sperduto PW et al. Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). JAMA Oncol 2017;3:827–31. 2. Doherty MK et al. Treatment options for patients with brain metastases from EGFR/ALK-driven lung cancer. Radiother Oncol 2017;123:195-202. 3. Bulbul A et al. Systemic treatment options for brain metastases from non-small-cell lung cancer. Oncology (Williston Park) 2018;32:156-63. 4. Churilla TM, Weiss SE. Emerging trends in the management of brain metastases from non-small-cell lung cancer. Curr Oncol Rep 2018;20:54. 5. Weickhardt AJ et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. J Thor Oncol 2012;7:1807-14. 6. Xu Q et al. Consolidative local ablative therapy improves the survival of patients with synchronous oligometastatic NSCLC harboring EGFR activating mutation treated with first-line EGFR-TKIs. J Thor Oncol 2018; May 28 [Epub ahead of print]. 7. Magnuson WJ et al. Management of brain metastases in tyrosine kinase inhibitor-naive epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. J Clin Oncol 2017;35:1070-1077.

Keywords: brain metastases, tailored therapeutic sequence, Driver mutation

PC09 APPROACHES TO MANAGEMENT OF ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

PC09.01 DEBATE 1: EARLY VS DELAYED TREATMENT OF ASYMPTOMATIC BRAIN METASTASES IN WILD-TYPE NSCLC - EARLY

Q. Zhou
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Brain metastases (BM) appear in about 25% patients at the diagnosis phase in non-small cell lung cancer (NSCLC), and almost half of the patients will eventually develop to BM during their disease progress. Median overall survival (OS) for NSCLC patients with BM ranges from 3–15 months. Metastatic NSCLC is difficult to treat in general. In ESMO guideline, we suggest treating patients with these effective systemic therapies upfront, delaying or omitting the use of local CNS treatments, and therefore avoiding their accompanying toxicities. This recommendation pertains particularly to oncogenic driven asymptomatic BM, since intracranial control can be achieved with TKIs in the first and in subsequent lines of therapy.[1] But it is different between wild-type and mutant NSCLC with brain metastases. Wild-type brain metastases occurrence rate is lower than oncogenic driven.[2] And more asynchronous metastases is in oncogenic driven. OS of wild-type is also shorter than oncogenic driven. Most importantly, there are less effective systemic strategies for wild-type NSCLC compared with mutant NSCLC. Systemic treatment is not enough for wild-type NSCLC with asymptomatic brain Metastases. Chemotherapy can't satisfy wild-type NSCLC with asymptomatic brain Metastases. Chemotherapy has limited BBB penetration. Brain response rate is only 20-40% without radiotherapy base on small sample. Pemetrexed seems to have a better survival benefit for adenocarcinoma brain metastasis. But the best chemotherapy regimen has not been established. Angiogenesis may be added on wild-type NSCLC with asymptomatic brain Metastases therapy. Angiogenesis reduces cerebral edema in BM patients, improves quality of life (QoL), and reduces neurological deficits and headaches. But Angiogenesis is excluded from Squamous cell carcinoma. Immune oncology initially appears effect in wild-type NSCLC with asymptomatic brain Metastases therapy. Currently, small sample subgroups, retrospective or real-world data are predominant. Extended and prospective studies are needed to further verify. An important role of radiotherapy is to achieve better local control and prevent the appearance of neurologic symptom. If local radiotherapy is delayed, the risk of changing from asymptomatic BM to symptomatic BM will dramatically increase. When asymptomatic patients develop brain symptoms, serious reductions in quality of life will be resulted. Some data have reported that BM severely impact patient's QoL (physical, cognitive, and functional impairments), as well as result in high healthcare resource utilization and substantial clinical, economic, and caregiver burden. A meta-analysis showed that NSCLC patients with even a single brain metastasis experience the greatest decline in QoL compared with other sites of metastasis, such as those located in the adrenals, liver, or bone. There are currently some effective local interventions: radiotherapy with less side effects, even the whole brain radiation therapy has progressed to precise. Besides, combination brings different treatments synergy. Systemic chemotherapy can be active by radiotherapy in NSCLC brain metastases. IO combining with radiotherapy produce remote effect in NSCLC. In short, asymptomatic brain metastases in wild-type NSCLC need early and active treatment and the treatment should be the combination of systemic and local strategies. 1.Tsakonas G, De Petris L, Ekman S. Management of brain metastasized non-small cell lung cancer (NSCLC) - From local treatment to new systemic therapies. Cancer Treat Rev. 2017 Mar;54:122-131. 2. Chen G, Chen X, Zhang Y, et al. A large, single-center, real-world study of clinicopathological characteristics and treatment in advanced ALK-positive non-small-cell lung cancer. Cancer Med. 2017 May;6(5):953-961.

Keywords: Early Treatment, Asymptomatic Brain Metastases, Wild-Type NSCLC

PC09 APPROACHES TO MANAGEMENT OF ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

PC09.05 DEBATE 2: LARGE CELL NEUROENDOCRINE CARCINOMA SHOULD BE TREATED LIKE NSCLC OR SCLC? - SCLC

S. Laurie
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Large cell neuroendocrine carcinoma (LCNEC) of the lung is rare, representing about 3 % of all lung cancers. In the 2015 World Health Organization classification of pulmonary neoplasms, LCNEC has been moved to the chapter on Neuroendocrine Tumours, alongside carcinoid and small cell carcinoma, and is no longer classified as a large cell carcinoma. It is a high-grade malignancy with a poor prognosis similar to that of small cell carcinoma in those with metastatic disease. The diagnosis of LCNEC requires specific histological features that can be difficult to appreciate on the small biopsy specimens that are frequently obtained from those undergoing a workup for suspected lung cancer, leading to a potential for misclassification. This potential for misdiagnosis hinders the interpretation of retrospective reports that do not have a central review of the pathology with confirmation of the diagnosis of LNCEC by expert pathologists. Its rarity has led to a lack of prospective evidence regarding the optimal treatment strategy and debate as to whether to use chemotherapeutic regimens for small cell or non-small cell lung cancer. The 2015 update of the American Society of Clinical Oncology Practice Guidelines for the treatment of stage IV non-small cell lung cancer suggests the use of platinum-etoposide chemotherapy (expert consensus, recognizing the lack of evidence) [1]. Other societies' guidelines are silent on the treatment of LCNEC. The prognosis of resected LCNEC appears to be poorer than that of an identical stage NSCLC [2]. Retrospective reviews suggest that adjuvant cisplatin-etoposide chemotherapy improves outcomes compared to matched historical controls that did not receive such treatment [3]. Furthermore unlike non-small cell lung cancer and more in keeping with data from resected small cell carcinoma, database analyses suggest a benefit to adjuvant multiagent chemotherapy even in stage IA disease [4]. An ongoing clinical trial in Japan (JCOG1205/1206) is randomizing patients to either adjuvant cisplatin-etoposide or cisplatin-irinotecan (a regimen commonly used for small cell carcinoma in that country). In the metastatic setting, retrospective reports have yielded conflicting data on whether outcomes in LCNEC are superior with platinum-etoposide chemotherapy or with standard platinum-based NSCLC regimens [reviewed in 5]. It does appear that response rates to platinum-etoposide in LCNEC may be lower than those obtained in small cell carcinoma. Only two prospective phase II trials have been performed specifically in LCNEC using small-cell carcinoma-type chemotherapy. The first, performed in Europe, treated 42 patients with cisplatin and etoposide [6]. On central pathology review, 11 were reclassified as something other than LCNEC. The response rate in the confirmed LCNEC subgroup was 34 %, with a disease control rate of 65 % and a median overall survival of 8 months. The second trial, performed in Japan [7], reclassified 10 of 41 enrolled LCNEC as small cell carcinoma and utilized cisplatin-irinotecan. The overall response rate and median survival in the confirmed LCNEC group was 47 % and 12.6 months, respectively, both of which were lower than the results in those reclassified as small cell carcinoma. Although response rates may be lower than in small cell, these regimens still have efficacy, and it is not clear that non-small cell lung cancer regimens are superior. Insights regarding the most appropriate treatment for LCNEC will come from more detailed genomic analyses of this lung cancer subtype. Similar to small cell carcinoma, studies have shown high prevalence of inactivation of *TP53* and *RB1*, although the latter is lower in frequency than in small cell [8,9]. From these studies, it appears that LCNEC can be segregated into two distinct subgroups based on whether the genomic profile is similar to that of small cell carcinoma (having co-alterations in *TP53*

and *RB1*), or non-small cell like, lacking this co-alteration, and instead having alterations in genes such as *KRAS* and *STK11*. Retrospective data suggests that *RB1* wild-type status may predict for better outcomes with non-small cell carcinoma chemotherapy regimens [10]. Moving forward in this rare malignancy will require international cooperation to conduct clinical trials to determine the optimal treatment in patients with centrally confirmed histology. These trials should evaluate whether a genomic signature predicts for differential chemosensitivity. It may be that *some* LCNEC should be treated like small cell carcinoma, while others may require a different approach. 1. Masters GA, et al. *J Clin Oncol* 2015; 33: 3488-3515. 2. Iyoda A, et al. *J Thorac Cardiovasc Surg* 2006; 132: 312-315. 3. Iyoda A, et al. *Ann Thorac Surg* 2006; 82: 1802-1807. 4. Kutjan L, et al. *J Thorac Oncol* 2018; 13: 707-714. 5. Derks JL, et al. *Eur Resp J* 2017; 49: 1601838. 6. Le Treut J, et al. *Ann Oncol* 2013; 24: 1548-1552. 7. Niho S, et al. *J Thorac Oncol* 2013; 8: 980-984. 8. Rekhtman N, et al. *Clin Cancer Res* 2016; 22: 3618-29. 9. George J, et al. *Nature Communications* 2018; 9: 1048 10. Derks JL, et al. *Clin Cancer Res* 2018; 24: 33-42.

MS01 CANCER PATHWAYS, TARGETED THERAPY AND RESISTANCE
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

MS01.01 DEFECTS OF THE SWI/SNF OR MYC/MAX PATHWAYS: EFFECTS IN CELL DIFFERENTIATION AND THERAPEUTIC OPPORTUNITIES

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The SWI/SNF complexes are ATP-dependent remodelers of the chromatin structure, by disrupting of DNA–histone interactions to activate or repress gene expression (Wilson et al. 2011). In healthy adults and during embryonic development, the complex is involved in the control of cell differentiation and in the specification of different tissues. Components of the SWI/SNF complex bind to various nuclear receptors, such as those of estrogen, progesterone, androgen, glucocorticoids and retinoic acid, thereby adapting the gene expression programs to the demands of the cell environmental requirements. The effect of the SWI/SNF complex on some of these processes is, at least in part, related to its involvement in regulating hormone-responsive promoters (reviewed Romero et al. 2014). A few years ago, we discovered that, in lung cancer, the SWI/SNF component, SMARCA4 (also called BRG1), is genetically inactivated in about thirty per cent of non-small cell lung cancers (NSCLC), and that its inactivation occurs in a background of wild type MYC (Medina et al. 2008). Nowadays, it is well established that other components of the complex are also commonly inactivated in most cancer types, including lung cancer (reviewed in Romero et al. 2014). Gene alterations of the SWI/SNF complex are significantly more common in NSCLC, as compared to small cell lung cancers (SCLC), and tend to associated with smoking habit. In addition, we reported the presence of tumor-specific inactivation of the MYC-associated factor X gene, MAX, in about ten percent of SCLC (Romero et al. 2014). The two events are mutually exclusive among them and with alterations at the MYC-family of genes. We also demonstrated that SMARCA4 regulates the expression of MAX and that depletion of SMARCA4 specifically in MAX-deficient cells strongly decreased cell growth, heralding a synthetic lethal interaction with potential therapeutic implications. Furthermore, MAX required of SMARCA4 to activate neuroendocrine transcriptional programs and to up-regulate MYC-targets, such as glycolytic-related genes. Finally, we observed genetic inactivation of the MAX dimerization protein, MGA, in lung cancers with wild type components of the SWI/SNF or MYC pathways. The widespread occurrence of alterations at genes encoding different components of the SWI/SNF complex reveals an important new feature that sustains cancer development. Retinoic acid (RA) and glucorticoids (GC) are well known modulators of cell differentiation, embryonic development and morphogenesis. GCs and RA are part of the curative treatment of some malignancies, mostly leukemias (Collins et al. 2002; Rutz et al. 2002; Pottier et al. 2008). However, most solid tumors, including lung cancers, are refractory to GC- and RA-based therapies. Underlying some cases of refractoriness to GC and RA is a dysfunctional SWI/SNF complex, for example due to alterations at SMARCA4 (Romero et al. 2002). On the other hand, compounds that modulate the structure of the chromatin are currently used to treat cancer. These include histone deacetylase (HDAC) inhibitors, in hematological malignancies and cutaneous T-cell lymphomas, and inhibitors of DNA methylation such as azacytidine for myelodysplasic syndrome (Liu et al. 2013). HDACs and DNA methylation inhibitors promote gene transcription by increasing DNA accessibility through the inhibition of histone deacetylation and DNA methylation, respectively. In a preliminary study, these drugs, in combination, have shown promising results in the treatment of lung cancer patients. In lung cancer cell lines, we observed that GC plus RA (GC/RA) in combination with the epigenetic drugs azacytidine and SAHA (A/S) reduced growth, triggered pro-differentiation gene expression signatures and downregulated MYC, in MYC-amplified but not in most SMARCA4-mutant cells (Romero et al. 2017). *In vivo*, treatments with GC/RA improved overall survival of mice implanted with MYC-amplified cells and reduced tumor-cell viability and cell proliferation. We also found some effect of the SAHA treatment, alone in reducing the cell growth of MYC-amplified lung cancer cells but not those that are SMARCA4-deficient. Thus, we propose that the combination of retinoids, corticoids and epigenetic treatments of lung tumors with MYC amplification constitute a strategy for therapeutic intervention in this otherwise incurable disease. Altogether, the genetic observations coupled with the functional evidence demonstrate that an aberrant SWI/SNF-MYC network is essential for lung cancer development and open novel therapeutic possibilities for the treatment of lung cancer patients. **REFERENCES** Collins SJ. The role of retinoids and retinoic acid receptors in normal hematopoiesis. Leukemia 2002; 16, 1896–905. Liu SV, Fabbri M, Gitlitz BJ, Laird-Offringa IA. Epigenetic therapy in lung cancer. Front Oncol 2013; 3, 135. Medina PP et al. Frequent BRG1/SMARCA4-inactivating mutations in human lung cancer cell lines. Hum Mut 2008; 29, 617-22a. Pottier N et al. The SWI/SNF chromatin-remodeling complex and glucocorticoid resistance in acute lymphoblastic leukemia. J Natl Cancer Inst 2008; 100, 1792-803. Romero OA et al. The tumour suppressor and chromatin-remodelling factor BRG1 antagonizes Myc activity and promotes cell differentiation in human cancer. EMBO Mol Med 2012; 4, 603-16. Romero OA et al. 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Keywords: SWI/SNF-complex, MYC/MAX, epigenetic therapies

MS02 THE FUTURE OF IO
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MS02.04 OPTIMIZING CLINICAL TRIAL DESIGNS IN IMMUNOTHERAPY

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Anti-PD (L)1 therapy is part of the standard of care approaches in 1st line and 2nd line therapy for NSCLC either as monotherapy (1) or in combination with chemotherapy (2) and has shown benefit for a subset of NSCLC defined as tumors with high tumor mutation burden (TMB) in combination with anti-CTLA4 therapy (3). Several questions remain though about how to optimally integrate immunotherapy in the standard of care setting. These include questions on the optimal biomarker testing, questions on whether immunotherapy should be sequenced with chemotherapy, optimal duration of therapy and the role of maintenance therapy and finally and most importantly evaluation of novel regimens for tumors that either refractory to immunotherapy or acquire resistance. Clinical trials with targeted therapy have demonstrated the power of biomarker integration in clinical trial design in settings where a matched driver mutation and a targeted therapy addressing that mutation is used. It is therefore envisioned that as novel biology emerges we will be able to characterize tumors and their microenvironment and define subsets that would be predicted to benefit from rational combinations. New trial design mandates partitioning patients into more select, precise populations, and identification of these unique groups requires clinical trials to evolve quickly to provide clinically relevant outcomes Therefore clinical trial designs that are envisioned to accelerate knowledge and expand the benefit to larger patient populations include:a)clinical trials in early NSCLC-neoadjuvant therapy providing the advantage of obtaining surgical specimens for biological correlates and potentially enhancing the cure rates b)Biopsy driven-clinical trials where biopsies are obtained pre and on therapy and possibly at progression to characterize biologic correlates of response or resistance c) umbrella clinical trials which allow for simultaneous enrollment of several subsets of patients and allocation to appropriate therapies. This latter category allows for modular designs with ineffective agents being replaced by more potent agents based on smaller signal-seeking studies. This paradigm is well represented by the LUNG-MAP (SWOG S1400) study using a multidrug, targeted screening approach to match patients in one of multiple trial substudies, each testing a different drug. This study, has recently incorporated a major focus for immunotherapy-resistant tumors and a new platform has been integrated in this public-private collaboration between the National Cancer Institute, academic institutions, and private industry (4). For the design of randomized phase III studies using overall survival (OS) as the primary endpoint, there is a shift from the conventional approach based on a proportional hazards model to those that account for the unique survival kinetics observed in immuno-oncology trials, such as long-term survival and delayed clinical effect. References 1.Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E, Ahn MJ, Felip E, Lee JS, Hellmann MD, Hamid O, Goldman JW, Soria JC, Dolled-Filhart M, Rutledge RZ, Zhang J, Lunceford JK, Rangwala R, Lubiniecki GM, Roach C, Emancipator K, Gandhi L; KEYNOTE-001 Investigators. **Pembrolizumab for the treatment of non-small-cell lung cancer.** N Engl J Med. 2015 May 21;372(21):2018-28. doi: 10.1056/NEJMoa1501824. Epub 2015 Apr 19. 2. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H,

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Keywords: Clinical trial design, immunotherapy

MS02 THE FUTURE OF IO
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MS02.05 CONVINCING POLICY MAKERS TO AFFORD IMMUNOTHERAPY

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Immunotherapy has revolutionized the field of oncology in an increasing number of tumor indications [1]. The challenge is how to incorporate these into the toolbox of medical oncologists, given the complexity and inequities of the distinct healthcare system throughout the globe, limiting financial resources and numerous health needs. Here we provide a series of recommendations that are likely to improve access and reduce the cost of these medications. Nonetheless, there are numerous challenges that must be overcome if the entire cancer population eligible to receive immunotherapy is to benefit from this remarkable advancement in health care. In the last 15 years cancer drugs prices have been escalating and have become an issue for patients and the entire healthcare system. Earlier to 2000, the average price for a year of therapy or total treatment was less than $10,000. By 2012, this had increased tenfold, with 92% of the new drugs approved for cancer indications that year costing more than $100,000 per year of treatment. Globally, the costs of oncology therapeutics and supportive care increased 11.5% from 2010 to 2015 [2]. Predictions that integrate trends in incidence, survival, oncology practice patterns, and cost of cancer therapeutics estimate that the total cost of cancer care in the U.S. will rise to $173 billion in 2020 [3]. Under the present system, drug manufacturers regulate pricing. The rapid approval of new immuno-oncology (I-O) agents, all of which carry substantial price tags, has pulled this issue clearly into view, since payers are key stakeholders in determining coverage and reimbursement for this treatment. Payers through the world are dealing with how to assess these drugs and determining whether they are worth the cost of making them available to patients [4]. The growing number of drugs combinations that are already expensive leaves payers even more worried. In a recent investigation done by "*Precision for Value"*20 payers representing 75 million lives and 10 integrated delivery systems secure were inquired about their concerns around combination immunotherapy regimens. The results were: 33% of respondents said it was either very or extremely important whether an immunotherapy was used as part of a combination treatment; 37% said they were more concerned about a particular combination as opposed to another. Of these, almost 75% said a combination of immunotherapies was more concerning than an immunotherapy-chemotherapy combination; 55% of respondents cited cost as their biggest concern around immunotherapy combinations [5]. In general payers focus on monitoring the use of this drugs applying severe precertification criteria [4]. Their main argument regards that payers articulates that the population is still not relatively wide-ranging, even if there are incredible response rates with some, and so, at the end, they are paying for all [6]. Solid data on patient selection and health economics aspects of I-O indications are eagerly needed. At this purpose the use of biomarkersappears as a significant therapeutic tool since it could predict the benefit from a specific treatment and consequently may help to reduce the cost of pharmacotherapy by enabling the selection of a drug that will offer greater benefit in a distinct population [7]. In fact, some studies have been showing that the use of biomarkers reduces the cost effectiveness of immuno-oncologic therapy [6]. Moreover, studies that include a biomarker-driven health economics analysis may show a value-based pricing strategy for immune-oncologic drugs [1]. The discussion on access to costly cancer drugs is global. The cost of a drug could directly influence the access and successively the number of patients treated; increasing the access would enable a growth in both economic and health outcomes for all stakeholders. The value-based delivery and reimbursement in oncology are also a cause for discussion. For instance, should a similar medication have distinctive costs for different indications if the results are not the same? Another pricing indication would constrain pharmaceutical producers to contend on costs and results [1, 7]. Whether the idea is move from a standard capitalism-based pricing model towards value-based oncology care an innovative model for interface between government, pharmaceutical industry, healthcare providers and society should be set up [7]. Moreover, payers should be committed with the provider community. Clear policies based on the most recent data available must be presented. The challenge may be the speed with which science is advancing and this can in any way hamper the updating of the policies.In addition to payers communicating with oncologists and provider networks, drug manufacturers can keep payers up to date on their products [7]. Finally, there should be some mechanism for all stakeholders to interact and develop strategies, such as what is occurring in Brazil in the context of the Health Industrial Complex Executive Group and Forum (GECIS [8]). This Forum foster the appreciation and utilization of new technologies in healthcare, including the immuno-oncology area. Furthermore, the greater the number of information and dissemination of knowledge important to recognize, understand and accept the introduction of new therapies, the closer we will be of being able to convince stakeholders and then introduce immuno-oncology drugs in the roll of available treatments. REFERENCES 1. Ferreira CG, *et al*. 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Keywords: immunotherapy, payers, access

MS03 NEW FRONTIERS IN OLIGOMETASTASES
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MS03.05 INTEGRATION OF IMMUNOTHERAPY IN THE OLIGOMETASTATIC PARADIGM

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Radiotherapy is a treatment modality commonly used in efforts to manage oligometastatic disease. It is now recognised that radiotherapy does not only directly kill tumour cells, but it also changes the tumour microenvironment, enhancing tumour cell recognition by the immune system, therefore acting as an *in situ* vaccine. Radiotherapy increases expression of tumour-associated antigens, causes the release of cytokines, stimulates recruitment of dendritic cells and most importantly stimulates the proliferation and priming of cytotoxic CD8+ T-cells in the tumour microenvironment. This immunologic cascade specifically generates activated T-cells able to induce immunogenic cell death directed against cancer cells bearing those antigens. The cellular changes induced by radiotherapy are becoming increasingly important as it is recognised that the majority of patients do not respond to currently available therapies based on immune checkpoint inhibitors. The benefit of those agents is limited to patients who have pre-existing active immune microenvironment that can be re-activated by immunotherapeutic agents. By its ability to overcome some tumour immune escape mechanisms, radiation provides a non-pharmacological and cost-effective approach to potentially improve the systemic response to immune checkpoints inhibitors. In the context of oligometastatic disease, it is unclear what the ideal integration of immunotherapy and radiotherapy should be. Most studies are currently investigating 'abscopal' effects with combination radio/immunotherapy strategies in patients with widespread metastases. In the oligometastatic state, does this make sense? Given the local efficacy of radiotherapy, treatment of all macroscopic sites of disease if safe would appear to be a prudent strategy in combination with immunotherapy. Additionally, what is the optimal duration of immunotherapy in this context? What is the ideal timing of radiotherapy, and should it be given upfront or as consolidation? These are some of the issues that will be explored in this short lecture.

Keywords: Oligometastases, abscopal, stereotactic

MS04.02 HOW IS LUNG CANCER SCREENING EVOLVING TO BE MORE EFFICIENT AND EFFECTIVE?

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At the time of writing this summary, only the US and Canada had approved national screening with low radiation dose computed tomography (LDCT) and this was based primarily on the US National Lung Screening trial (NLST).[1]Since this landmark study, there has been much debate and further research work to clarify the best way to undertake a screening programme. Initially, uncertainty about the detail of an optimal programme that ensures that benefits outweigh harms in a cost-effective manner, was a reason to delay initiation of programmes in other countries.[2] However, many now believe that there is sufficient evidence to design a programme that will deliver a substantial reduction in mortality well within the commonly quoted willingness to pay thresholds in developed countries.[3]What is making policy makers cautious is the fact that the results of the only other randomised trial powered to detect a lung cancer mortality difference, the Dutch-Belgian NELSON trial, are still awaited. Figure 1 shows some of the factors that may be crucial in producing a favourable balance between benefits and harms and these are summarised below. **Selecting** people at high risk of lung cancer, who are more likely to benefit than those at low risk makes the intervention more cost effective. The use of multivariable risk prediction models increases the cost effectiveness over simple age and smoking criteria used in NLST. It is important that people who are at too low risk, some being the 10-15% of people who develop lung cancer but have never smoked, understand why they should not be screened. There is also an intermediate risk group where cost is the main consideration. Modelling has shown that annual **scanning** is more cost effective than biennial. However, where a previous CT is negative (no significant pulmonary nodules) the risk of cancer a year later is low, allowing a 2-year interval and cost savings. Imaging and reporting standards are well-developed. **Indeterminate findings** need to be managed according to guidelines that employ initial interval LDCT, recognising that the risk of malignancy is low, avoiding overdiagnosis, higher radiation dose imaging and false positive diagnostic tests[4, 5]. The false positive rate is 1-3% where this patient-centred definition is applied. **Clinical work-up** and **treatment** should also follow modern pulmonary nodule management and other clinical guidelines[4, 5]to reduce overdiagnosis and harms from biopsies and surgery by reducing intervention where the risk of malignancy is low or when cancers are indolent and unlikely to cause harm. Applying this "intelligent" approach yields a benign resection rate of around 10% and the in most recent UK pilot it was 2%. [6-8] **Smoking cessation** support should be integral as the overall quit rates are greater than in the general population and further increased by intermediate findings. Some issues are unresolved and could further improve cost-effectiveness. **Participation** in screening has been disappointing in the US and active research into ways to increase this is needed to ensure an impact at population level. The value of **add-on health interventions** and addressing **incidental findings** needs to be carefully evaluated using the same principle of benefit outweighing harm. **Information** to support people to make an informed decision about whether screening is right for themis an area of continuing research and relies heavily on the input of patients and the public. An undoubted challenge to implementation in some countries is the demand on human and physical **resources**. Screening for lung cancer makes logical sense and has a strong evidence base but delivering an optimum programme is dependent on attention to detail. It is important that country-specific pilot programmes now underway adhere to best practice so we see detection of early stage disease and high curative treatment rates with low rates of intervention for benign disease. This will help clinicians and opinion leaders, in partnership with advocates, to convince policy makers and governments of the need for investment. References 1. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, et al: **Reduced lung-cancer mortality with low-dose computed tomographic screening.***New England Journal of Medicine* 2011, **365:**395-409. 2. Field JK, Aberle DR, Altorki N, Baldwin DR, et al: **The International Association Study Lung Cancer (IASLC) Strategic Screening Advisory Committee (SSAC) Response to the USPSTF Recommendations.***J Thorac Oncol* 2014, **9:**141-143. 3. 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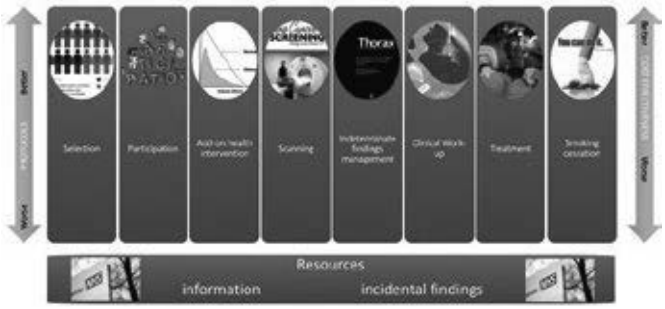
Figure 1: Key factors that should be addressed in an optimal LDCT screening programme



Keywords: Role of Advocates, CT screening, cost effectiveness

MS04.03 EXPLORING SMOKING STIGMA, NEGATIVITY AND LUNG CANCER - WHAT CAN BE DONE?

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Misinformation or false myths about cancer generate fear and a negative perception of a person affected by this disease. Lung cancer patients experience a higher level of cancer-related stigma than other cancer patients, because the general negative attitude about smoking, recognized as one of the main risk factors, contributes to the stigmatization of people who live with this condition. Although the relation between tobacco use and lung cancer is established, worldwide lung cancer patients are affected by a noteworthy and unjustified stigma and considered responsible of their disease in a different way from other cancer patients. For it, they are often reluctant to disclose the disease, because of fear to be discriminated, and patients' stories show that stigma could be harmful and detrimental to them and their loved ones and may cause limitations in working toward a cure. The lack of public empathy and support adds an emotional burden to an already frustrating situation that can affect quality of life and may contribute to depression, anxiety, poor self-esteem, guilt, shame, blame, negatively impacting psychological adjustments and interpersonal communication. Low public support for lung cancer is not restricted to popular perceptions and attitudes, but can also be seen in research funding. Lung cancer remains an underfunded disease and despite the higher mortality, it received less funding compared to other common cancers, such as breast cancer. **What can be done?** Stigma impacts all spheres of a person's life and patients, caregivers, advocates and healthcare professionals have started years ago actively working in this area developing programs and campaigns that can help to change this situation, partly persisting because smoking is still considered more as a bad habit rather than a serious addiction. It's important to motivate and encourage smokers to quit rather than blaming them, and even when the lung cancer has already been diagnosed, smoking cessation is important for a better quality of life. Providing smoke-free policies and tailored and effective campaigns is essential for improving the people awareness about the issue that smoking contributes to a number of diseases and cancers even if most people associate it exclusively with lung cancer. But, lung cancer is not just a smoker's disease, there are additional factors to consider and the education of patients, the general public and the health care personnel on these topics plays a valuable role. To help dispel stigma it is crucial the dissemination of correct and up-to-date information, the commitment of celebrities, patient families and friends, doctors in campaigning and advocating on their behalf, sharing the stories of lung cancer patient's in order to increase the visibility of this disease and to generate a movement able to create a support network more sympathetic with these people, because they need and deserve care and support, not an evaluation of the possible causes of the disease. Raising the awareness is one of the main goals of any Lung Cancer Advocate worldwide and in conjunction with Lung Cancer Awareness Month, observed annually in November, many advocacy groups improve their efforts independently or in cooperation for promoting public campaigns about prevention, screening, new treatments and other issues. With the purpose of harmonizing the action, some years ago the International Association for the Study of Lung Cancer (IASLC)

proposed and lead a unified effort among a consortium of non-profit lung cancer patient organizations and individuals to produce a coordinated public awareness campaign for Lung Cancer Awareness Month (LCAM) in November in order to reach the maximum amount of impact on media coverage, policy makers and public support. Reducing stigma is also one of pillar of the global action of GLCC (Global Lung Cancer Coalition) that in 2010, commissioned a research carried out by Ipsos MORI, which surveyed over 16,000 people in 16 countries, and found some evidence that sympathy levels were influenced by rates of smoking in each country. Between 10% and 29% of people admitted to feeling less sympathetic towards lung cancer sufferers because of its association with smoking. In 2017, GLCC commissioned a new multi-national study to Populus agency to undertake an online survey of adults across 25 countries for understanding attitudes towards lung cancer among the public. The results confirmed that 21% of people, out of least 1,000 adults per country still agree that they have less sympathy for people with lung cancer than other forms of cancer. In conclusion, in lung cancer there is a strong need to overcome many challenges to ensure that all of the patients may have the same hope and equal chances to fight against this disease. Lung cancer patients and caregivers still face a number of significant challenges and more has to be done to increase public awareness, to provide diagnostic tools and access to safe and effective treatments, to support efficient research and to combat the stigma. We've come a long way, and we certainly have a long way to go. We should work all together to effectively diminish the stigma that surrounds lung cancer and move forward in a positive way. References: 1) Lung cancer stigma, depression, and quality of life among ever and never smokers Janine K. Cataldo, Thierry M. Jahan, and Voranan L. Pongquan 2) Public attitudes about lung cancer: stigma, support, and predictors of support Jared Weiss,1Briana J Stephenson, Lloyd J Edwards, Maureen Rigney, and Amy Copeland 3) Lung cancer in never smokers: clinical epidemiology and environmental risk factors Jonathan M. Samet, Erika Avila-Tang, Paolo Boffetta, Lindsay M. Hannan, Susan Olivo-Marston, Michael J. Thun and Charles M. Rudin 4) Global Perception of Lung Cancer: An Ipsos MORI report for the Global Lung Cancer Coalition 5) Based on WHO data (2005) on prevalence of tobacco used by country (full data and further information can be found at http://www.who.int/mediacentre/factsheets/fs297/en/index.html

Keywords: lung cancer, stigma, awareness

MS04 JOINT GLCC/IASLC SESSION: EXPLORING HOT TOPICS FOR ADVOCATES
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

MS04.04 E-CIGARETTES - WHAT DO LUNG CANCER ADVOCATES NEED TO KNOW?

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Since the release of the IASLC Statement on e-cigarettes in 2014(1), opinion in relation to their role has become more not less polarised. E-cigarettes are not going away as an issue and advocates should be aware of the state of knowledge generally and of reputable information to which they can refer. Lung cancer advocates and patient supporters should have enough knowledge to assist individual patients to make an informed decision, to educate if that is their role and to advocate for the best care environment for those who have lung cancer or are at elevated risk for the development of lung cancer in the future. Some scenarios are worthy of consideration. The smoker who needs surgical resection. Smoking cessation is standard-of-care before thoracic surgery. Cessation reduces respiratory and cardiac morbidity and improves wound healing. Almost all smokers in this situation quit easily. Limited studies suggest an adverse effect of e-cigarettes on wound healing that is similar to smoking. More disturbingly, a bronchoscopy study found severe bronchial inflammation(2). There is sufficient, reasonable concern about impaired healing of the bronchial stump and compromised sputum clearance to explicitly recommend against the use of e-cigarettes before surgery even if smoking cessation is achieved. Patients with advanced lung cancer Advanced lung cancer is no longer rapidly and uniformly fatal. In the previous era, before recent treatment advances, with targeted small molecules and immunotherapy, it was difficult to show a survival advantage but continued smoking was associated with impaired quality of life and longer periods in hospital stay in cancer patients. There are no similar data for the complete substitution of smoking for e-cigarettes. Cessation should still be the aim. There are also practical problems with few health-care providers permitting e-cigarette use in enclosed spaces. NRT in contrast can be used in any location. Current smokers involved in lung cancer screening programs or with incidental nodules This is unquestionably a high value group for effective smoking cessation intervention. The considerations are those for the availability and recommendation for e-cigarettes in the community generally. *What is the benefit of e-cigarettes in promoting cessation* In its report, NASEM concluded that there is *limited evidence* that e-cigarettes are effective aids to promote smoking cessation, *moderate evidence* from randomized controlled trials that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine and that There is *insufficient evidence* from randomized controlled trials about the effectiveness of e-cigarettes as cessation aids compared with no treatment or FDA–approved smoking cessation treatments(3). Since that report was released, the largest RCT of e-cigarettes vs other treatment options published in NEJM found no benefit for e-cigarettes(4). *What are the harms especially long-term when long term use is encouraged* There are probably few harms of a short-course (6 weeks or less) of e-cigarette use but a statistically significant decline in lung function is detected at 3 months. Airway inflammation is also seen rapidly. Some Much attention has been focussed on the claim that e-cigarettes are 95% safer than smoking. This claim is supported by no evidence. It is true that tobacco smoke contains putative cancer-causing chemicals that are at low levels in e-cigarette vapour but the real situation is more complex. In the bronchoscopy study looking at airway protein levels, there was a cluster of adverse changes seen only with smoking, another seen with smoking and e-cigarette use and a third seen only with e-cigarette vapour(2). Whether these are from the base chemicals, nicotine or flavourings is uncertain. Long-term studies are few. Use of e-cigarettes for two years in a study sponsored by a tobacco-company subsidiary detected very rapid (5%/year) loss of lung function(6). There are no meaningful long-term studies for CV risk and smoking-related cancers. *What are the wider harms in promoting smoking in youths and young adults?* The NASEM report concludes that there is "*substantial evidence* that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults". Based on a meta-analysis, after adjustment for all reasonable confounders the risk is about 3-fold. It is inevitable that promotion amongst children and young adults will occur generating concerns as now seen with the JUUL product. Where is the role of e-cigarettes at the present time as a smoking cessation aid? E-cigarettes represent an intuitive solution for some smokers and there is a wealth of non-evidence-based information accessible on the internet. It is challenging for health advocates to accede to the use of a treatment that appears to be ineffective yet having this evidence-based approach is seen by many wedded to harm reduction as negative. Subject to the regulatory environment in each country, it may be reasonable to tolerate, under supervision, e-cigarette use where an individual will only attempt smoking cessation with e-cigarette use. This should be time-limited to perhaps 6-8 weeks with cessation of e-cigarettes if smoking continues; leading to a consideration of other options. If cessation is achieved, e-cigarette use should be withdrawn. There should be no compromise on the question of concurrent smoking/e-cigarette use that offers no health benefit and is unstable with many patients reverting to smoking. References: 1. Cummings KM, Dresler CM, Field JK et al. E-cigarettes and cancer patients. J Thorac Oncol. 2014; 9: 438-41 2. Ghosh A, Coakley RC, Mascenik T et al. Chronic E-Cigarette Exposure Alters the Human Bronchial Epithelial Proteome. Am Rev Resp Crit Care Med 2018; 198: 67-76. 3. National Academies of Sciences and Engineering and Medicine. Public health consequences of e-cigarettes. Washington. DC: The National Academies Press, 2018. 4. Halpern SD, Harhay MO, Saulsgiver K, et al. A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation. N Engl J Med 2018; 378:2302-2310 5. McNeill A, Brose LS, Calder R et al. Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England. London: Public Health England. 6. Walele T, Bush J, Koch A et al. Evaluation of the safety profile of an electronic vapour product used for two years by smokers in a real-life setting. Regulatory Toxicology and Pharmacology 2018; 92:226–238.

Keywords: smoking, electronic cigarettes

MS05 DIAGNOSTIC DILEMMA IN LUNG CANCER
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MS05.01 STAGING AND PATHOLOGY OF MULTIPLE LUNG NODULES

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The evaluation of patients with multiple lung nodules, which include situations of synchronous as well as metachronous presentations, has become an area of focused interest. This is in part due to valuable outcome datasets that have evolved in conjunction with staging during the adoption of the AJCC 7th and now 8th edition for lung tumor staging. It has become evident that the evaluation requires an integration of clinical, radiologic, pathologic and molecular data to produce the most precise stage to guide patient management. In earlier staging editions, multiple nodules were largely assumed to represent advanced disease; however, the survival data pointed to a more heterogeneous patient group. Differences in histology were cited as reasons for a conclusion of synchronous primary tumors, but these differences needed to

be relatively stark – for example adenocarcinoma versus squamous carcinoma. Three major shifts in knowledge impacted this field - 1) in pathology, movement away from the "lumping" of adenocarcinoma into mixed subtype with recognition of categories of early non-mucinous lepidic tumors 2) imaging advances, including the advent of successful lung cancer screening and imaging correlates of early lepidic pattern tumors and 3) the explosion of molecular pathology in lung cancer, particularly in adenocarcinoma. The result of these advances is a sophisticated approach that integrates these data into a stage as well as a conceptual conclusion regarding tumor biology and pathogenesis. Once lung malignancy is confirmed pathologically in a patient, the radiologist can use imaging features, especially ground glass nodules and the configuration of part solid nodules, to lead to clinically relevant conclusions about the likelihood of synchronous primaries when multiple nodules are encountered. In fact, other parameters, such as persistence, size, growth, imaging characteristics and evolution of a solid component in a part solid lesion may lead to relevant predictions in the absence of histologic confirmation. For the pathologist, non-mucinous lepidic tumors (adenocarcinoma-in-situ, minimally invasive adenocarcinoma and lepidic predominant adenocarcinoma) and the recognition of unusual patterns of invasive carcinoma, function well in the decision making process, as non-mucinous AIS, MIA and LPA are considered primary tumors and unusual patterns of invasive carcinoma (e.g. micropapillary or invasive mucinous) within the multifocal lesions are an important feature in recognizing intra-pulmonary metastasis. This area still requires refinement, especially among the LPA tumors and tumor in which common patterns such as acinar patterns predominate. Several molecular features can also be introduced into the discussion. Certain molecular events, such as particular patterns of copy number alterations, may occur in an individual patient's tumor but would otherwise be uncommon in that tumor type overall. Such a feature or set of features can assemble to form a molecular fingerprint of that primary tumor that is likely to be preserved in metastatic foci but unlikely to occur by chance in a new primary. In a similar fashion early molecular drivers of adenocarcinoma such as EGFR mutation and KRAS mutation, most often persist in metastatic foci. Discordance in such drivers can be valuable evidence to support synchronous primary carcinoma when used in conjunction with other information. Use of a wider set of mutational alterations may lead to more accurate information with regard to the likelihood of tumor evolution from one primary (i.e. intrapulmonary metastasis). After integration of these data, the authors of the AJCC staging 8th edition recognize 4 disease patterns with associated imaging, pathology, TNM classification and conceptual viewpoint. Second primary lung cancer (unrelated tumors), multifocal ground glass or lepidic nodules (separate tumors, despite common non-mucinous lepidic morphology), pneumonic-type adenocarcinoma (often mucinous, single tumor with diffuse pulmonary involvement), and separate tumor nodule (single tumor with intrapulmonary metastasis). While data already exist suggesting the staging, often downstaging, of multiple pulmonary carcinomas, widespread use of the AJCC 8th edition and accrual of cases, with survival information, that fit the above conceptual approach are needed to support its biological significance. References: Detterbeck FC et al. The IASLC Lung Cancer Staging Project: Background Data and Proposed Criteria to Distinguish Separate Primary Lung Cancers from Metastatic Foci in Patients with Two Lung Tumors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016 11(5):651-65. Detterbeck FC et al. The IASLC Lung Cancer Staging Project: Background Data and Proposals for the Application of TNM Staging Rules to Lung Cancer Presenting as Multiple Nodules with Ground Glass or Lepidic Features or a Pneumonic Type of Involvement in the Forthcoming Eighth Edition of the TNM Classification. J Thorac Oncol. 2016;11(5):666-80. Nicholson AG et al. Interobserver Variation among Pathologists and Refinement of Criteria in Distinguishing Separate Primary Tumors from Intrapulmonary Metastases in Lung. J Thorac Oncol. 2018;13(2):205-217. Girard N et al. Genomic and mutational profiling to assess clonal relationships between multiple non-small cell lung cancers. Clin Cancer Res. 2009;15(16):5184-90. Asmar et al, Use of Oncogenic Driver Mutations in Staging of Multiple Primary Lung Carcinomas: A Single-Center Experience. J Thorac Oncol. 2017;12(10):1524-1535.

MS05 DIAGNOSTIC DILEMMA IN LUNG CANCER
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MS05.02 DEFINING INVASION IN MINIMALLY INVASIVE ADENOCARCINOMA

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For pathological diagnosis of early invasive forms of adenocarcinoma, such as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and early-stage lepidic adenocarcinoma, morphological criteria for "invasion" were defined by the recent WHO classification in 2015. However, the inter-observer agreement rate has not been examined in detail. The IASLC pathology committee has initiated a trial of the diagnostic reproducibility of morphological criteria for invasive lung adenocarcinoma, especially the minimally invasive form. Although the study is still ongoing, several interesting results have emerged. First, although total tumor size showed a good k-ratio, the extents of tumor invasion calculated by the participants revealed a very low k-ratio. Secondly, although the areas determined by the participants were similar, the criteria upon which their judgements were based varied, and the same morphological features were not always employed. These results suggest that the morphological criteria used for defining tumor invasion are very difficult to generalize. On the other hand, driver oncogene mutations such as *EGFR*, *BRAF*, and *RAS*, and activated fusion proteins such as ALK, ROS, and RET have been detected in invasive adenocarcinoma. Except for EGFR mutation, however, other genetic alterations have not been detected in AIS. My group has been investigating the expression and genetic profiles of AIS and early but invasive lung adenocarcinoma using a molecular biological approach, and characterized several genomic and epigenetic abnormalities in these tumors. Among them, stratifin (SFN) appears to be a promising biomarker of tumor malignancy at the early stage, its overexpression being very specific to the stage when AIS progresses to early invasive adenocarcinoma (Fig. 1). SFN, a member of the 14-3-3 protein family (14-3-3 sigma), is completely suppressed epigenetically in normal lung tissue. However, during the course of malignant progression, its promoter region becomes di-methylated and expression of SFN increases. SFN binds specifically to SKP1 and inhibits the function of E3 ubiquitin ligase, thus preserving the functions of specific proliferation-associated proteins such as p-cyclin E1 and p-c-Jun. Abnormally high expression of SFN is thought to be a biological marker of lung adenocarcinoma invasion. Interestingly, several inhibitors of SFN-SKP1 binding are very effective for suppressing tumor growth in nude mice. Another interesting biomarker of early adenocarcinoma is epithelial cell transforming sequence 2 (ECT2), a guanine nucleotide exchange factor physiologically localized in the nucleus and functioning to regulate cytokinesis. ECT2 is also localized in the cytoplasm of cancer cells. Aberrant cytoplasmic expression of ECT2 is thought to drive tumor growth and invasion. Cytoplasmic expression of ECT2 in 167 lung adenocarcinomas was evaluated by immunohistochemistry and its clinical significance was examined (Fig. 2). Cytoplasmic expression of ECT2 was found to increase during cancer progression. Cytoplasmic positivity for ECT2 was associated with a poor outcome in terms of both disease-free and overall survival (both $P<0.001$), and was an independent prognostic factor related to overall survival ($P= 0.025$). Reference Kosibaty Z, Dai T, Murata Y, Minami Y, Kano J, Nakagawa T, Sakashita S, Noguchi M. Cytoplasmic expression of epithelial cell transforming sequence 2 (ECT2) in lung adenocarcinoma and its implication for malignant progression. *Lab Invest*, 2018 (in press) Kim Y, Shiba-Ishii A, Nakagawa T, Iemura SI, Natsume T, Nakano N, Matsuoka R, Sakashita S, Lee S, Kawaguchi A, Sato Y, Noguchi M. Stratifin regulates stabilization of receptor tyrosine kinases via interaction with ubiquitin-specific protease 8 in lung adenocarcinoma. *Oncogene*, 2018. [Epub ahead of print] Shiba-Ishii A , YunJung Kim, Toshihiro Shiozawa, Shinji Iyama, Kaishi Satomi, Junko Kano, Shingo Sakashita, Yukio Morishita,Masayuki Noguchi. Stratifin accelerates progression of lung adenocarcinoma at an early stage. *Molecular Cancer, 2015,*14:142. Murata Y, Minami Y, Iwakawa R, Yokota J, Usui S, Tsuta K, Shiraishi K, Sakashita S, Satomi K, Iijima T, Noguchi M.ECT2 amplification and overexpression as a new prognostic biomarker for early-stage lung adenocarcinoma. *Cancer Sci*, 2014,105(4):490-7. Figure 1

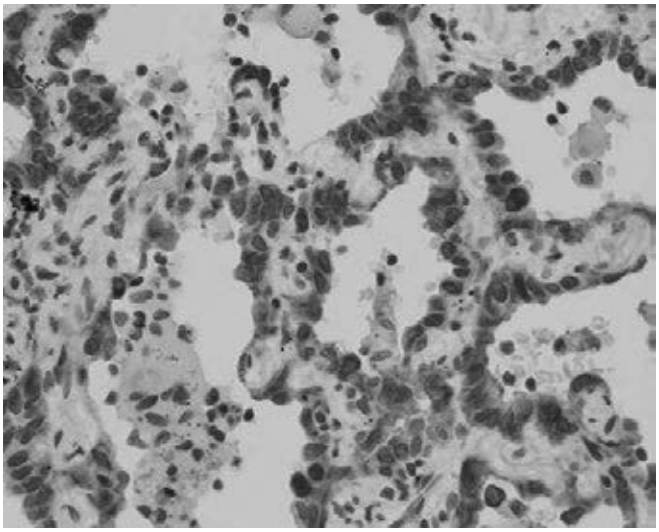
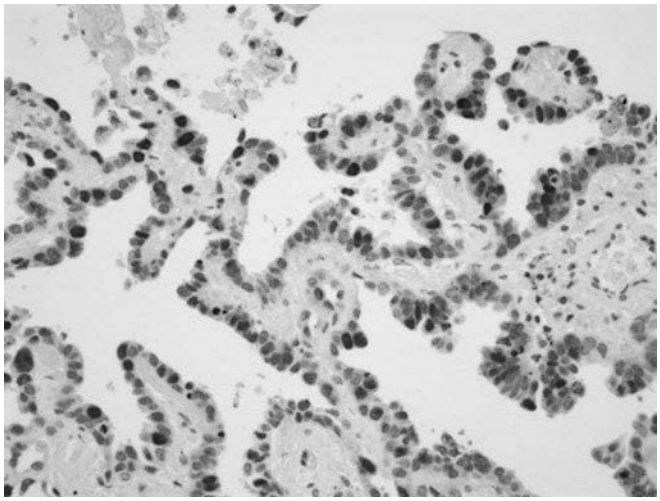


Figure 2



Keywords: biomarker, SFN, ECT2

MS05 DIAGNOSTIC DILEMMA IN LUNG CANCER
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MS05.03 TUMOR HETEROGENEITY IN LUNG CANCER

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Lung cancer are composed of populations of cells with distinct molecular genetics , epigenetics and phenotypic features : this phenomenon called intra-tumor heterogeneity (ITH) adds complexity to the already well known inter-tumor heterogeneity which is responsible for the huge number of types and subtypes in each main histological category type as defined in the 2015 WHO classification. Intra-tumor heterogeneity impacts on tumor biopsy strategy, characterization of actionable targets , treatment planning and drug resistance. Tumor types which display the highest histological heterogeneity are adenocarcinoma (ADC) , adenosquamous carcinoma, pleomorphic carcinoma and the high grade neuroendocrine tumor small cell lung carcinoma (SCLC) and large cell neuroendocrine(LCNEC) when combined . However intra-tumor heterogeneity is not restricted to histology since molecular heterogeneity at the levels of genetics (mutations , copy number alterations), DNA methylation , mRNA expression profiling and immune context /PDL1 expression show high intra-tumor variability in most conventional lung tumor histologies. Capturing the full molecular landscape of each tumor and choosing the right target is indeed a crucial clinical dilemma facing intra-tumor heterogeneity . Although histological main type correlates with characteristic genomics (1) , histological heterogeneity relies more on transcriptomic expressions profiles and functional pathways (embryonal, stemcellness, EMT .) than on driver mutations , challenging the mechanisms of tumor plasticity and resistance.(2) A -Histological Heterogeneity 1-Adenocarcinoma (60% of lung cancer) present with up to 5 histological patterns declined as predominant or not , lepidic, papillary, acinar/cribriform, micropapillary and solid (WHO 2015) requiring resection samples to allow an accurate diagnosis of combinations. Advantages derive from this complexity: some patterns have high prognostic value : high grade patterns solid , micropapillary and cribriform (even not predominant >= 5%) are independent determinants of short survival, whereas the pure lepidic pattern (AIS) or minimally invasise MIA predict 100% 5 years survival and predominant lepidic invasive ADC have statistically better prognosis than all other ADC .Spatial heterogeneity is well conserved temporally allowing discrimination of multiple primaries versus lung metastases when different or same combinations are compared . Disadvantage resides in interpretation of small samples showing only a part of the patterns . At molecular levels (genomics, expression profiling, immune context) adenocarcinoma show extended intra-tumor heterogeneity. Unfortunately each pattern does no predict specific driver mutations (EGFR,KRAS, BRAF, gene amplification) . 2- Adenosquamous carcinoma (2% of lung cancer) is typically composed of both squamous cell carcinoma (SQCC) and adenocarcinoma (ADC) components (at least 10%). Both components might be morphologically obvious (ADC pattern, keratinizing SQCC) or one is obvious and IHC is necessary to identify the other as SQCC (P40+) or ADC (TTF1) .Diagnostic challenges include size of the sample, one component missing on small sample with its associated mutations ,and variable components in primary and metastases. Molecular features are characteristic of one or both components: 56% tyrosine kinase mutations (32% EGFR; 11% KRAS;1-4% others) in ADC or in both ,FGFR1 amplification in SQCC. Dual histospecific mutations indicate common cell of origin with early clonal trunk mutation maintained at progression (2) 3-Pleiomorphic carcinoma : (0.5% of lung cancer) is the most heterogeneous entity , composed of one or several components of NSCLC (ADC, SQCC, large cell) with at least 10% of spindle or giant cell carcinoma a clear feature of EMT (epithelial mesenchymal transition). Diagnosis requires resection sample. In undifferentiated areas IHC (TTF1/P40) will identify the NSCLC component and predict mutations. Mutations regionality is predicted and parallels histological components, if ADC (Kras, EGFR,BRAF Met ,ALK rearrangement) if SQCC FGFR1 amplification. The most frequent MET exon 14 skipping mutation (20%) is heterogeneously distributed. Tumors with SMARC4 mutations described also in adenocarcinoma with obvious EMT transformation and BRG1 negative IH are now considered as pleomorphic carcinoma. 4.Combined high grade tumors : Combined SCLC small cell Lung Carcinoma (SCLC) and combined Large cell neuroendocrine carcinoma LCNEC account for 20% of each in resected samples ,less readily detectable on small samples ,10% SCLC or LCNEC are sufficient. The genetic alterations are not therapeutically actionable yet, excepted in trials (DLL3) .Occurrence of mutations in the non- neuroendocrine component deserve recognition since it can induce drug resistance and transdifferentiation. Transformation of SCLC to NSCLC has been reported after cytotoxic SCLC chemotherapy (E. Brambilla JCO 1991) suggesting intra-tumor heterogeneity or cell plasticity under therapeutic pressure, and a common initiating stem cell between SCLC and NSCLC . Inter-tumor heterogeneity at molecular level is better documented than is intra-tumor heterogeneity, in absence of multi-region sequencing. NOTCH and DDL3 therapeutic targets shows both inter and intra-tumor heterogeneity(7) B-Temporal intra-tumor heterogeneity Genetic dynamics characterizes tumor progression , well studied during ADC progression from AAH to invasive ADC. The conservation of driver clonal but not subclonal mutations occur in metastases *vs* primary. Transdifferentiation is a typical exemple of temporal heterogeneity where a tumor treated ,more rarely spontaneously, transforms in another tumor type , SCLC to NSCLC , EGFR mutant adenocarcinoma to SQC or SCLC or pleiomorphic carcinoma with EMT, showing that tumor plasticity conferred by EMT results in temporal intra-tumor heterogeneity with transdifferentition (2) C-Spatial intra tumor heterogeneity across histology All studies (2-3) establish the concept of trunk and branches in the phylogenetic tree , the clonal trunk mutations are present in all regions (EGFR MET BRAF TP53 ALK ...)in 75% of tumors and additional variant subclonal mutations in some but not all regions. Lessons : -One biopsy may not capture the extent of landscape ITH but trunk mutation are homogeneously distributed whereas branched mutations are heterogeneouly distributed . Cell free DNA overtime better capture genetic landscape. References: 1-A genomic-based classification of human lung tumors, Sci Transl. 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Keywords: Lung cancer , intratumoral heterogeneity, pathology and genetics

MS05 DIAGNOSTIC DILEMMA IN LUNG CANCER
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MS05.04 DIAGNOSIS AND CLASSIFICATION IN BIOPSIES

A. Moreira

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In the last decade, significant progress has been made in the field of thoracic oncology, mostly in the management of patients with non-small cell carcinoma (NSCLC). The determination of subtypes of NSCLC is now directly linked with options of chemotherapy regimens, and further screening for targetable molecular alterations. In the 2015 W.H.O Classification of Lung cancer, the importance of small biopsies has been highlight as well as the use of immunohistochemical stains as an ancillary test to separate adenocarcinoma from squamous cell carcinomas. Despite the use of IHC, the classification of NSCLC remain based on histologic features and IHC is recommended in cases with no clear evidence of differentiation between adenocarcinoma and squamous cell carcinoma. It is important to notice that the diagnosis of Large Cell Carcinoma is not recommended in small biopsy specimens. For the histological diagnosis of adenocarcinoma, the following features need to be presence in the biopsy: acinar, papillary, micropapillary and lepidic patterns, and for the histological diagnosis of squamous cell carcinoma, the presence of

keratinization and intracellular bridges must be presence. Therefore, in a biopsy with solid growth pattern and no evidence of keratinization, the use of IHC is recommended. The use of IHC improved diagnostic accuracy in the lung carcinoma classification, but the interpretation can be challenging and the pathologists must be aware of many interpretation pitfalls that can involve antibody clones, interpretation of the staining pattern and when to add more stains to the panels. When confronted with a tumor of likely lung origin for which the main question is subtyping of adenocarcinoma versus squamous carcinoma, the recommendation is to use a limited panel that includes TTF1 and p40. The use of this panel can classify most tumors and saves tissue for biomarker testing. Napsin-A can be added to the panel in challenging cases but there is no clear evidence that the latter marker is superior to TTF-1. Differences in sensitivity and specificity for napsin-A depends on whether a monoclonal or polyclonal antibody is used. Keratin 7 is not useful to separate adenocarcinoma from Squamous cell carcinoma. According to the classification, a NSCLC with immunohistochemical evidence of adenocarcinoma differentiation (any nuclear TTF-1 positivity) should be diagnosed as NSCLC-favor adenocarcinoma, whereas a tumor with evidence of squamous differentiation (strong and diffuse p40 positivity) should be classified as NSCLC, favor squamous cell carcinoma. In tumors with inconclusive immunoprofile, the best diagnostic term is NSCLC-NOS. For tumors with double positivity (TTF1/p40), it is important to remember that double positivity in the same cells does not define an adenosquamous carcinoma. For the diagnosis of adenosquamous carcinoma each marker should be seen in different components/areas of the tumor. Double staining is seen in adenocarcinomas or in NSCLC-Nos that carries mutations similar to adenocarcinoma. For double negative tumors (TTF-1 neg/p40 neg) in patients with no other history of malignancy, the diagnosis of NSCLC-NOS can be accepted because approximately 20-30% of adenocarcinoma of the lung are negative for these markers. If clinical history is not known, however, other stains should be added to the panel to rule out metastatic disease. One important marker is keratin, because metastatic melanomas or other non-epithelial tumors may mimic carcinoma, especially in small biopsy samples. For patients with known history of other malignancies, histological comparison with prior tumors should be pursued, targeted IHC with organ specific markers (PAX-8, GATA-3, NKX3.1, etc.) provides strong support to this interpretation, particularly when previous materials are unavailable for review. The current WHO classification recommends that neuroendocrine (NE) markers should be performed only when NE morphologic features are present. IHC positivity for NE markers alone is not diagnostic of a NE tumor because positivity for NE markers may be encountered in approximately 10-30% of adenocarcinomas. A panel of chromogranin A, synaptophysin and CD56 is the best combination for the diagnosis of NE tumors. There is no consensus on how many markers should be used for the diagnosis of NE, most cases of NE tumors are positive for ≥2 out of the 3 NE markers. Positivity for at least one NE marker is necessary for the diagnosis of Large Cell Neuroendocrine Carcinoma (LCNEC) in association with histological features (chromatin pattern, palisading etc). The diagnosis of LCNEC in a biopsy or cytology specimen is not recommended but can be suggested if a combination of histological features and NE markers positivity is encountered. A proliferative marker such as Ki-67 is very useful for the classification of NE tumors in small biopsy specimens, especially in samples with significant crush artifact. In small biopsies Ki-67 stains can separate a low-grade NE tumor (carcinoid) from a high grade tumor such as small cell carcinoma. Ki-67 is not recommended in the classification of typical from atypical carcinoid in excision specimens. In cytology samples, the marker does not work well in alcohol-fixed specimen and can lead to misclassification of NE tumors. Suggested reading: Sauter JL, Grogg KL, Vrana JA, et al. Young investigator challenge: Validation and optimization of immunohistochemistry protocols for use on cellient cell block specimens. *Cancer Cytopathol* 2016;124:89-100 Rekhtman N, Kazi S. Nonspecific reactivity of polyclonal napsin a antibody in mucinous adenocarcinomas of various sites: a word of caution. *Arch Pathol Lab Med* 2015;139:434-436. Rekhtman N, Ang DC, Sima CS, et al. 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Keywords: Histological classification, immunohistochemical, biopsy

MS06 PRACTICAL ISSUES IN THE MANAGEMENT OF OLIGOMETASTATIC NSCLC
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MS06.02 THE ROLE OF INTERVENTIONAL PULMONOLOGY AND RADIOLOGY

K. Fong

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The Role of Pulmonology and Interventional Radiology in the Management of Oligometastatic NSCLC Oligometastatic disease is a difficult management issue when encountered in NSCLC. Often defined as low metastatic burden and limited organ involvement disease, with clinical impact perceived as between truly localised potentially curable disease and a extensive incurable metastatic tumour, therefore with major implication for the patient in terms of treatment, with the potential to pivot the decision making from palliative to curative intent. In addition the site(s) of oligometastatic disease is heterogenous with potential to affect any site in the body, both intra and extra- thoracic, thus requiring a truly multidisciplinary approach to its management. It is essential to make an accurate diagnosis, to consider synchronous cancers and to rule out more extensive metastatic disease given the differing management strategies required. For the Pulmonologist and Interventional Radiologist, for intrathoracic oligometastatic disease, the issues are the diagnostic challenges and potential therapeutics. The use of image guided trans thoracic needle biopsy has long been used effectively by Interventional Radiology for the pathological diagnosis of suspected lesions. With modern endobronchial ultrasound, Pulmonologists are able to contribute more by accessing central and peripheral lung lesions by navigation and guided bronchoscopy e.g. ultrasound guided, electromagnetic navigation and transparenchymal approaches. With the increasing use of molecular techniques to distinguish cancers even of the same morphological appearance, such diagnostic approaches are of increasing clinical utility. For intrathoracic therapeutics, local Interventional Radiology ablative techniques such as radiofrequency ablation has long been used, with microwave ablation increasingly popular. In parallel with diagnostics, emerging Pulmonology techniques are also researching the potential application of these techniques applied endobronchially in addition to new modalities such as steam ablation. Interventional Radiologists also have a useful role to play in the management of extra-thoracic oligometastatic disease, as techniques such as radiofrequency and microwave ablation can be used such as for liver lesions. This session will review the emerging data for the key role of Pulmonology and Interventional Radiology in the Management of Oligometastatic NSCLC.

Keywords: Pulmonology, Interventional Radiology, Oligometastatic NSCLC

MS06 PRACTICAL ISSUES IN THE MANAGEMENT OF OLIGOMETASTATIC NSCLC
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MS06.03 THE ROLE OF SURGICAL RESECTION

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Lung cancer is an aggressive malignancy with low (< 10%) 5-year survival rates when metastases appear. Historically, surgical resection in metastatic setting has not been beneficial in term of survival; this was especially true when options for effective systemic therapy were limited. It is now recognized that up 50% of patients who presents with metastatic NSCLC have a limited (up to 5) number of metastases. Common sites of metastases include brain, lungs, adrenal glands, bones, or liver. In appropriately selected patients, surgical resection in metastatic lung cancer may be considered for the control of primary tumor, regional nodal disease, and metastases present within the same surgical field (example: metastases in ipsilateral ribs, or another lobe in the same lung as primary tumor). Surgical resection of selected extra-thoracic metastases is also possible; however, radiation is more commonly employed in those circumstances. The main goal of surgery in oligometastatic setting is to achieve complete disease control. Careful patient selection must account for the extent and the location of primary tumor and nodal disease, physiologic status and reserve of the patient, tumor histology, biomarkers, synchronous or meta-chronous presence of metastases and number of metastases, previous therapies and planned post-surgical systemic or other local therapies. Invasive mediastinal staging with either mediastinoscopy or endobronchial ultrasound is of utmost importance prior to proceeding with surgery. Long-term outcomes with positive ipsilateral mediastinal N2 or contralateral N3 lymph nodes are poor as compared to N0 or N1 nodal status; N2 and N3 disease should be considered contraindication for surgical therapy outside of a clinical trial. Lobectomy with mediastinal node dissection is a preferred procedure for primary tumor in oligometastatic circumstances. Pneumonectomy, especially on the right side should be avoided, and its need should be

regarded as a relative contra-indication. If brain metastases are present, they should be treated first; other metastatic sites maybe addressed based on symptoms. Commonly, systemic platinum-based chemotherapy has been administered as the 1st line therapy for 3-4 cycles to sort out the cancer biology and response to chemotherapy. Stable or improved disease following chemotherapy makes proceeding with surgical resection of primary tumor and control of oligometastases reasonable. However, this paradigm continues to evolve in the era of immunotherapy and targeted therapy. There are a number of advantages to surgical resection of lung cancer in oligometastatic setting, as compared to other local modalities. Complete resection provides the best chance for prolonged local and regional disease control. It hypothetically removes all or at least the majority of cancer clones, it allows for detailed pathological analysis of the tumor and lymph nodes, and it provides adequate tissue for translational studies or personalized experimental treatment approaches. With current minimally invasive approaches such as video assisted or robotic assisted thoracic surgery recovery from surgical treatment of lung cancer can be expeditious. With the use of enhanced recovery pathways, even recovery after thoracotomy mimics recovery after minimally invasive thoracic surgery. Potential disadvantage of surgical therapy in oligometastatic lung cancer is the risk of post-operative cardiac or pulmonary complications, resolution of which may require time and may delay other necessary therapy. This again highlights the importance of patient selection for surgical therapy. *Surgical Resection of Oligometastatic Lung Cancer in the Era of Targeted Therapy and Immunotherapy.* Within the last year, immunotherapy has become the frontline treatment modality for metastatic lung cancer. Response rates, durability of responses, and toxicity profiles with immunotherapy are all better than with chemotherapy. Although imperfect, PD-L1 expression and tumor mutation burden serve as predictive biomarkers for immunotherapy. Many studies of combined chemo-immune regimens, or combination immune regimens are underway. These results are encouraging, however, as we improve systemic disease control, loco-regional lung cancer control will become even more important. The role and timing of local treatments following immunotherapy or targeted therapy in oligometastatic setting are currently under study. While there are reports of radiation therapy potentiating immunotherapy, evidence is not conclusive and biomarkers are still under investigation. Surgical therapy and radiation therapy should be considered complementary modalities in oligometastatic lung cancer. If lobectomy is possible for primary disease control in an acceptable-risk surgical candidate, it should not be discarded as an option over radiation. Considering current operative experience following prolonged immunotherapy, it is hypothesized that salvage surgical resections for local recurrence following immune-radio therapy may be difficult and may convert possible routine early lobectomy to an eventual salvage pneumonectomy. As the therapeutic options for oligometastastic lung cancer continue to evolve with much improved systemic options, effective local and regional therapy will become more important. Novel surgical techniques and enhanced recovery pathways have decreased the morbidity and sped up patients' surgical recovery. Surgical resection should therefore continue to play a role in the multi-modality setting for oligometastatic lung cancer in appropriately selected patients. References: Gomez DR, Blumenschein GR Jr, Lee JJ, Hernandez M, Ye R, Camidge DR, Doebele RC, Skoulidis F, Gaspar LE, Gibbons DL, Karam JA, Kavanagh BD, Tang C, Komaki R, Louie AV, Palma DA, Tsao AS, Sepesi B, William WN, Zhang J, Shi Q, Wang XS, Swisher SG, Heymach JV. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol. 2016 Dec;17(12):1672-1682. doi: 10.1016/S1470-2045(16)30532-0. Epub 2016 Oct 24. Patrini D, Panagiotopoulos N, Bedetti B, Mitsos S, Crisci R, Solli P, Bertolaccini L, Scarci M. Surgical approach in oligometastatic non-small cell lung cancer. Ann Transl Med. 2018 Mar;6(5):93. doi: 10.21037/atm.2018.02.16. Review. Stephens SJ, Moravan MJ, Salama JK. Managing Patients With Oligometastatic Non-Small-Cell Lung Cancer. J Oncol Pract. 2018 Jan;14(1):23-31.

Keywords: Surgery, Oligometastases, lung cancer

MS06 PRACTICAL ISSUES IN THE MANAGEMENT OF OLIGOMETASTATIC NSCLC
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MS06.04 SYSTEMIC THERAPY FOR OLIGOMETS: BEFORE, DURING, OR AFTER LOCAL THERAPIES?

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Oligometastatic disease reflecting the concept of limited metastatic spread may be discussed in the setting of the sites of disease at diagnosis of stage IV disease. However, an analogous situation may also occur at progression on a therapy controlling all other sites of disease – so called oligoprogressive disease. Both may be considered for local ablative therapies (usually radiation or surgery, but also some other techniques such as radiofrequency ablation). When considering systemic therapy this may be before the local therapy as induction treatment for initial oligometastatic disease; as part of the radical local therapy (for example, combination chemoradiation therapy); or as maintenance therapy after the local therapy. The latter could reflect continuation of a tyrosine kinase inhibitor, pemetrexed or bevacizumab and could also apply to the oligoprogressive scenario. The issues to address are the adequacy of assessing oligometastatic disease at the time local therapy is considered; the details that appropriately define oligometastatic or oligoprogressive disease suitable for local therapy; and the potential for a direct interaction with the local therapy.

MS07 ANTIBODY-DRUG CONJUGATES IN ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MS07.01 BASIC SCIENCE

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While in some cases antibodies that specifically bind tumor surface antigens can have therapeutic effects, many unmodified (naked) antibodies lack anti-cancer activity. Conjugation to cytotoxic drugs, radionuclides, or toxins can expand the utility of monoclonal antibodies and improve their potency. In this way, antibodies are employed as a means to target and deliver a toxic payload to the selected tissue. Factors critical to the success of antibody drug conjugates include the target antigen, antibody, linker, and payload. The target antigen should be overexpressed in the tumor relative to healthy tissue. The antibody should have high affinity and avidity for the targeted tumor antigen. The linker should be stable in circulation but must efficiently release the payload after internalization within the cancer cell. The payload should be a highly potent (picomolar range) cytotoxic agent with efficacy against the cancer under treatment, with a reproducible and optimal drug-to-antibody ratio (usually 3-4 drug molecules per antibody molecule), that does not meaningfully compromise the antibody's biophysical and pharmacokinetic properties. The steps entailed in the mechanism of antibody-drug conjugate action include: (a) antigen binding; (b) antigen-antibody-drug conjugate complex internalization into endosomal vesicles; (c) processing along the endosomal-lysosomal pathway; (d) degradation in this acidic and proteolytic-rich environment; (e) intracellular release of cytotoxic compound. Antibody-drug conjugates may also retain antibody interactions with host immune effector functions, including antibody-dependent cellular cytotoxicity (ADCC). Mechanisms of resistance include (a) reduced target gene expression or presence of increased antigen mutations resulting in reduced target antigen on cell surface; (b) reduced antibody-drug conjugate internalization due to reduced cell surface trafficking or recycling; (c) multidrug resistance ransporter efflux out of the targeted cell. In addition to differential expression on tumor cells, antibody-drug conjugate target antigens need to (1) have an extracellular epitope amenable to specific antibody binding, and (2) be able to undergo internalization via receptor-mediated endocytosis into target cells, where the drug payload can be released. High-level expression is advantageous but not necessary. The higher the cell surface density of the target antigen, the more antibody-drug conjugate can be taken up and metabolized by the cell, to release the active cytotoxic agent. Rapid uptake of antibody-drug conjugate not only enhances efficacy, but also reduces opportunity for extracellular payload release. Antigens that are shed should be avoided. Antibody-drug conjugate technology has improved considerably in recent years. The employed antibodies are now chimeric, humanized, or fully human, and therefore less immunogenic than early murine antibodies. Efficient linkers (disulfide, dipeptide, hydrazine) have improved stability in circulation as well as better release of active drug within the tumor cell. Finally, highly potent agents with IC_{50} in the subnanomolar range (maytansine derivatives [DM1, DM4], auristatin [MMAE, MMAF], both of which are microtubule disrupting agents) have replaced conventional chemotherapy drugs such as doxorubicin, vinca alkaloids, and methotrexate. Despite the targeted nature of antibody-drug conjugates, toxicities may occur through multiple mechanisms: (1) Non-specific systemic release of the cytotoxic drug payload; (2) Non-selective cytoxicity of target-negative cells in proximity to target-positive cells (bystander effect); (3) internalization of the antibody-drug conjugate by target-negative cells. Prior experience has shown that unrecognized expression of target antigen on healthy tissue can result in profound toxicities: Lewis^{y} antigen (gastric mucosaàhemorrhagic gastritis); CD446v6 (deep layers of skinàfatal exfoliation); CA9 (intestinal mucosaàfatal gastrointestinal toxicity). Further complicating the development of antibody-drug conjugates, preclinical models may not adequately predict clinical activity and tolerability. In mouse models, the target antigen is not commonly expressed in host tissues, resulting in misleadingly favorable preclinical activity. As evidence of the inherent challenges facing antibody-drug conjugates, only two have been approved by the U.S. Food and Drug Administration: ado-trastuzumab

emtansine (anti-HER2; for HER2-positive breast cancer) and brentuximab vedotin (anti-CD30; for Hodgkin's lymphoma and anaplastic large-cell lymphoma). Target antigens relevant to non-small cell lung cancer under investigation include mesothelin (antetumab ravtansine), folate receptor (mirvetuximab soravtansine), sodium-dependent phosphate transporter (NaPi2b) (lifatuzumab vedotin; DNIB0600A), glycoprotein nonmetastatic B (gpNMB; osteoactivin) (glemtumumab vedotin), and epidermal growth factor receptor (depatuxizumab mafodotin), Perhaps the most developed antibody-drug conjugate in thoracic oncology, rovalpituzumab tersirine (Rova-T) targets delta-like ligand 3 (DLL3), which is highly expressed in approximately two-thirds of small cell lung cancer, but not NSCLC. Ultimately, several factors may influence the efficacy of an antibody-drug conjugate, among them target expression, sensitivity to the payload, and aspects of target biology that may impact internalization and intracellular trafficking. Revisiting longstanding principles of cytotoxic therapy may improve the performance of antibody-drug conjugates. These principles include the importance of combination therapies and the recognition that not all tumors are sensitive to microtubule-disrupting agents.

Keywords: Targeted therapy, personalized medicine, biologic therapy

MS07.03 CLINICAL DATA

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Antibody drug conjugates (ADC's) are currently being developed for several thoracic malignancies, and preliminary studies have revealed activity in patients with progressive disease after standard therapy for non-small cell lung cancer (NSCLC). Sacituzumab govitecan targets the Trop-2 which is overexpressed on many epithelial cancers compared to normal tissues and the antibody is bound to SN-38 which is the active metabolite of irinotecan.[1,2] .A single arm phase 2 trial (n=54) investigated in patients with NSCLC with disease progression after at least one line of therapy. The ORR was 17%, median PFS was 5.2 months, and median OS was 9.5 months. The grade ≥ 3 adverse events observed were neutropenia, anemia, diarrhea, nausea, and fatigue. Trop-2 staining was not associated with benefit from therapy and the majority of patients had high Trop-2 staining. Telisotuzumab vedotin (ABBV-399) targets the c-Met protein and is conjugated to monomethyl auristatin E, a microtubule inhibitor.[3] A phase 1 trial in metastatic solids tumor included an expansion cohort of in patients with NSCLC who were c-Met + (defined as IHC H-score of ≥ 150). An objective response was observed in three of 16 patients (18.8%) with c-Met positive NSCLC, and at week 12 six of 16 (37.5%) experienced disease control The treatment related adverse events observed (at all dose levels) were fatigue, nausea, neuropathy, decreased appetite, vomiting, and hypoalbuminemia. No responses were observed among patients with c-Met negative tumors. Ado-trastuzumab emtansine (T-DM1) is an ADC that uses the trastuzumab monoclonal antibody which targets the HER2 protein and delivers the maytansinoid antimicrotubule agent DM1. A single arm phase 2 trial investigated this agent in patients with HER2 positive NSCLC (defined as IHC score of 3+, IHC score or 2+ and FISH positivity, or *HER2* mutation).[4] Of the 15 patients enrolled 1 patient experienced a partial response (6.7%), the median PFS was 2.0 months, and median OS was 10.9 months. This study was terminated at the interim analysis since it did not meet the predefined efficacy criteria to proceed to the second stage. A phase 2 basket trial investigated T-DM1 in patients with *HER2* mutant or amplified NSCLC.[5] In the HER2 mutant cohort the ORR was 44% (8 of 18), median PFS was 5 months, and median OS was 11 months. In the HER amplified cohort the ORR was 50% (3 of 6), and the median PFS was 6 months, and the median OS was 12 months. The *HER2* mutant cohort met the study's primary end-point and the HER2 amplified cohort was expanded as per the Simon two-stage design. A phase 2 study investigated T-DM1 in patients with IHC 2+ or 3+ NSCLC, and each cohort was analyzed independently.[6] Among the 29 patients enrolled on the IHC 2+ cohort no responses were observed, and the ORR in the IHC 3+ cohort was 20% (4 of 20). In the IHC 2+ cohort the median PFS and OS was 2.6 and 12.2 months respectively, and in the IHC 3+ cohort the median PFS and OS was 2.7 and 12.1 months, respectively. The grade ≥ 3 adverse events observed have been neutropenia, thrombocytopenia, anemia, fatigue, dyspnea, and hepatotoxicity, and have been consistent with the adverse events observed in breast cancer. These studies have revealed preliminary activity of ADC's in patients NSCLC with disease progression after standard therapies. The rate of adverse events to the ADC's are manageable. Refinement in the biomarker selection of patients for these therapies may improve the efficacy. 1. Heist RS, Guarino MJ, Masters G, et al. Therapy of Advanced Non-Small-Cell Lung Cancer With an SN-38-Anti-Trop-2 Drug Conjugate, Sacituzumab Govitecan. *J Clin Oncol.* 2017;35(24):2790-2797. 2. Gray JE, Heist RS, Starodub AN, et al. Therapy of Small Cell Lung Cancer (SCLC) with a Topoisomerase-I-inhibiting Antibody-Drug Conjugate (ADC) Targeting Trop-2, Sacituzumab Govitecan. *Clin Cancer Res.* 2017;23(19):5711-5719. 3. Angevin E, Kelly K, Heist R, et al. First-in-human phase 1, dose-escalation and -expansion study of ABBV-399, an antibody-drug conjugate (ADC) targeting c-Met, in patients (pts) with advanced solid tumors. *Annals of Oncology.* 2016;27(suppl_6):371P-371P. 4. Hotta K, Aoe K, Kozuki T, et al. A Phase II Study of Trastuzumab Emtansine in HER2-Positive Non-Small Cell Lung Cancer. *J Thorac Oncol.* 2018;13(2):273-279. 5. Li BT, Shen R, Buonocore D, et al. Phase 2 Basket Trial of Ado-Trastuzumab Emtansine in Patients with HER2 Mutant or Amplified Lung Cancers. *WCLC 2017: 18th World Conference on Lung Cancer in Yokohama, Japan. October 15-18.* 2017. 6. Stinchcombe T, Stahel RA, Bubendorf L, et al. Efficacy, safety, and biomarker results of trastuzumab emtansine (T-DM1) in patients (pts) with previously treated HER2-overexpressing locally advanced or metastatic non-small cell lung cancer (mNSCLC). *Journal of Clinical Oncology.* 2017;35(15_suppl):8509-8509.

Keywords: non-small cell lung cancer, antibody drug conjugates, clinical trials

MS07 ANTIBODY-DRUG CONJUGATES IN ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MS07.04 FUTURE DIRECTIONS

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Despite the success achieved by molecularly targeted agents in oncogene-addicted NSCLC over the past decade, patients inevitably develop acquired resistance with subsequent disease progression. Moreover, most lung tumors still do not present actionable targets derived by driver genetic alterations. To circumvent these issues, alternative strategies to target tumor cells have been studied. Antibody drugs conjugates (ADC) represent a novel class of anti-cancer treatment designed with the aim to combine the cytotoxic activity of chemotherapeutics with the selectivity of target agents, thus increasing the therapeutic interval of available compounds. The paradigm of ADCs is to convey cytotoxicity selectively into tumor cells, by way of a monoclonal antibody (MoAb) bound to cytotoxic chemicals via synthetic linkers. This complex is able to recognize tumor antigens which serve as Trojan horse for ADC internalization into cancer cell. To date, two ADCs have entered clinical practice, brentuximab vedotin for hematological malignancies and trastuzumab emtansine in advanced breast cancer overexpressing human epidermal growth factor receptor 2 (HER2) [1]. In the field of thoracic malignancies, ADC research has focused on rarer "orphan" diseases, for which neither target therapies nor valuable second-line treatment options are available. In fact, the two ADCs currently underway in most advanced phases of clinical trials are rovalpituzumab tesirine for SCLC and anetumab emtansine for unresectable mesothelioma; however, with suboptimal early results [2;3]. In NSCLC, no ADC has been experimented yet in phase III trials. However, several basket trials are currently evaluating anti-cancer activity and safety of ADCs mostly targeting HER2, Trop2 and NaPi2b, among others [4-6]. In NSCLC treatment, as well as in other malignancies, ADC development has been limited by several factors. First, to realize a suitable ADC numerous criteria must be fulfilled [7]. About the cytotoxin (also known as warhead), this must be a small molecule showing high potency, relative hydrophilicity and a lack of susceptibility to P-glycoprotein, which is a very common resistance mechanism for ADCs. Linkers connecting the MoAb to the warhead must be stable in blood, but they are also required to be able to release the drug inside the target cancer cells. Apart from these technical issues, which are underway of further improvement, the major unaddressed concern for ADCs in clinics may be finding the optimal antigen target. Cancer antigen must be transmembrane and able to internalize into the target cell after MoAb binding. Importantly, the ideal antigen should be tumor specific or at least with a minimal expression on healthy tissues, to reduce off-target toxicity. However, the type of non-cancerous cells on which the target antigen is exposed may also play a role in predicting ADCs toxicity. Because of the cell cycle-dependent mechanism of action, non-highly proliferating cells may be less vulnerable to the ADC cytotoxic damage. [8] Despite these limitations, the fact that the tumor target antigen is not required to drive tumor growth, constitutes an appealing advantage for ADCs application in malignancies lacking acknowledged driver mutations. In the context of thoracic cancers, squamous lung carcinoma or less differentiated entities would be amenable for greater research efforts in finding an adequate ADC antigen target. A further barrier to the design of viable ADCs is the unavailability of a reproducible, standardized and economic technique to identify and validate valuable target antigens. So far, the techniques used are immunohistochemistry or - more recently - functional genomic mRNA profiling, with the latter failing to localize the predicted protein into cancer cells [1]. In NSCLC setting, concern is raised by the ruthless competition with the numerous systemic treatments

already available or on study. A smart approach to find a place for ADCs in the NSCLC treatment algorithm, may be to explore combination strategies with drugs already on market. In the era of immune-oncology we are living, great attention is dedicated to combination strategies with immune checkpoint inhibitors (ICI). ADCs in most advanced phases of clinical experimentation are currently being tested in association with ICIs. Notably, a phase I/II trial of anetumab plus atezolizumab in advanced NSCLC patients has already been planned [9]. The supporting rationale is based on the demonstrated immunogenic cell death properties displayed by ADCs. Moreover, additional ADC immunogenicity is warranted by their antibody-dependent cell-mediated cytotoxicity potential. [10] A last and unsolved question regards tumor heterogeneity, which makes it unlikely to eliminate a whole neoplasm by using a single ADC target. As a future perspective, we could envision extensive tumor sequencing that allows for efficient antigen prediction and for the design of tailored ADCs targeting, contemporarily, multiple tumor specific antigens. Long and winding is the path for the ADC entry in NSCLC clinical practice. However, the rapidly evolving landscape in tumor sequencing and proteomics along with the clinical research experiences, may pave the way to find the most appropriate setting for ADCs in terms of manageable side effects and NSCLC patients' selection. *1. Moek KL, de Groot DJA, de Vries EGE et al. The antibody–drug conjugate target landscape across a broad range of tumour types. Ann Oncol. 2017 Dec 1;28(12):3083-3091. 2. NCT02610140. 3. NCT03061812. 4. Hamilton EP, Barve MA, Bardia A et al. Phase 1 dose escalation of XMT-1522, a novel HER2-targeting antibody-drug conjugate, in patients with HER2-expressing breast, lung and gastric tumors. J Clin Oncol 36, 2018 (suppl; abstr 2546). 5. Sands JM, Shimizu T, Garon EB et al. First-in-human phase 1 study of DS-1062a in patients with advanced solid tumors. J Clin Oncol 36, 2018 suppl; abstr TPS2605. 6. NCT03319628. 7. Beck A, Goetsch L, Dumontet C et al. Strategies and challenges for the next generation of antibody-drug conjugates. Nat Rev Drug Discov. 2017 May;16(5):315-337. 8. Damelin M, Zhong W, Myers J, Sapra P. Evolving Strategies for Target Selection for Antibody-Drug Conjugates. Pharm Res. 2015 Nov;32(11):3494-507. 9. NCT03455556. 10. Gerber, HP, Sapra P, Loganzo F et al. Combining antibody–drug conjugates and immune- mediated cancer therapy: what to expect? Biochem Pharmacol 2016. 102, 1–6.*

MS08 LUNG CANCER IN THE REAL WORLD
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MS08.01 HOW CAN REAL WORLD DATA IMPROVE CLINICAL EVIDENCE GENERATION AND IMPACT REGULATORY BODIES - EUROPEAN PERSPECTIVE

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Health technology assessment (HTA) evaluates the efficacy and effectiveness of new interventions, integrates these data with the costs to define efficiency and addresses future availability and distribution. As such, HTA focuses on accessibility, affordability and equity. Economic evaluations are central in this concept: weighing costs and effects, they support evidence-based decisions on reimbursement, thus endorsing the introduction of innovative healthcare interventions in daily practice. After more than 20 years of voluntary cooperation on HTA in Europe, more than 50 HTA bodies are currently operating in the European Union (EU), be it still fragmented with different systems, different procedures and different requirements regarding the type of clinical evidence. Efficacy, the outcome a new intervention provides in the well-defined circumstances of a randomised controlled trial (RCT) and typically the input used to derive cost-effectiveness evidence, may not provide the best insight into the impact of an intervention in daily clinical care. Moreover, in contrast to what is the case for pharmaceuticals, it is much more difficult to perform RCTs on radiotherapy or surgery, especially when it comes to evaluating the incremental evolution typical for new techniques and technologies, or the long-term benefits anticipated to follow more accurate treatment delivery. This has resulted in different regulatory systems for systemic and non-systemic treatment strategies, with attempts to come to a more homogenised HTA approach in the EU having so far failed. Real-world data are gradually expanding their role in the evidence generation of lung cancer radiotherapy. A first step moving away from RCTs is to adopt a more pragmatic approach to evidence generation, as is the case in the OligoCare project. This joint ESTRO-EORTC initiative is evaluating the outcome of oligometastatic patients, amongst others from primary lung cancer, treated with radical radiotherapy in a large prospective cohort study. Various patterns of care studies have generated clinical evidence on the uptake of new treatment techniques such as SBRT (Stereotactic Body Radiotherapy), on the value of multimodality treatments for locally-advanced non-small cell lung cancer (NSCLC) beyond the context of RCTs, or have allowed to develop prediction models to support shared decision-making. Furthermore, the wealth of data available in cancer registries and other nation-wide databases can be leveraged to learn more about the quality of care, actual access to different treatment strategies, geographical and institutional variations and their potential impact on lung cancer survival. Real-life data can also be used to generate the cost information necessary to perform cost-effectiveness evaluations. Besides the more frequent approach to derive this evidence from reimbursement data, actual resource costs can also be computed in daily practice. One such initiative was undertaken in Belgium, using Time-Driven Activity-Based Costing to compute real-life costs of radiotherapy, and more specifically of innovative radiotherapy techniques such as SBRT. Whereas all these examples provide interesting insight into the clinical and financial consequences of access to standard-of-care and innovative lung cancer radiotherapy, there is a dearth of information on how this evidence defines policy. One interesting approach to change practice is using coverage with evidence generation to provide early access to radiotherapy innovations, while stimulating the further generation of data. Such a programme of provisional financing has been set-up in Belgium to generate evidence from daily practice on SBRT for primary tumours, most typically early-stage NSCLC, and for oligometastatic disease. While this programme allowed radiation oncology centres to develop and provide SBRT without being financially penalised, it also generated the reassuring clinical evidence that will soon lead to the inclusion of SBRT in the formal national radiotherapy reimbursement system.

Keywords: Effectiveness, costs, real-world data

MS09 TUMOUR BOARD - TISSUE ACQUISITION AND STAGING
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MS09.02 CASES PREPARED BY DRS. EDELL/MURGU

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Lung cancer remains the leading cause of cancer-related mortality worldwide. In order to provide adequate and appropriate treatment, staging is crucial. The TNM staging system is the established uniform method of staging lung cancer, both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The revised classification of the most recent edition (TNM8) of the TNM staging system, proposed by the International Association for the Study of Lung Cancer (IASLC) and introduced in 2016, is based on detailed analysis of a new large international database of almost 78000 lung cancer cases from 16 countries. The first part of this talk will focus on tissue diagnosis, specifically CT-guided core biopsy. In the era of targeted therapies and customized treatment, the acquisition of an adequate and representative sample, especially in non-surgical patients, is pivotal. Complications, pitfalls and pearls of CT-guided lung biopsies will be addressed. The second part of the talk will be focussing on the changes between TNM-7 and TNM-8 – downstaging of lung atelectasis and pneumonitis, upstaging of diaphragmatic invasion, reclassification of extra-thoracic metastatic disease; the IASLC recommends that radiologists should document the number of metastatic lesions, the diameter of individual metastatic lesions and the number of involved organs at staging examinations. The conundrum relating to nodal staging with CT and FDG-PET imaging will be explored. Lung cancer with multiple sites of pulmonary involvement – multiple primary lung cancers, lung cancer with separate tumour nodules, multiple ground glass/lepidic lesions and lung cancer manifesting as consolidation - will be discussed.

MS10 PART SOLID NODULES, GGN AND STAS
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MS10.03 CT VERSUS NEEDLE BIOPSY ASSESSMENT BEFORE RESECTION OF PART SOLID NODULES

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Increasing number of lung cancer screening program detects pulmonary ground glass nodules (GGN) and those are frequently found to be an adenocarcinoma or its precursors, particularly if they are persistent or increase in size. Preoperative diagnosis of GGNs by trans-bronchial or trans-thoracic fine-needle aspiration biopsy can be performed with reasonable diagnostic accuracy [1]. However, they have limitation for the pathologic confirmation of GGNs as they can fail to sample small invasive foci [2, 3]. In addition, hemoptysis has been reported to occur more frequently after needle biopsy in GGNs [4]. Accordingly, needle biopsy for GGNs are not used in our current practice and if the suspicion for malignancy is high on CT, surgical biopsy is performed without preoperative needle biopsy. Recently published Fleischner recommendations for the management of GGNs may help to make a clinical decision. During the surgery, especially in minimally invasive surgery, GGNs are often difficult to palpate. Thus, preoperative marking

techniques have been utilized for localization of the GGNs using various methods [5]. That can be done either percutaneously or transbronchially, using various materials including a dye, colored collagen, barium, lipiodol, micro coil, metallic wire, or fiducial [6]. In our center, we have been using various methods for preoperative localization and but currently, we favor to use electromangetive navigational bronchoscopy (ENB) guided dye marking technique. Once surgery is decided, deciding the extent of resection is another issue. The size of solid portion measured on the CT can be helpful. If it is less than 5 mm, a simple wide wedge resection can be performed by which the goal of diagnosis and treatment can be achieved. If it is larger than 5 mm, the specimen is examined by frozen section and if the malignancy is confirmed, anatomic lung resection is conducted.

However, the CT findings have not yet proven sufficiently reliable to guide the management plan. Intraoperative frozen section diagnosis is an alternative that can guide the extent of the subsequent surgical procedure. The problem of frozen section is, however, the fact that deflated lung specimens often makes the correct diagnosis difficult. To obviate this problem, the technique of inflating the lung specimen with the embedding medium for frozen section (EMIT) has been used, which allows better interpretation, and facilitated correct diagnosis in the frozen section [7]. In our center, we have been using EMIT and found a high diagnostic accuracy with the concordance rate of 90.6% between EMIT and permanent pathology. Based on our experience, it is our current practice to perform a wide wedge resection of the GGNs and send the specimen for EMIT. If the result of EMIT is pre-invasive lesions (benign, AAH, AIS, or MIA), we do not perform additional resection. If the invasive adenocarcinoma is diagnosed, we prefer to proceed anatomic lung resection with systematic lymph node dissection. Several studies showed that limited resection could be beneficial, especially in early stage lung adenocarcinoma, including GGN [8]. On the contrary, in one prospective study that reported a long-term outcome, limited resection of GGNs showed a low disease-control rate. They reported adenocarcinomas developed in four out of 26 patients in the surrounding area of initial resection site after more than five years [9]. However, as GGNs usually show favorable prognosis, limited resection could be generally recommended [10]. Additionally, in cases of deeply located GGNs, where wedge resection is not technically feasible, direct segmentectomy without wedge biopsy for the purpose of diagnosis and treatment, is recommended. For the segmentectomy, various technics can be used, but it is our current practice to use ENB guided dye marking to define an adequate parenchymal resection margin during the segmentectomy. To summarize, although there are several CT findings that can differentiate between pre-invasive and invasive lesions, those findings have not yet proven sufficiently reliable to guide the management plan for GGNs. In addition, attempt to sample solid component in GGNs using a biopsy needle is often not feasible and therefore, not helpful for being used in clinical decision. Currently, the best practice for the management of GGNs is to carefully follow the patient with CT, and if malignancy is suspected, to perform a surgical biopsy with the guide of various localization methods and/or other innovative methods to differentiate between pre-invasive versus invasive adenocarcinoma. 1. Yamagami T, Yoshimatsu R, Miura H, et al. Diagnostic performance of percutaneous lung biopsy using automated biopsy needles under CT-fluoroscopic guidance for ground-glass opacity lesions. Br J Radiol 2013;86:20120447.

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Keywords: GGN, biopsy, Adenocarcinoma

MS10 PART SOLID NODULES, GGN AND STAS
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MS10.04 THERAPEUTIC IMPLICATIONS OF SPREAD THROUGH AIR SPACES (STAS)

W. Travis[1], R. Gaber[1], S. Lu[2], T. Eguchi[3], N. Rekhtman[4], P. Adusumilli[5]

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Spread through air spaces (STAS) is a recently recognized pattern of invasion in lung cancer defined as spread beyond the edge of the main tumor into the air spaces surrounding the tumor. It was originally described as a poor prognostic factor in Stage I lung adenocarcinoma.[1] STAS has been observed in 15-62% of lung adenocarcinomas and associated with poor prognosis in multiple independent cohorts worldwide.[2-4] In addition, it has now been shown to occur with prognostic significance in most all major types of lung cancer including squamous cell carcinoma (SQCC),[5] small cell carcinoma SCLC),[6] large cell neuroendocrine carcinoma (LCNEC),[6] atypical carcinoid (AC)[6] and pleomorphic carcinoma.[7] Three dimensional evaluation has shown most STAS clusters are attached to alveolar walls rather than floating in air spaces suggesting a mechanism of detachment then reattachment perhaps by vessel co-option.[8] Criteria for STAS The original definition of STAS by Kadota et al and the 2015 WHO consisted of tumor cells within the first alveolar air spaces in the lung parenchyma beyond the edge of the main tumor. It can occur as one of three morphologic patterns including 1) micropapillary structures within air spaces; 2) solid nests or tumor islands and 3) scattered discohesive single cells.[1, 9] The solid nest pattern is characteristic in other lung cancer histologies. Although other criteria have been proposed our group has used these same criteria for STAS to demonstrate its prognostic significance in SQCC, LCNEC, SCLC and AC. Warth et al defined STAS with different criteria including a detachment of small solid cell nests of least 5 tumor cells where < 3 alveolar spaces were regarded as limited STAS and tumor cells nests >3 alveolar spaces away from the tumor as extensive STAS.[4] Distance of and Quantitation of STAS Gaber R et al found that circumferential STAS was associated with a higher risk of recurrence free probability (RFP) than focal STAS (5yr RFP in circumferential vs focal; 67% vs 87%, p=0.027) and that longer distance of STAS was associated with a higher risk of recurrence (5yr RFP >7 alveoli vs ≤ alveoli, 69% vs 91%, p=0.003).[9] However, Quantitation of STAS was not prognostic (5yr RFP in >3/HPFs vs ≤3/HPF, 75% vs 88%, p=0.15).[9] Uruga H et al found that high vs low STAS (≥5 vs 1-4 single cells or clusters) was an independent predictor of worse (p=0.015).[2] Warth did not find a prognostic difference between extensive vs limited STAS as described above.[4] Implications of STAS for Radiation Therapy In the setting of sterotactic body radiation therapy (SBRT) for lung cancer, the documentation of microscopic extension has been appreciated for many years.[10] Radiologic and pathologic studies have shown that tumor cells can extend beyond the edge of the tumor from 1.3 centimeters to 2.6 cm.[10] Although the concept of STAS emerged many years later, it provides morphologic and clinical support to radiation therapists concerns to address microscopic extension and STAS in planning the radiation field. Implications of STAS for Surgical Management There is limited data evaluating pathologists ability to recognize STAS in frozen section. Kameda et al found the sensitivity and specificity of frozen section for prediction of STAS were 71%, 92.4% respectively and the accuracy was 80%.[11] Kappa statistics for interobserver agreement were 0.4-0.74. Walts AE et al studied frozen section for evaluation of STAS and recommended that current evidence did not warrant frozen section evaluation for STAS.[12] However, frozen section sensitivity to detect STAS positivity was 50%, with a 100% positive predictive value and an 8% negative predictive value. So from the two studies, it appears if a pathologist sees STAS on a frozen section there is a 92-100% likelihood it will be present on permanent sections. Both of these were retrospective studies where tissue sampling for frozen sections was not made to include the tumor edge and adjacent lung to search for STAS. More studies are needed to evaluate the potential role of frozen section in detecting STAS and guiding intraoperative decisions by surgeons. **REFERENCES** 1. Kadota K, et al. Tumor Spread through Air Spaces is an Important Pattern of Invasion and Impacts the Frequency

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Keywords: Spread Through Air Spaces, STAS, lung cancer

MS11 STIGMA AND LUNG CANCER: UNINTENDED TRANSLATIONAL CONSEQUENCES OF EFFECTIVE TOBACCO CONTROL
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MS11.01 IDENTIFYING CONSEQUENCES OF STIGMA ON LUNG CANCER CARE DELIVERY AND PATIENT OUTCOMES

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Lung cancer stigma (the experience and internalization of negative appraisal and devaluation from others) is a formidable barrier to fulfilling the promise of high quality patient care and reduced lung cancer burden. Attention to the robust causal connection between smoking and lung cancer, although crucial for tobacco control, may have unintended consequences that generate blaming responses and biased negative perceptions toward lung cancer patients. Lung cancer stigma can have far-reaching, deleterious effects that range from reduced involvement in prevention and early detection interventions, negative psychosocial impact, impaired patient-clinician communication, inadequate access to diagnosis and treatment, and limited funding and public support for lung cancer research and care. The goals of this presentation are to describe the nature of lung cancer stigma and highlight research that addresses consequences of stigma on lung cancer care delivery and patient outcomes. The presentation also focuses on multilevel interventional opportunities to mitigate the negative effects of stigma. Based on both qualitative and quantitative assessment, our team has identified three primary components of patient-reported lung cancer stigma: perceived stigma, internalized stigma, and constrained disclosure (Hamann et al., 2018). Cross-sectional data indicate associations between stigma and impaired patient/provider communication, higher rates of depressive symptoms, and reduced engagement in care among lung cancer patients. Recent work has also demonstrated potential provider-level stigma toward lung cancer patients, with implications for treatment decisions and other aspects of lung cancer care. Interventional opportunities include patient-based education and counseling to address the psychosocial and behavioral consequences of lung cancer stigma. Focusing on provider communication training also represents a promising opportunity to reduce stigma toward lung cancer patients.

Keywords: psychosocial, care outcomes, stigma

MS12 IMMUNOTHERAPY AND RT
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MS12.01 BIOLOGY IO+RT

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Checkpoint inhibitors have changed the outcome of patients with metastatic non-small cell lung cancer (NSCLC) in first and in second line, with improved progression-free survival (PFS), overall survival (OS) and quality of life. Radiotherapy has consistently been shown to activate key elements of the immune system that are responsible for resistance for immune therapy. Radiation upregulates MHC-class I molecules that many cancer cells lack or only poorly express, tumor-associated antigens, provokes immunogenic cell death, activates dendritic cells, decreases regulatory T-cells (Tregs) in the tumor, broadens the T-cell repertoire and increases T-cell trafficking, amongst many other effects. Radiation may convert a completely or partly poorly or non-immunogenic tumor immunogenic. Radiotherapy in combination with different forms of immune therapy such as anti-PD-(L)1, anti-CTLA4,immunocytokines, dendritic cell vaccination and Toll-like receptor agonists improved consistently local tumor control and very interestingly, lead to better systemic tumor control (the “abscopal” effect) and the induction of specific anti-cancer immunity with a memory effect. Moreover, as PD1/PD-L1 is upregulated by radiation and radiation can overcome resistance for PD-(L)1 blockage, their combination is logical. The best timing, sequencing and dosing of all modalities is a matter of intense research, but in pre-clinical models, the concurrent administration of anti-PD-(L)1 was superior to sequential. Clinical studies in NSCLC such as the subgroup analysis of the KEYNOTE-001 trial, the PACIFIC trial and the phase II results of NICOLAS support the rationale to view radiation as an immunotherapeutic drug that may enhance the immune response without limiting side effects when combined with the correct immunotherapy drugs for a given tumor and patient.

Keywords: non-small cell lung cancer, radiotherapy, immune therapy

MS12 IMMUNOTHERAPY AND RT
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MS12.02 CLINICAL DATA AVAILABLE

F.M. Kong

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The role of radiation is evolving in the era of immunotherapy. The abscopal effect of radiation on immune modulation has been discussed and researched greatly during recent days, and there is a significant amount of laboratory data suggesting its positive effect on tumor control. This presentation will focus on an objective review of clinical evidences for the clinical significant outcomes of radiation on immune function aiming to maximize the positive effect of Radiation Immunomodulation. Standing from the clinic, I will not only review the GOOD side of abscopal effect, i.e. the increased tumor control distant from a focused local radiation, and examine the BAD effect of radiation immunomodulation, i.e. radiation immunosuppressive effect which can worsen the tumor control outcome and overall survival. Starting from an overview of these two conflicted effects of all solid tumors in general, the presentation will specifically focus on the literature of radiation immunomodulation effects in patients with non-small cell lung cancer. Predictive and correlative biomarkers for both GOOD and BAD effects will also be reviewed through thorough literature search. The ultimate goal of this presentation is to motivate us, the oncologists to search, and research on finding a way to deliver a more effective radiation therapy and a more effective way of combined therapy with radiation and immunotherapy, to maximize the GOOD abscopal benefit while minimize the BAD effects of radiation on immunofunction.

Keywords: Radiation abscopal effect, radiation immunosuppression, biomarker

MS12.04 IMPLICATIONS FOR ROUTINE PRACTICE

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Over the last 3 years checkpoint inhibitors (CPI) have become established as key components in the treatment of stage III and IV NSCLC. The established CPI are PD-1 and PD-L1 inhibitors and more recently CTLA4 inhibitors, with ongoing research into other modulators of T-cell function. Used alone, these agents have their greatest efficacy in a subset of patients while combination with other treatment modalities may enhance efficacy. Already concurrent pembrolizumab and chemotherapy has been shown to be more effective than chemotherapy alone for first-line metastatic NSCLC. [1] In the clinic there are two major issues to consider when combining immunotherapy and radiotherapy. The first is safety, particularly when irradiating lung or the brain. The second issue is, can we harness radiotherapy to improve the efficacy of immunotherapy? Pneumonitis is a major concern when combining radiotherapy to the lung. Lower dose palliative radiotherapy is less of a concern but when treating primary lung cancer with curative intent, especially concurrent with chemotherapy, toxicity may impact on patient survival. In the phase III PACIFIC trial, of the 476 stage III NSCLC patients who received concurrent chemoradiation to the lung followed by durvalumab consolidation, grade ≥3 pneumonitis was 4.5% and no different from chemoradiation alone. [2] In 93 stage III patients treated with concurrent chemoradiation followed by 12 months pembrolizumab consolidation grade ≥3 pneumonitis was 6.5%. [3] We now have safety data for stage III patients with nivolumab given concurrently with thoracic chemoradiotherapy, followed by consolidation nivolumab. For the 58 patients evaluable for toxicity in the NICOLAS trial, grade ≥3 pneumonitis was 10.3%. [4] We now also have safety data for SABR (Stereotactic Ablative Radiotherapy) combined with CPI. Seventy nine patients (53 NSCLC) received SABR to multiple metastases, followed within 7 days by pembrolizumab. The toxicity was as expected for pembrolizumab alone. [5] Similarly Campbell has reported on treatment with concurrent SABR and pembrolizumab with either melanoma or NSCLC, with no increased toxicity. [6] Treating brain melanoma metastases with radiosurgery concurrent with ipilimumab in 57 patients, Mortier found toxicity to be as expected for immunotherapy alone [7] , while a similar study by the same group found toxicity was not increased beyond that for pembrolizumab alone. There have been multiple reports, mostly of single cases, whereby local radiotherapy to a tumour causes shrinkage of a distant non-irradiated metastasis, termed an abscopal effect. [8] It is hoped that likewise radiotherapy will enhance the effectiveness of CPI. Prior to CPI entering the clinic, in the START trial stage III patients treated with consolidation tecemotide (liposomal MUC1) vaccine following concurrent chemoradiation showed a 10 month survival advantage not seen in those who had received sequential chemoradiotherapy. [9,10] Although overall the START trial was negative for the primary endpoint, this suggested that concurrent chemoradiotherapy might enhance immunogenicity. In the PACIFIC trial of stage III NSCLC, all patients received concurrent chemoradiation. Patients randomised to a year of consolidation durvalumab had markedly improved PFS (HR 0.52) irrespective of tumour PD-L1 expression, and overall survival data are awaited. [2] There are also now data suggesting an outcome benefit for NSCLC patients treated with concurrent SABR and CPI. In the PEMBRO-RT trial 74 NSCLC patients were randomised to receive SABR (3 x 8GY) to a single metastasis followed within 7 days by pembrolizumab, or pembrolizumab alone. [11] All endpoints trended in favour of the combination. The primary endpoint of response rate at 12 weeks was 39% vs 21% (p=0.28), for SABR + CPI vs CPI respectively, while PFS (HR 0.61 p=0.08) and OS (HR 0.58 p=0.1) favoured combined SABR and pembrolizumab. A similar trial, NIVORAD, is being conducted by the ALTG co-operative group, where patients are randomised to receive nivolumab with or without SABR to a metastasis site during week 2. [12] There are now good data to indicate that combining CPI and radiotherapy is safe, including radiotherapy to the lung and to the brain. Sequential concurrent chemoradiation in stage III NSCLC followed by durvalumab is highly effective. Emerging data suggest that radiotherapy may enhance the effectiveness of immunotherapy in stage IV disease but further randomised data are required. 1 Gandhi L. Pembrolizumab plus chemotherapy in metastatic NSCLC. N Engl J Med 2018: 378; 2078-2092 2 Antonia S. Durvalumab after chemoradiotherapy in stage III NSCLC. 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NIVORAD: a randomised phase 2 trial of nivolumab and stereotactic ablative radiotherapy in advanced NSCLC progressing after first or second line chemotherapy. J Clin Oncol 2017; 35: suppl. TPS9097

Keywords: Checkpoint inhibitors, radiotherapy, NSCLC

MS13.03 UBIQUILIN AS A NOVEL MEDIATOR OF LUNG CANCER INVASION AND METASTASIS

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Data from large, publicly available datasets indicate multiple somatic non-synonymous recurrent mutations in Ubiquilin (UBQLN) family genes or loss of either UBQLN1 or UBQLN2 loci in over 50% of human lung adenocarcinoma patient samples. The UBQLN family consists of 5 related proteins (UBQLN1-4 and UBQLNL) that all contain ubiquitin-like (UBL) and ubiquitin-associated (UBA) domains. Our work was the first to show that UBQLN proteins regulate processes involved in tumorigenesis. In fact, our work now conclusively demonstrates that Ubiquilin1 is a *bona fide* metastasis suppressors in human lung adenocarcinoma. Importantly, since the vast majority of patients that succumb to lung cancer, die from the metastatic disease and not from the primary tumor burden the combination of these data suggest that nearly 700,000 people die world-wide every year from lung cancers that have decreased or altered UBQLN function. The exact mechanism by which loss of UBQLN proteins leads to metastatic progression remains unclear, however metastatic cancer progression requires cells to acquire new aggressive properties, such as increased migration, invasion, survival and growth at the metastatic site. The identification of regulators of these properties will be crucial for our future success in decreasing metastatic progression and thus cancer mortality rates. The goal of our lab is to understand the detailed mechanisms by which disruption of UBQLN proteins contributes to the metastatic progression of hLAC. We demonstrate that (i.) loss of UBQLN1 or UBQLN2 increases proliferation, EMT, migration and invasion of hLAC cells, *in vitro*; (ii.) loss of UBQLN1 activates multiple signaling pathways known to regulate cell motility, such as IGF1R and Integrin/FAK; (iii.) inhibition of SRC kinase blocks migration, but not proliferation of cells lacking UBQLN1; (iv.) and finally, loss of UBQLN1 increases metastasis of hLAC cells *in vivo*. By understanding how UBQLN1 functions to protect cells from tumor progression and metastatic dissemination we may be able to use UBQLN1 status as a predictive biomarker for disease staging or as an indicator for which patients will respond to a given therapeutic. Further, by understanding how UBQLN1 alters signaling pathways that contribute metastatic progression, we may be able to target these downstream pathways specifically in tumors with altered UBQLN1 function to block metastasis, thus potentially affecting millions of lung cancer patients in the coming decades.

Keywords: Ubiquilin, metastasis, lung cancer

MS14.01 BASIC SCIENCE RATIONALE OF IO IN EARLY STAGE NSCLC?

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The 5-year overall survival (OS) of patients with surgically treated early stage NSCLC ranges from 92% (stage IA) to 36% (stage IIIA). Numerous clinical trials over the last decades tried to improve on these results by either adding adjuvant therapy (i.e. in addition after a radical local

therapy) or neoadjuvant therapy (i.e. cytoreductive before a radical local therapy). Adjuvant setting Adjuvant therapy for resected NSCLC came into place in 2004, when the large International Adjuvant Lung cancer Trial (IALT) demonstrated OS benefit with cisplatin-based chemotherapy. No further progress with other types of adjuvant therapy has been made since then. The progress in patients with advanced NSCLC in stage IV with pemetrexed, bevacizumab and EGFR-directed TKIs was not translated in the adjuvant setting [1]. As for immunotherapy, the MAGRIT trial assessed antigen-specific immunotherapy directed to the MAGE-A3 antigen in completely resected MAGE-A3 positive NSCLC [2]. The adjuvant setting – where the aim is to eliminate sparse tumor cells remaining after surgery – was judged to be the ideal setting for this approach. Unfortunately, the trial did not improve survival. One of the hypotheses why is that the generated MAGE-A3 directed T-cells with cancer killing properties did not travel nor enter easily in tumors, and even if they did, they encountered checkpoints that blocked their potential benefit. Immune checkpoint inhibitor (ICI) immunotherapy, which revolutionized the approach to metastatic NSCLC, is now tested in the post-surgical setting with micrometastatic disease and low tumor burden. In contrast to directly cytotoxic chemotherapy, however, agents blocking the PD-1/PD-L1 axis require an interaction between antigen-presenting cells, CD8+ T cells, and tumor cells. It is far from certain that these intercellular interactions will occur sufficiently in patients with micrometastatic disease, where low tumor (mutation) burden may not sufficiently incite the tumor microenvironment. Because of the adjuvant setting, without detectable disease, no early effectiveness read-outs of efficacy nor translational tissue research is feasible. The results of the different ongoing trials with adjuvant ICI therapy in early stage NSCLC needs to be awaited. Neoadjuvant setting Because of the aforementioned limitations, the neoadjuvant use of PD-1/PD-L1 blockade is of greater interest for several reasons. From a biologic perspective, PD-1/PD-L1 blockade before surgery, when the tumor mass and intact locoregional lymph nodes with ongoing activation of T cells may be present, might be more rational. In a breast cancer model in mice, it has been suggested that neoadjuvant ICI is more effective than adjuvant ICI [3]. In the neoadjuvant setting, there was a stronger systemic antitumor T-cell response with maintenance of tumor specific CD8+ T cells in the blood early after immunotherapy. High levels of CD8+ T cells predicted long-term survival in this mouse model. Moreover, induction of this systemic immune response could lead to immune memory that may prevent metastatic relapse over time. From a clinical perspective, the neoadjuvant strategy has advantages, as we learned from the chemotherapy era. The systemic therapy has better distribution because of the intact vascularization, which may reduce the locoregional tumor extension. There is an early attack microscopic metastatic disease and the effectiveness can be evaluated in vivo with pre- and post-imaging. From a clinical trial perspective, a big advantage is the possibility to study surrogate endpoints. The crucial outcome in this setting is OS, but this endpoint requires many years of follow-up. Here as well, lessons learnt from neoadjuvant chemotherapy followed by surgical resection are of use. Tumor-free lymph nodes and pathological response in the primary tumor have been associated with significantly better outcome. In a dedicated study on the prognostic impact of morphometric tissue analysis of tumor regression, the latter was graded in I: no regression; II: remaining vital tumor tissue ≥10% (grade IIa) or <10% (grade IIb); and III: no evidence of vital tumor tissue [4]. Patients with tumors of regression grades IIb or III showed significantly longer OS than the others (3-year OS 52% vs 9%, *P*=0.02). These findings, however, do not help to select patients for surgery, as they are *post-hoc* analyses on the resection specimen. Ideally, one should have pre-surgical (*pre-hoc* analysis) predictors, but the standard clinical restaging with repeat CT after neoadjuvant only is a raw tool for this purpose. Our group first demonstrated that morphometric tissue analysis of mediastinal lymph nodes after induction was a strong prognosticator in that setting [5]. This was then validated in a prospective multi-center setting, using the first video-mediastinoscopy after neoadjuvant chemotherapy [6]. Patients with a grade IIA or III regression (<10% viable tumor) had much better outcome than the others: 5-year OS 43% versus 19%. A recent pilot study evaluated the clinical, pathological, and immunologic effects of short-term neoadjuvant PD-1 blockade in NSCLC [7]. Here again, major pathological response was defined as ≤10% residual viable tumor on sections of the resected tumor. With this criterion, 45% of the patients had a major pathological response, with clear infiltration of CD8+ T cells in regressing tumors. Moreover, a systemic immune response with T-cells of similar T-cell receptor repertoire as in the tissue were described. Even with its small sample (N=21), this strategy has a strong mechanistic principle, both in the tumor and on distant sites, and has resulted in a promising surrogate endpoint effect. Whether this will translated in better 5-year OS now needs to be defined in larger multi-center phase 3 trials, several of which are currently started. References 1. 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Keywords: early stage, Immunotherapy, neoadjuvant

MS14 IO IN EARLY STAGE NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MS14.03 CONCERNS ABOUT IO FOR THE THORACIC SURGEON?

B. Passlick

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Perioperativ immunotherapy is a relative new field in thoracic oncology. Although several studies are ongoing, there are until now only two publications describing the effect of preoperative immunotherapy and the intraoperative and the postoperative course of patients with thoracic malignancies. The first study is a publication by Forde and colleagues **(1)**, dealing with patients with resectable lung cancer who received one or two preoperative doses of PD-1-inhibitior Nivolumab. The immunotherapy was administered intravenously every 2 weeks, with surgery planned approximately 4 weeks after the first dose. The authors described an acceptable side-effect profile and no delays in surgery. Treatment-related adverse events of any grade occurred in 5 of 22 patients (23%) an only one event was a 3 grades side effect. This was a patient with a pneumonitis who could be resected thereafter that without any complications. The median interval between the administration of the second dose of Nivolumab and surgery was 18 days (range 11 to 29). Twenty of 21 eligible patients underwent a complete resection. The preoperative imaging showed that the majority of the patients (86 %) had stable disease. The other report **(2)** deals with the safety and feasibility of lung resection after immunotherapy for metastatic or unresectable tumors. This is a retrospective study on 19 patients treated between 2012 and 2016. The majority of them had lung cancer (47 %) followed by metastatic melanoma. Various types of immunotherapeutic agents were used. Anatomic resections (lobectomy or greater) were performed in 11 patients. Complications occurred in 32 % but the majority of them were again only minor. One patients developed postoperative pneumonitis in the contralateral lung approximately 2 weeks after VATS-resection on the other side. In summary, preoperative immunotherapy seems to be applicable with only minor side effects. However, there are only few reports and theoretically other complications might occur. Especially if the side effect spectrum in patients with metastatic disease and immunotherapy is considered **(3)**. Frequent side effects are pneumonitis, hepatitis or even myocarditis. The development of such side effects should be excluded in each patient undergoing surgery after immunotherapy. **References** 1. Forde PM, Chaft JE, Smithe KN et al. Neoadjuvant PD-1-Blockade in Resectable Lung Cancer. N Engl J MED 2018 378;21. 2. Matthew JB, Cools-Lartigue J, Tan KS et al. Safety and Feasibility of Lung Resection after Immunotherapy for Metastatic or Unresectable Tumors. Ann Thorac Surg 2018; .... 3. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med 2018 378;22.

Keywords: Thoracic surgery, immunotherapy

MS15 DISRUPTIVE TECHNOLOGY AND LUNG CANCER RISK
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MS15.01 JUST WATER VAPOR? TOXICOLOGY PERSPECTIVES ON ELECTRONIC CIGARETTES

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Electronic cigarettes (e-cigarettes) were introduced to the global market in the mid 2000's. While it is common to hear the term "e-cigarettes", this label is a broad term referring to a heterogeneous class of devices that differ in shape, size, and functional characteristics. Common features of e-cigarettes include a heating element that heats a propylene glycol and/or vegetable glycerin based solution ("e-liquid" /"e-juice") that contains stabilizers, flavorings and often, nicotine. Numerous flavors are available, including tobacco, menthol, fruit, and sweet flavors. Heating of e-liquids produces an aerosol, which is then inhaled by the user. Due to their relatively short existence, data on the long-term health effects of e-cigarette use are not currently available. In the interim, evidence from animal studies, in vitro and in vivo laboratory studies, observational studies, and small-scale clinical trials may provide important information on the potential harms of e-cigarette use [1]. Many studies conducted on e-cigarettes have focused on the measurement of potentially harmful chemicals that may be produced by these products. Chemicals identified in e-cigarette aerosol include nicotine, tobaccospecific nitrosamines (TSNAs), metals, polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), and aldehydes. Within these classes, there are several respiratory irritants and toxicants, as well as carcinogenic substances linked to the development of respiratory cancers. In our work, we have tested emissions from numerous e-cigarette brands [2] and identified the presence of formaldehyde, acetaldehyde, and acrolein in e-cigarette emissions. Overall, concentrations of toxicants identified

in e-cigarette aerosols were 9 to 450 times lower than in tobacco smoke [2]. Concerns have also been raised about the presence of metal particles in e-cigarette aerosol (particularly nickel and chromium, two main elements in heating coils).The inhalation of these metals in larger quantities may cause respiratory diseases, bronchitis, and pneumonia [3], however, these effects have not been definitively elucidated. The size of particulate matter generated from e-cigarettes affects pulmonary nicotine absorption and determines settlement of particulate matter into various parts of the upper or lower airways. There is likely substantial variation across generations of ecigarette devices, and across brands. Results from laboratory studies indicate that e-cigarettes may expose users to small particles and lower amounts of particulate matter in general. While inhalation of high levels of particulate matter has been linked to greater mortality risk from cardiopulmonary illnesses, the available data indicate that e-cigarette particulate emissions expose users at a level akin to WHO guidelines and are far lower than those of conventional cigarettes. Issues raised about toxicological effects mostly question effects on cells, with a special interest in lung epithelial cells. For instance, many flavorings used in ecigarettes (e.g. cinnamaldehyde, benaldehyde, diacetyl) are already approved for use in food, yet their impact on respiratory health via repeated inhalation is currently unknown. Several studies have shown that e-cigarette flavorings could lead to lung cell damage (mostly by releasing free radicals) and inflammation in lung tissue [4]. Studies on cytotoxic effects of e-cigarette constituents have also identified negative effects on DNA. In one in vitro research, e-cigarette liquids aerosolized at biologically relevant doses induced increased DNA strand breaks and apoptosis while decreasing survival in both normal epithelial and head and neck squamous cell carcinoma cell lines [5]. Moreover, in experiments conducted by Yu et al. [6] e-cigarettes aerosol has shown cytotoxic effects on epithelial cell lines and acted as a DNA-breaking agent. Given multiple potential etiologic mechanisms related to incident case development coupled with the long latency period in developing illness, there is currently no definitive evidence to commenting on the role of e-cigarettes in increasing lung cancer risk. As an intermediate assessment, cross-sectional biomarker data can be suggestive of possible carcinogen exposures related to cancer development. For instance, Shahab et al. [7] examined a large panel of biomarker data among e-cigarette users, cigarette users, and users of both products ("dual users"). The e-cigarette–only users had significantly lower metabolite levels for tobacco-specific nitrosamines (TSNAs), particularly NNAL, a metabolite of potent lung carcinogen NNK. Several observational longitudinal studies also showed a substantial reduction in exposure to NNK and several VOCs, including respiratory toxicants like acrolein, acrylamide, acrylonitrile, 1,3-butadiene (human carcinogen), and ethylene oxide among smokers who switched to e-cigarette [8]. Although evidence from biomarker studies are insufficient to evaluate causative mechanisms, but show users of e-cigarettes display lower levels of exposure to biomarkers of lung carcinogens when compared to smokers, such as NNK. Since e-cigarettes have only been on the market for a decade, it is presently not possible to assess all potential long-term harmful effects of e-cigarette use. To date, findings from clinical studies have demonstrated that e-cigarettes are likely less harmful compared to conventional tobacco cigarettes, and any harmful side effects are noticeably milder compared with regular cigarettes. Furthermore, it is also clear that e-cigarette aerosols are not "a harmless water vapor", as claimed by manufacturers and retailers, and potential health effects from vaping may emerge after long-term use. **References** 1. National Academies of Sciences, Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academies Press; 2018. 2. Goniewicz et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control. 2014;23:133-139 3. Lerner et al. Environmental health hazards of e cigarettes and their components: oxidants and copper in e-cigarette aerosols. Environ Pollut. 2015;198:100-107 4. Leigh et al. 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Keywords: smoking, e-cigarettes, vaping

MS15 DISRUPTIVE TECHNOLOGY AND LUNG CANCER RISK
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MS15.02 PRO- ELECTRONIC CIGARETTES: A CESSATION TOOL

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Should clinicians recommend electronic cigarettes (e-cigarettes) to their lung cancer patients who continue to smoke? For many clinicians the answer to this question is a resounding NO WAY. However, I hope to persuade you that there are good reasons why clinicians should strongly consider recommending e-cigarettes to at least some of their patients who smoke. No one disputes the enormous health risks posed by cigarette smoking, or the need to find better treatments to help smokers overcome addiction to cigarettes. In theory, a product that can deliver nicotine like a cigarette without the toxins found in smoke could be used instead of cigarettes would be a welcome invention. E-cigarettes were first introduced into the marketplace in 2003 and were initially promoted as an aid to help smokers to stop smoking. However, concerns have been raised about whether e-cigarettes are an effective cessation aid or if they would actually reduce successful quitting by adult smokers, whether they are safe to use, and if they may be a gateway into smoking for youth. Admittedly, the science is in a state of flux and evolving rapidly. The National Academy of Sciences, Engineering, and Medicine (NASEM) report on the public health consequences of e-cigarettes, and a new evidence review on e-cigarettes and heated tobacco products commissioned by Public Health England (PHE) both come to similar conclusions. Both reports acknowledge that available evidence indicates that e-cigarette use is less risky than use of combustible tobacco cigarettes; that e-cigarettes may be helpful to smokers who are trying to stop smoking cigarettes, and that e-cigarettes should not be used by non-smokers, especially youth. However, both reports also state that e-cigarettes contain constituents that are not inert and are likely to have some negative health effects on their own. Given uncertainties regarding e-cigarettes, clinicians should advise cigarette smokers seeking to stop smoking to use evidence-based, FDA-approved, safe, and effective smoking cessation pharmacotherapies as first-line treatments in preference to e-cigarettes. So why consider e-cigarettes as a treatment option? First, many patients have already tried the evidence based methods and have found them not to be helpful. We need better treatments and e-cigarettes, in theory, might work for some patients. Second, nicotine seeking is the primary motivation for continued smoking so providing addicted smokers with an alternative that delivers nicotine without most of the harmful toxins in smoke makes sense. Nicotine is not the problem, it is the smoke. E-cigarettes are not lit, they do not burn, and do not produce cigarette smoke. Finally, many smokers simply prefer e-cigarettes over other aids to quitting. It is great to have government approved stop smoking treatments, but if smokers are unwilling to use them, they don't do much good. Sales of e-cigarettes have grown exponentially over the past decade, and they have become the most popular quitting aid used by smokers in many countries. For those smokers and ex-smokers who are already using the e-cigarettes, clinicians need to be informed and prepared to answer questions regarding potential harms and benefits and to advise patients about use.

Keywords: Cigarettes, Smoking Cessation, Nicotine

MS15 DISRUPTIVE TECHNOLOGY AND LUNG CANCER RISK
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MS15.04 THE RISE OF HEAT-NOT BURN TOBACCO IN JAPAN: A "HOT" ISSUE FOR TOBACCO CONTROL

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Just like in other developed countries, public health has been of major public interest in Japan. Reduced-risk tobacco alternative that exposes smokers who cannot quit and non-smokers around them to lower levels of harmful and potentially harmful constituents (HPHC) has long been a goal. In many countries, electronic nicotine delivery systems (ENDS) have been introduced into the market for that purpose. However, there is a high hurdle for ENDS in Japan. Nicotine is classified as a medicinal drug, and devices using nicotine require governmental approval under the pharmaceutical affairs law. Although Japanese citizens can privately import ENDS as an unapproved pharmaceutical product for private use, bureaucratic formalities are troublesome, and the monthly amount able to be imported is limited. In 1997, Japan Tobacco (JT) started to sell AIRS®, the R.J. Reynolds' Premia® product but with a slight modification. AIRS® had a charcoal heat source at one end, and heated air was inhaled through tobacco leaves. This product did not sell well and was discontinued in 2004. Then in 2010, the next alternative was ZERO STYLE STIX®, also by JT. This product has no heat source. It is a snuff

variant, and ambient air is simply inhaled through tobacco leaf powder. When its nicotine was measured by ISO metrics, the amount of inhaled nicotine was shown to be less than a half of low nicotine cigarette. Following these alternatives, heat-not burn tobacco (HNBT) came into the market. Tobacco manufacturers aimed at public tobacco harm reduction in total by reducing HPHC emissions from their products and encouraging public acceptance of such products. The tobacco manufacturers understood that Japanese value cleanliness and physical fitness. Most Japanese people are very anxious about their reputation within their community. An American anthropologist Ruth Benedict described it as "Shame Culture" in her book "The Chrysanthemum and the Sword" in 1946. Many Japanese smokers feel shame at releasing HPHC and ash. The manufacturers also know Japan is a country of electric gadget geeks. The first of the updated or more recent heated tobacco products was Ploom® from JT in 2013, which was updated to Ploom TECH® in 2016. These were bought from a Californian company Ploom Inc. They are not HNBT but aerosol-not burn or e-cigarette, to be precise. Glycerin, propylene glycol and water vapor passes through a tobacco capsule at the maximum temperature of 30℃. Philip Morris International introduced their true HNBT, iQOS®, to the Japanese market in 2015, and British American Tobacco product named glo® in 2016. All these HNBT's were sold in limited areas of Japan at first and gradually extended to nation-wide sales, in response to the demand for HNBT, expanding their production lines. HNBT sales increased rapidly, and heated tobacco category usage among all tobacco users grew up to over 30% in early 2018 from about 4% in late 2015. Cigarette ads on TV, radio, or Internet have been allowed in Japan if it is technically possible to restrict access only to the adults, and this is true for the HNBT ads. According to the guidelines set down by the Ministry of Finance, access to HNBT advertising/information web sites and purchase at virtual/real shops have been strictly restricted, requiring proof of age such as a driving license. In their web sites and on product packages, there are always some messaging to the effect of reduced HPHC, but not necessarily guaranteeing less harm to health, which is in accordance with the Ordinance for Enforcement of the Tobacco Business Act. Reduction in HPHC exposure and lower levels of biomarker responses have been vigorously reported in peer-reviewed journals, but many of them are funded, studied and reported by the tobacco manufacturing companies themselves. There have been several contradictory articles and in media coverage suggesting that some HPHC are released more from HNBT than from cigarettes. However, manufacturers refute the findings by pointing out inappropriate methods, evaluation and data presentation in these reports. The truth will need to wait for the academic and public health community to sort out the reality of the potential for HNBT to reduce the morbidity and mortality caused by tobacco product use. Currently, it seems reasonable to understand that HNBT is likely to expose users and bystanders to lower levels of most HPHC. Although the extent of the reduction found so far varies between studies, reduced exposure to some HPHC is reported to be associated with less short-term harm. To this extent, HNBT might be beneficial for smokers who cannot quit and non-smokers around them. However, less is not zero. It will take 15-20 years to confirm long-term health harm caused by reduced HPHC, such as clinical carcinogenesis. It requires tremendous effort to maintain and watch a large cohort of HNBT users for that long period of time. It is questioned which party ought to do and publish the study. Another question is who pays the cost and whether the study is worth the cost. Because zero is zero, tobacco products including HNBT are desired to be completely abandoned in the future, eliminating the need for long-term harm studies.

Keywords: Reduced-risk tobacco alternative, Heat-not burn tobacco, Harmful and potentially harmful constituents

MS15 DISRUPTIVE TECHNOLOGY AND LUNG CANCER RISK
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MS15.05 HEAT-NOT-BURN TOBACCO: REAL RISK REDUCTION OR INDUSTRY'S NEXT PROMISE

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So, the question is: what are we to think about the products emerging from the global tobacco manufacterers that are being marketed in upper income countries? To be clear the topic is not about electronic nicoitne delivery systems (ENDS) that have been sweeping the world's marketplaces - those arise from a multitude of mostly small companies. ENDS are an interesting topic that is quickly changing also - but, not the topic of this dissertation. Rather the topic for this paper will discuss the current market-disrupters which are the so-called 'heat not burn' cigarettes (HNB). The tobacco control community tends to call them 'heated tobacco products' (HTP), as some of them do come close to 'burning' (combusting) the tobacco, so, HTP is a more accurate, broad term for the category. The question to be addressed is whether they are less harmful than cigarettes or are they the usual 'oversell' or untrue marketing claims that have been the usual practice of the global tobacco manufacturers. A brief review: the global tobacco manufacturers are: Philip Morris, International. (PMI-Switzerland); British American Tobacco (BAT-UK); Imperial Tobacco (UK); Altria (USA) and Japan Tobacco International (JTI- Japan).(see: https://www.statista.com/statistics/259204/leading-10-tobacco-companies-worldwide-based-on-net-sales/). Altria is really just a spin-off from Philip Morris International who sells their products in the USA, including trying to do so for their HNB product (iQOS). Each of them have their own offerings in the HNB category: PMI/Altria is the current leader with iQOS, quipped as standing for: I quit ordinary smoking; BAT has 'glo'; and Imperial has not embraced/marketed a HNB product but had thought to stay with their ENDS (blu) product. Reportedly, Imperial is considering getting their own HNB, as this category appears to be growing (commerically renumerative). JTI has PloomTECH. IQOS and glo use a lithium battery to heat compressed/powdered tobacco to around 300 Celsius which creates an aerosol for inhalation. PloomTech heats a liquid that has nicotine in it (closer to an ENDS) A recent paper by Farsalinos et, tested iQOS, an ENDS and a regular cigarette for emitted carbonyls, like formaldehyde and acrolein. (1) They found that iQOS emitted 82-98% less carbonyls compared to smoking 20 tobacco cigarettes. The ENDS emitted 92-99.8% less carbonyls. So, iQOS were better than cigarettes by alot, but the ENDS was better still. In a webpage hosted by RIVM (National Institute for Public Health and the Environment, misistry of Health, Welfare and Sport), their research to date is quoted as: "Heated tobacco products are newly available on the market. An example of such a product is the heatstick which is heated with an iQOS, a device that looks like an e-cigarette. Heating the heatstick leads to the formation of carcinogenic and other harmful substances. The use of heatsticks with the iQOS is harmful to health, but probably less harmful than smoking tobacco cigarettes. This is RIVM's conclusion, based on its research into heated tobacco products (HTPs)."(2) In another recent paper from Japan, HTPs (iQOS, glo and Ploom TECH) were compared with 'reference cigarettes'(research cigarettes that are well-defined and not for human consumption (as if any should ever be)). (3) Chemists interested in these findings should check out this paper. For the rest of us - it just demonstrates the tremendous variability in the products. Cigarettes deliver nicotine better than the other tested products, and iQOS does better than glo which does better than PloomTech. Since users are going for the nicotine, it seems that the order of preference will be cigarettes, iQOS, glo and PloomTech. However, the manufacturers are constantly changing their products, so they could be different next month. (This is the problem of unregulated products) Most of the published/available research is by the tobacco industry. For the hardy, there is a very large amount of scientific information from PMI on their iQOS submission to the USA FDA. (4) This is all publicly available information - and actually, a very interesting read. The question always remains when reviewing tobacco industry research - can it be verified? Overall, however, it does seem that heated tobacco products (or, ENDS) deliver lower levels of most toxicants to the human lung. Low enough to prevent disease is a different question. BUT, cigarettes kill more than half of the people who use them, cause a huge amount of morbidity and healthcare costs - and, are addictive. So, the question facing society - or, public health - is it possible or probable that if people who are already addicted to nicotine and using cigarettes switch (completely) to HTP products - would there be lower morbidity and mortality than we currently experience from cigarttes? No one knows the answer at present - and, we are unlikely to know for a few decades the real answer. However, are we horrified enough at the currently greater than 7 million deaths globally per year from cigarettes to radically alter our passionless inactivity and push, by regulation (and social pressure) for people to quit cigarettes. If they use HTPs (or ENDS) to quit the unacceptably deadly cigarettes, so be it. I don't know how they could be worse than what we currently allow. {Disclaimer: I am still passionate about the standard tobacco control measures that are working in some countries, per the Framework Convention for Tobacco Control. I do not trust the global tobacco manufacturers that they are willing to help everyone in the world to quit cigarettes, particularly in low income countries, where these HTP products would be more expensive (unaffordable?) for their current customers. I believe the industry is still intersted in maintaining tobacco addiction - I want to ultimately reduce it as far as possible. First however, I want people who are nicotine addicted to stop dying from that addiction.} 1. Farsalinos KE at al. Addiction 2019 June 19. doi: 10.1111/add 14365 2. https://www.rivm.nl/en/Documents_and_publications/Common_and_Present/Newsmessages/2018/Addictive_nicotine_and_harmful_substances_also_present_in_heated_tobacco (accessed 6/29/2018) 3. Uchiyama S. et al. Simple Determination of gaseous and particulate compounds generated from heated tobacco products. Chem. Res. Toxicol 2018. 4. https://www.fda.gov/tobaccoproducts/labeling/marketingandadvertising/ucm546281.htm (accessed 6/29j/2018)

Keywords: heated tobacco products, new tobacco products

MS16.02 NELCIN B3 SCREENING PROGRAM IN CHINA

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Lung cancer is the leading cause of cancer-related death in the world, and lung cancer mortality has steadily declined in some developed countries due to effective tobacco control and improvement of early detection and treatment. In U.S, Lung cancer death rates declined 45% between 1990 and 2015 among males and 19% between 2002 and 2011 among females[1]. However, as the sequence of population age, high smoking prevalence and serious air pollution, Lung cancer in China increased 465% during the past 30 years, and has ranked the highest among all types of cancer since the beginning of this century[2]. As a highly lethal disease, the 5-year survival of lung cancer in China was 19.5% and 11.2% in urban areas and in rural areas respectively[3]. Though smoking control is the most effective measure for the primary prevention of lung cancer, an upward trend of lung cancer incidence and mortality is still expected in future decades in China because of the high prevalence of smoking and severe air pollution. In addition, Lung cancer survival is closely related to the stage at diagnosis, that is, its prognosis is more favorable when diagnosed at an earlier stage. Accordingly, as a measure of secondary prevention, screening and early detection play a important role in lung cancer control. With the increasing disease burden from lung cancer, the widespread availability of spiral CT scanners in China, and the excellent survival of early lung cancer cases detected by LDCT, in 2009, lung cancer screening with LDCT were included into program of early detection and treatment of cancer which was the public health special subsidy from the central government*(33)*. And later, this prospective, multi-centre observational program was renamed as early detection and treatment of cancer in rural China[4]. From 2009 to 2015, lung cancer screening in this program has expanded from 2 centers to 10 centers from 6 provinces/ Municipalities. Up to July 2007, a total of 54164 LDCT scans among about 13000 high risk individuals were conducted which including 19068 baseline screens and 35096 annual screens. The detection rate and early detection rate were 1% and 40% in baseline screening and were 0.4% and 56% in annual screening respectively(table 1 and 2).

The early detection rates in this screening program whether in baseline or annual screening were significantly improved compared to the detection rate of early lung cancers diagnosed at hospital in China(about 7%)(figure 1). Besides, another government-sponsored LDCT lung cancer screening program were initiated in urban China in 2012[5].

Table 1 Baseline screening results in lung cancer screening program in rural China

Centre	Time	Numbers	LC cases	Detection rate (%)	Early LC	Early detection rate (%)
Tianjin	2010.1-2017.6	4069	25	0.6	10	40.0
Xuanwei	2010.1-2017.6	4059	116	2.9	38	32.8
Gejiu	2013.7-2017.6	2024	9	0.4	4	44.4
Beijing	2012.7-2013.6	2842	4	0.1	1	25.0
Sichuan	2013.6-2017.6	2687	10	0.4	4	40.0
Liaoning	2014.7-2017.6	2186	23	1.1	17	73.9
Zhejiang	2014.7-2015.6	1201	4	0.3	2	50.0
Total		19068	191	1.0	76	39.8

Table 2 Annual screening results in lung cancer screening program in rural China

Centre	Time	Numbers	LC cases	Detection rate (%)	Early LC	Early detection rate (%)
Tianjin	2011.7-2017.6	8810	20	0.2	18	90.0
Xuanwei	2011.7-2017.6	10377	82	0.8	38	46.3
Gejiu	2013.7-2017.6	5877	6	0.1	3	50.0
Beijing	2014.7-2017.6	5336	14	0.3	7	50.0
Sichuan	2015.7-2017.6	1820	7	0.4	5	71.4
Liaoning	2015.7-2017.6	2058	7	0.3	4	57.1
Zhejiang	2016.7-2017.6	818	5	0.6	4	80.0
Total		35096	141	0.4	79	56.0

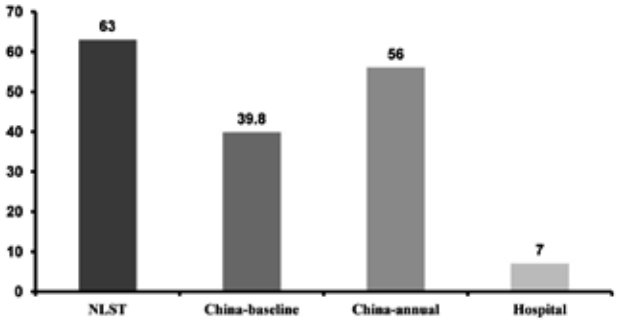

Figure 1 Proportions of early lung cancer in screening programs or local hospital in China. **NLST**: National Lung Cancer Screening Trial(US); **China-baseline**: baseline result in lung cancer screening program in rural China. **China-annual**: annual screen results in lung cancer screening program in rural China. **Hospital**: local hospitals in screening centers.

Based on the protocol of lung cancer screening program in rural China, experts developed lung cancer screen guideline in China in 2015, and revised it recently[6, 7]. Besides LDCT screening, the above two screening program involved several other items including health promotion to increase screening acceptance, technical training for local doctors and technical personnel, delivery of smoking cessation intervention, biomarker discovery and validation to evaluate whether early lung cancer biomarker can refined high risk population and augment LDCT accuracy through classify nodules detected by LDCT. In addition, to keep a sustainable development of a national screening program, the two program has been included into the special program of medical insurance system reform in China to explore the possibility of incorporating lung cancer screening in the routine health insurance system in China.

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Keywords: Lung Cancer, Screening, early diaognosis, lung cancer

MS16 IMPLEMENTATION OF LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MS16.03 RECRUITMENT STRATEGIES FOR THE LUNG CANCER SCREENING

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The National Lung Cancer Screening Trial (NLST) randomized current or former smokers who had quit within 15 years, 55-75 years of age, to low dose CT or chest x-ray and demonstrated a 20% reduction in lung cancer mortality.*[1]* Screening for lung cancer is different from other screening programs as those at risk are not clearly defined by age or sex. Potential recruitment strategies include provider referral; media or internet campaigns; or mass mailing to individuals identified through mailing lists. Direct mailing was used by the NLST, ITALUNG, NELSON, and the Prostate, Lung, Colorectal and Ovarian (PLCO) Screening trials [2,3,4,5]. This reached large numbers of potential participants but it was inefficient and costly. Almost 35% of the total enrollment in the NLST was recruited by direct mailing but this is only 0.2-3.7% of those contacted by mail[2]. Media advertising and community outreach were used in PLCO, but were ineffective [4]. The Lung Screening Study (LSS) mailed 653,417 potential participants, and 4,828 (0.7% of the original mailing) were eligible [6]. The Pan Canadian Early Detection of Lung Cancer Study (PanCan) used mass mailing but also media, posters, websites, and general practitioners and a toll- free number. Of 7044 individuals initially considered, 36% were ultimately eligible for screening [7]. The Veterans Affairs Lung Cancer Screening Program used the Electronic Medical Record (EMR) to

identify potential participants but primary care physicians determined if patients were appropriate for screening. Of 18,083 potential candidates, only 5035 were assessed by their primary care physician. Of those considered appropriate, 50% went on to be screened. Tthe participation of the primary care physician was key to successful recruitment [8]. The UK Lung Screen (ULKLS) used a population based approach through local primary care records, 23,794 (26.8%) of those contacted indicated willingness to participate in a screening study. Ex-smokers, those of higher socioeconomic status and in the 66-70 year age group were more likely to participate. Men and women were equally willing to participate[9]. Wake Forest University School of Medicine identified that their NLST participants` did not reflect local demographics as only 3% of participants were black whereas blacks represented 25% of the local population [10]. PLCO strategies to increase participation among the black population included support from a prominent black business owner and local churches, including black individuals in the planning team, in community outreach and as interviewers. Focus groups or semi-structured interviews have identified that using members of ethnic minorities to promote or recruit are more likely to be successful in these groups [11]. Recruitment through primary care or other respected individuals in the community is also important. [12] Observations from NLST included: "go to where the smokers are"; build trust through local physicians; and use recruiters of the same ethnicity as target populations [3]. Interviews with current smokers identified themes that may contribute to reduced participation including fatalism, fear of diagnosis/ treatment, pessimism about survival and stigma that lung cancer was a self-inflicted disease [13] Cancer Care Ontario High Risk Lung Cancer Screening Pilot Cancer Care Ontario (CCO) launched a pilot screening program on June 1, 2017, at three centers that differed based on demographics, geography and academic or community hospital. Individuals are recruited, assessed for eligibility, screened and followed. The Tammemägi Risk Prediction model was used to identify eligible individuals. Those with a risk score ≥2% were eligible. Provider and public-led recruitment strategies were used. A major aim of the pilot was to recruit individuals who are known to have the highest rates of cigarette smoking: lower socioeconomic status (SES) and First Nations, Inuit and Metis. Areas of predicted high risk populations were identified within the catchment area of each pilot site. Market research was used to recommend recruitment modalities (eg TV, radio or print) for specific sub-groups such as lower SES, older middle-income suburbanites, and rural populations. An accredited Continuing Professional Development course was developed for primary care and collaborative educational sessions were held with primary care providers and First Nations, Inuit and Métis provider groups. In the first year, 3294 individuals were recruited. The majority 3294 (81%) were physician referred (Table 1). The leading methods of recruitment were physician referrals (65%), newspaper advertisements (11%), word of mouth (6%) and nurse practitioners (6%). Only 4% of individuals identified as First Nations, Inuit or Métis. Level of education at high school or lower was self-reported by 48% of individuals. Based on early results, June – November 2017, approximately 27% of eligible individuals were recruited from low income postal codes (average annual household income < $70,000 CAD). Health Sciences North used primary care providers to identify and refer potential participants leading to the highest participation rate across all three centres. The Ottawa Hospital utilized media recruitment methods which led to a high number of applicants but eligibility was lower than for physician referred participants. Provider-led recruitment was more successful at reaching target populations and enlisting eligible participants. At Lakeridge Heath, provider-led strategies were less successful, so public-led recruitment strategies were increased. Public-led methods such as road shows and newspaper were used and led to a boost in volumes. **Conclusions** First year CCO pilot results have shown that provider-led recruitment strategies have been effective in enrolling appropriate individuals and is the primary source of recruitment for the pilot. Importantly, the proportion of eligible individuals recruited through their primary care physician is double that reported in the PANCAN study. Providers were also important in the VHA study. Use of Emr is helpful in identification of potentially eligible individuals. Mass mailing may reach more individuals, but is costly and inefficient. Our results demonstrate that support from primary care physicians is important in successful recruitment to lung cancer screening. Recruitment of First Nations, Inuit or Métis and those with a lower socioeconomic status remains a challenge. Utilizing previously identified strategies such as respected individuals in FNIM communities as well as members of ethnic minorities to promote the program and recruit participants will likely improve recruitment in these hard to reach populations.

Table 1:

2017-2018	The Ottawa Hospital/ Renfrew Victoria Hospital	Lakeridge Health	Health Sciences North	Total
# Recruited	1898	650	746	3294
# Physician - referred	1533 (81%)	508 (78%)	640 (86%)	2681 (81%)
How individuals learned about the pilot				
Family Doctor	67%	68%	56%	65%
Newspaper	15%	10%	4%	11%
Social Media	2%	2%	2%	2%
Nurse Practitioner	1%	1%	21%	6%
Word of Mouth	6%	2%	8%	6%
Other	3%	11%	1%	4%

First Nations, Inuit or Métis	3%	2%	7%	4%
High School Education or Lower	39%	55%	60%	48%
Age 55-64 vs. 65+	59% vs. 41%	62% vs. 38%	61% vs. 39%	60% vs. 40%
Male vs. Female	48% vs. 52%	49% vs. 51%	53% vs. 47%	50% vs. 50%
Current vs. Former Smoker	47% vs. 53%	62% vs. 38%	62% vs. 38%	54% vs. 46%

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MS16 IMPLEMENTATION OF LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MS16.04 NATIONAL LUNG SCREENING PROGRAM IN TAIWAN

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Lung cancer remains the leading cause of cancer mortality worldwide. Early-stage lung cancer is usually asymptomatic and most patients present with symptoms are diagnosed at advanced stages with poor treatment outcome. Early detection is the most effective way to improve survival of lung cancer patients. Low-dose computed tomography (LDCT) scan is a proven tool for lung cancer screening[1]. The National Lung Screening Trial (NLST) demonstrated a 20% mortality rate reduction in high-risk smokers who had undergone LDCT screening as compared to conventional chest X-ray[2]. The effectiveness of LDCT screening among never-smokers is unknown. Evidence showed that the incidence of lung cancer among never-smokers is increasing. It is estimated that 10-25% of the lung cancer occurs in never-smokers and the prevalence is relatively high in East Asian women[3]. In Taiwan, more than half of the lung cancer patients are never-smokers. We hypothesized that the diagnostic consensus reached and the risk models developed in non-Asian populations may not be suitable for Asians. Based on this unmet clinical need, we conducted a four-year LDCT screening program that enrolled 12,000 subjects with a three-year follow-up period. We also tempted to validate the risk SNPs we previously identified that associated with lung cancer susceptibility in never-smokers[4-6]. **Methods:** This is a prospective, nationwide, a multicenter study sponsored by the Ministry of Health and Welfare, Taiwan. The study protocol was approved by the institutional review boards. Informed consent was obtained from every participating subject. Individuals who fulfill the following criteria are eligible for the study: (1) aged between 55-75 years, (2) being a never-smoker, and (3) having one of the following risk factors: (i) family history of lung cancer within third-degree relatives, (ii) passive smoke exposure, (iii) history of pulmonary tuberculosis or COPD, (iv) cooking index ≥ 110, or (v) not using ventilator during cooking. The LDCT was conducted according to the guideline suggested by the American College of Radiology. A solid or part-solid (PS) nodule larger than 6 mm in diameter or a pure ground glass nodule (GGN) larger than 5 mm in diameter was designated as positive on LDCT. The LDCT were performed annually for three consecutive years. If LDCT was positive, short-term follow-up (3-6 months) or tissue diagnosis would be arranged. DNAs were extracted from peripheral blood mononuclear cells for SNP typing (*TERT, TP63, VTI1A, BPTF, HLA-DRB1/HLA-DQA1, HLA-DRB9/HLA-DRB5, DCBLD1 and YAP1*) in every enrolled subject. In addition, a risk score prediction model integrated effects from family history and SNPs were developed and the risk of each individual was calculated. **Results:** This is the interim report. The data cut-off date was May 13, 2018. A total of 10,397 subjects were enrolled (Table1), with 4,498 subjects completed in Stage 1(2014-2015), 4,679 in Stage 2(2016-2017), and 1,220 in Stage 3(2018), respectively. A total of 329 subjects received biopsy for tissue poof (31 by bronchoscopy or CT guide, 298 by surgery) prior to the date of data cut-off. The final pathology diagnoses revealed 12 atypical adenomatous hyperplasias, 42 (17.3%) adenocarcinoma in situ, 46 (19.0%) minimally invasive adenocarcinoma, 152 (62.6%) invasive lung adenocarcinoma, one adenosquamous cell carcinoma, one squamous cell carcinoma, and one small cell carcinoma. In 243 lung cancer patients, 240 patients were adenocarcinoma, 208 patients were stage 1A and 23 patients were stage 1B. The lung cancer detection rate was 2.34% (243/10,397) with 95.1% being stage I. The SNP typing validated 4 SNPs*(TERT, TP63, HLA-DRB9/HLA-DRB5, HLA-DRB1/HLA-DQA1)* that were significantly associated with the risk of lung cancer. The risk score point was significantly different between normal (mean±SD= 50.1±28.84) and case (mean±SD= 59.4±28.23)(p <0.0001). In addition,the group with risk point < 25 as the reference, odds ratios of 3 groups (risk point 25-50, 50-75, and 75-100) were 1.71 (p= 0.046), 1.98 (p= 0.006), and 2.54 (p< 0.0001), respectively. **Conclusions:** In the NLST study, the LDCT detection rate in the first stage was 1.03% (270/26,309). Our interim results showed that, in our pre-defined never-smoking high-risk population, the LDCT lung cancer detection rate was higher than NLST study (2.34% vs 1.03%). Previously reported 4 SNPs were still significant in this cohort. In addition, risk score model showed a high odds ratio of the high score group, suggesting that may be useful to predict the risk of lung cancer in never-smokers. References: 1. Oudnerk M, Devaraj A, Vliegenthart R, et al.European position statement on lung cancer screening. Lancet Oncol 2017;18(12):e754-e766. 2. The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409. 3. Couraud S, Zalcman G, Milleron B, Morin F, Souquet PJ. Lung cancer in never smokers -- a review. Eur J Cancer 2012;48(9):1299-311. 4. Hsiung CA, Lan Q, Hong YC, et al. The 5p15.33 locus is associated with risk of lung adenocarcinoma in never-smoking females in Asia. PLoS Genet 2010;6(8) pii: e1001051. 5. Lan Q, Hsiung CA, Matsuo K, et al. Genome-wide association analysis identifies new lung cancer susceptibility loci in never-smoking women in Asia. Nat Genet. 2012;44:1330-5. 6. Chen HY, Yu SL, Ho BC, et al. R331W missense mutation of oncogene YAP1 Is a germline risk allele for lung adenocarcinoma with medical actionability. J Clin Oncol. 2015;33:2303-10. Table1. Selected characteristics of the study subjects

Characteristic	Number(%)	P-value[e]
All participants	10,397(100)	
Sex		
Male	2,694(25.9)	
Female	7,703(74.1)	
Age[a]	61.2±6.0yr	
Male	61.6±6.1yr	
Female	61.1±6.0yr	
Risk factor[b]		
Family history of lung cancer	4,449(42.8)	
Environmental smoking exposure	7,924(76.2)	
TB/COPD	917(8.8)	
Cooking index≧110	4,176(40.2)	
Not using ventilator during cooking	572(5.5)	
Invasive procedure	329(3.2)	
Histologic diagnosis		
Adenocarcinoma in situ	42	
Minimally invasive adenocarcinoma	46	
Invasive adenocarcinoma	152	
Adenosquamous cell carcinoma	1	
Squamous cell carcinoma	1	
Small Cell lung cancer	1	
Atypical adenomatous hyperplasia	12	
Benign	66	
Others	8	
Lung cancer detection rate	243(2.34)	
Stage		

Stage IA		208		
Stage IB		23		
Stage IIA		2		
Stage IIB		2		
Stage IIIA		3		
Stage IV		5		
Unknown		0		
SNP allele[c] and MAF[d]		Control (n=5837)	Case (n=176)	
rs2395185 (HLA-DRB9/HLA-DRB5)	G/T	33.17%	38.64%	0.0324
rs2736100 (TERT)	A/C	42.17%	48.30%	0.0223
rs28366298 (HLA-DRB1/HLA-DQA1)	A/C	31.98%	39.77%	0.0022
rs4488809 (TP63)	T/C	49.85%	38.07%	<0.0001
rs7086803 (VTI1A)	G/A	30.36%	34.94%	0.0661
rs7216064 (BPTF)	G/A	67.22%	69.60%	0.348
rs9387478 (LOC100132917, DCBLD1)	A/C	48.18%	50.28%	0.435
rs193100333 (YAP1)	C/T	0.27%	0%	0.963
Risk score point		50.1±28.8	59.4±28.2	p <0.001

a Mean ± SD. b Some subjects may have more than one factor. c Risk allele listed second. d Major allele frequency. e Estimated from allelic model.

MS16 IMPLEMENTATION OF LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MS16.05 OPTIMAL APPROACH TO INTEGRATE SMOKING CESSATION INTO SCREENING PROGRAM

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Smoking cessation should be an integral part of low dose CT (LDCT) screening for lung cancer. Smoking cessation and LDCT screening have additive effects on reducing lung cancer mortality, with 7 years smoking abstinence delivering a mortality reduction comparable with the benefit of screening itself [1]. It is well known that a positive screening result increases the likelihood of quitting [2]. However, the majority of people undergoing screening receive a negative result (73% and 78% in the National Lung Screening Trial at prevalence and incidence rounds, rising to 86% and 94% when scans were re-evaluated using the Lung-RADS classification) [3]. A negative result has the potential to falsely reassure participants and thus reduce the incentive to quit - the so-called 'licence to smoke' effect. This effect can only be properly assessed by comparison with an unscreened control population. Analysis from the NELSON study suggested such an effect may exist by demonstrating a higher quit rate in the unscreened control group compared to screened participants, although the effect lost statistical significance following intention to treat analysis [4]. However, this finding has not been replicated in two subsequent European studies. LDCT screening appeared to have no effect on smoking behaviours in the Danish Lung Cancer Screening Trial [5], and the LDCT screened arm had a higher quit rate than non-screened controls in the UK Lung Screening Pilot [6]. All three studies showed higher quit rates in both study arms compared to the background population, although such comparisons are likely to be subject to significant bias related to participation in a CT screening study. Thus although there is no convincing evidence of a licence-to-smoke effect, smoking cessation interventions in screening programmes are vital to guard against this, and to maximise the mortality benefits of these two interventions combined. One of the key questions regarding smoking cessation and screening is whether interventions that have worked in other settings should simply be transferred to screening programmes, or whether bespoke smoking cessation interventions are needed for this particular scenario. LDCT screening for lung cancer is itself a relatively recent phenomenon, having been introduced in the US and Canada following recommendations in 2013 and 2016 respectively. Accordingly, research into Smoking Cessation in the context of Lung Cancer Screening is in its relative infancy, a point acknowledged by the joint guideline on this topic produced by the Association for the Treatment of Tobacco Use and Dependence, and the Society for Research on Nicotine and Tobacco published in 2016 [7]. Most of the active research in this area is occurring within the SCALE collaboration (Smoking Cessation within the Context of Lung Cancer Screening) [8], constituting 8 clinical trials, 7 funded by the National Cancer Institute and 1 by the Veterans Health Administration. These trials are assessing various strategies of smoking cessation support including on-site individual counselling, use of a telephone quit-line, digital cessation tools, motivational interviewing, nicotine replacement medications and message framing (gain vs. loss). Many of these studies are assessing the cost-effectiveness of these interventions, as incorporation of successful smoking cessation interventions into screening is likely to significantly improve the cost effectiveness of the bundle. Whilst outcome data is awaited from these studies, interventions that have been shown to be effective in other settings should be applied to lung cancer screening programmes. Brief interventions by clinicians should cover the 5As of smoking cessation (ask, advise, assess, assist, and arrange follow-up). Analysis of primary care-delivered smoking cessation in NLST showed that arranging follow-up was associated with the highest chance of quitting (OR 1.46; 95% CI 1.19-1.76) but was only delivered in 10% of cases [9]. The UK National Institute for Clinical Excellence (NICE) has produced evidence based guidelines for Stop Smoking Interventions and Services [10]. These include providing behavioural support by trained stop smoking staff together with provision of bupropion, varenicline or nicotine replacement therapy; setting quit dates; and checking self-reported abstinence using carbon monoxide monitoring at 4 weeks after the quit date. Studies mentioned above are testing whether less labour intensive alternatives might achieve similar results to on-site individual smoking cessation counselling. However, until such proof of equivalence is available, it might be argued that given the importance of combining screening with effective smoking cessation, the 'gold-standard' described by NICE or equivalent bodies should be routinely available to any current smoker undergoing LDCT screening.

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Keywords: Low dose CT screening for lung cancer, Smoking Cessation

MS17 LIFE AFTER LUNG CANCER: SURVIVORSHIP
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MS17.01 UNMET NEEDS AND QOL OF LUNG CANCER SURVIVORS

M. Giuliani

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Patients with lung cancer are living longer and more are being cured of their disease with advances in surgery, radiotherapy, systemic therapy and earlier detection through screening programs[1,2]. However, these treatments can result in physical disability, psychological morbidity and increased care needs. Lung cancer patients frequently have unmet survivorship needs and these needs are often complex. In addition, lung cancer patients are less likely than other cancer patients to utilize supportive services[3]. This session will review the magnitude of unmet needs in lung cancer survivors, the nature of these unmet needs and potential mitigating interventions. The majority of lung cancer survivors report unmet needs and often patients experience multiple unmet needs. In one study, the mean number of unmet needs per patient was 7.6. The most common domains of unmet needs are in the psychological domain followed by the physical and the health system & information domains. Patients with more advanced disease and those with increased symptoms

are more likely to have unmet needs. The nature of common unmet needs include fears of the cancer returning, fatigue, facing an uncertain future, coordination of medical care, completing house work and having information on managing health[4]. Addressing and mitigating the unmet survivorship needs in lung cancer patients is a complex undertaking. There are patient and caregiver factors, cancer center factors and systems level factors which must be addressed. This session will explore the role physical activity, survivorship care plans and self-management approaches to mitigate unmet needs and promote improvements in quality of life. Increased physical activity has been shown to have a significant impact on improving quality of life in lung cancer survivors[5]. Increased physical activity is also associated with improving cancer related fatigue[6]. The Institute of Medicine has recommended that each cancer survivor receive a survivorship care plan. These survivorship care plans should include all aspects of their cancer diagnosis and treatment, contact information for the cancer team, information on prognosis, recommended surveillance activities for treatment related toxicity and cancer recurrence, recommendations for healthy behaviors and any additional supportive resources[7]. Finally, employing effective self-management programs for lung cancer survivors can be an effective strategy to reduce unmet needs[8]. There are other critical issues faced by lung cancer survivors. Surveillance for secondary cancers is an important aspect of survivorship care as patients cured of one lung cancer are at risk of developing a subsequent malignancy. Patients who survive with lung cancer can face significant financial toxicity and returning to work can be challenging. Resources to assist patients to return to work are an integral part of cancer survivorship programs. Finally, assisting lung cancer patients who use tobacco products to quit is critical, not only to improve cancer outcomes including disease control and survival, but also to improve quality of life and to reduce morbidity from other tobacco related conditions such as cardiovascular. These three topics will be covered in greater detail in other presentations in this session. **REFERENCES: 1.** Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Dec 10 2010;28(35):5153-5159. **2.** Mery CM, Pappas AN, Bueno R, et al. Similar long-term survival of elderly patients with non-small cell lung cancer treated with lobectomy or wedge resection within the surveillance, epidemiology, and end results database. *Chest.* Jul 2005;128(1):237-245. **3.** Brown NM, Lui CW, Robinson PC, Boyle FM. Supportive care needs and preferences of lung cancer patients: a semi-structured qualitative interview study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* Jun 2015;23(6):1533-1539. **4.** Giuliani ME, Milne RA, Puts M, et al. The prevalence and nature of supportive care needs in lung cancer patients. *Current oncology.* Aug 2016;23(4):258-265. **5.** Sloan JA, Cheville AL, Liu H, et al. Impact of self-reported physical activity and health promotion behaviors on lung cancer survivorship. *Health and quality of life outcomes.* Apr 29 2016;14:66. **6.** Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. *The Cochrane database of systematic reviews.* Aug 15 2012(8):CD008465. **7.** Hewitt M GS, Stovall E. *From Cancer Patient to Cancer Survivor: Lost in Transition.* Washington, D.C: Institute of Medicine and National Research Council; 2005. **8.** Reb A, Ruel N, Fakih M, et al. Empowering survivors after colorectal and lung cancer treatment: Pilot study of a Self-Management Survivorship Care Planning intervention. *European journal of oncology nursing : the official journal of European Oncology Nursing Society.* Aug 2017;29:125-134.

Keywords: unmet needs, survivorship, quality of life

MS17 LIFE AFTER LUNG CANCER: SURVIVORSHIP
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MS17.02 FINANCIAL TOXICITY AND OUT OF POCKET COSTS

B. Gyawali
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Increasingly, patients are sharing the brunt of high cancer care costs, even when patients have insurance, due to increases in co-payments and high-deductible health plans. The out of pocket (OOP) costs borne by patients with cancer in the US was $4 billion in 2014. In an analysis between 2011-2014, the average per patient OOP costs in the first year after diagnosis were between $3,600 and $5,500 depending on the cancer type. The OOP costs were the highest on the month of diagnosis and declined subsequently but never reached the pre-diagnosis level. In countries without health insurance system, patients bear 100% of the drug costs OOP. This usually means that the patient and family must cut down on other daily living expenses or draw from savings and even sell their properties to compensate for the extra health care expenditures. Sometimes, it can mean treatment non-adherence, bankruptcy, or personal or familial stress. Such adverse outcomes due to economic impact of cancer treatment on patient and family are now collectively referred to as "financial toxicity" of cancer treatment. Financial toxicity refers to all the downstream detrimental effects on the survival, quality, and daily life activities of patients and their families as a result of excess financial strain caused by the diagnosis of cancer. In my presentation, I will discuss the causes and effects of financial toxicity in the context of lung cancer and propose some solutions.

Keywords: financial toxicity, cost of cancer drugs, out-of-pocket

MS17 LIFE AFTER LUNG CANCER: SURVIVORSHIP
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MS17.03 SURVEILLANCE & SECOND PRIMARY MALIGNANCIES IN LUNG CANCER SURVIVORS

V. Westeel
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Surgery is the treatment cornerstone of stage I to IIIA operable non-small cell lung cancer (NSCLC), along with perioperative chemotherapy and/or radiotherapy, depending on stage. Five-year survival rates vary between 73 and 90% in pathological stage I, 56 and 65% in stage II, and 41 % in stage IIIA. Disease recurrences occur mainly during the first two postoperative years, up to 10% per year in stage I-II NSCLC, up to 40% per year after surgery for a stage IIIA NSCLC (1). The risk of second primary malignancies, and particularly second primary lung cancer, remains over time, reported around 6% per year during the fifth postoperative year (2). The rationale for surveillance is the early detection of recurrences and second primary malignancies. No follow-up strategy has never been demonstrated to increase survival. The only large phase III trial conducted to date is the IFCT (French Cooperative Thoracic Intergroup) 0302 study, reported at the ESMO meeting in 2017 (3). The IFCT-0302 trial questioned the interest of chest CT-scan in the follow-up of resected stage I-IIIA NSCLC patients. Patients were randomised 1/1 between two follow-up strategies: a minimum follow-up based on history, physical examination and chest X-ray, and a maximal follow-up including history, physical examination, chest X-ray with the addition of chest CT-scan (with sections of the upper abdomen and contrast enhancement) and fiberoptic bronchoscopy (only mandatory for non-adenocarcinomas). In both groups, follow-up procedures were performed every six months during the first two postoperative years and annually from the third to the fifth year. The main objective of the trial was overall survival. A total of 1775 patients were included between January 2005 and November 2012. Eighty-eight percent of patients had undergone a lobectomy. Stage was I or II in 82 % cases. Thirty-nine percent of patients had received adjuvant chemotherapy and 7% postoperative radiotherapy. There was no difference in overall survival between both follow-up groups, with a 5-year survival rate of 66.7% in the minimal follow-up arm and 65.8% in the maximal follow-up arm (HR=0.95; 95% CI=0.82-1.09; p=0.37). There was a trend toward increased disease-free survival (DFS) in the minimal follow-up arm, with 5-year DFS rates of 54.1 and 49.7 %, respectively (HR=1.14; 95% CI= 0.99-1.31; p=0.07). Subgroup analyses identified no survival difference in any subgroup. Detailed analysis of recurrences and second primary malignancies, showed that CT-scan surveillance detected significantly more asymptomatic events (128/291 (44%) vs 42/245 (17%), p<0,0001) for recurrences; 60/97 (62%) vs 37/101 (37%), p<0,0001 for second primary cancers). The risk of second primary malignancy was 11%, comparable in both groups. Among the 198 second primary malignancies, the most frequent sites were lung cancer (n=66), prostate cancer (n=26) and ENT cancers (n=19). Metachronous lung tumours were considered as recurrences or second primary lung cancers using the definition by Martini and Melamed (4). Second primary lung cancers were significantly more frequent in the maximal follow-up arm (n=40 *vs* 26; p=0.02) and more frequently treated with surgery alone (18 *vs* 5; p=0.03). Exploratory analysis of survival in patients who had experienced no recurrence or second primary malignancy at 2 years, showed a significant survival advantage from the CT-scan-based surveillance (median survival not reached *vs* 10 months; p=0.04). On the contrary, in patients who had experienced an event within the two postoperative years, there was no survival difference with median survival durations of 48 months in both arms. These results show that the CT scan-based follow-up did detect recurrences and second primary cancers earlier than the control follow-up with only clinic visits and chest X-rays. However, recurrences, which occur mostly within the two postoperative years reflect the aggressiveness the disease and treatment, even if delivered earlier with curative intent, did not translate into survival benefit. CT-scan might be more useful in patients with a late recurrence or a second primary lung cancer, detecting a more indolent disease or a new pulmonary nodule for which locoregional therapy can be given with better chances of cure. After complete resection for NSCLC, most guidelines recommend to follow up patients with regular clinic visits and chest CT scans (5) (https://www.nccn.org). Although such follow-up

was not demonstrated to increase survival over clinic visits with chest X-rays, CT-scans may be proposed for long-term surveillance with the objective of detecting second primary lung cancers. Patients who have undergone surgery for lung cancer are just logically good candidates for lung cancer screening. In the first two postoperative years, chest CT-scan does probably not need to be performed as often as every six months. Beyond five years, in the absence of solid data, hypothesizing that the risk of second primary lung cancer is at least constant, chest CT-scan surveillance can be extended, extrapolating from lung cancer screening. If long-term chest CT-scan screening is considered, CT-scan should be performed with minimal invasiveness, avoiding contrast enhancement and minimising radiation exposure. References: 1. Lou F, Sima CS, Rusch VW, Jones DR, Huang J. Differences in patterns of recurrence in early-stage versus locally advanced non-small cell lung cancer. Ann Thorac Surg. 2014 Nov;98(5):1755–60; discussion 1760-1761. 2. Lou F, Huang J, Sima CS, Dycoco J, Rusch V, Bach PB. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg. 2013 Jan;145(1):75–81; discussion 81-82. 3. Westeel V, Barlesi F, Foucher P, Lafitte J-J, Domas J, Girard P, et al. Abstract 1273O. Results of the phase III IFCT-0302 trial assessing minimal versus CT-scan-based follow-up for completely resected non-small cell lung cancer (NSCLC). Ann Oncol. 2017 Sep 1;28(suppl_5):mdx378.012-mdx378.012. 4. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg. 1975 Oct;70(4):606–12. 5. Vansteenkiste J, Crino L, Dooms C, Douillard JY, Faivre-Finn C, Lim E, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2014 Aug;25(8):1462–74.

Keywords: follow-up, surveillance, resected lung cancer

MS18 MANAGEMENT OF SCLC PATIENTS NOT REPRESENTED IN CLINICAL TRIALS
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MS18.01 TREATMENT OF PATIENTS WITH POOR PERFORMANCE STATUS (ECOG 3-4)

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Performance status (PS) is a strong prognostic factor in most solid tumors, often impacting on oncologists' approach.[1] In small cell lung cancer (SCLC), treatment decision in patients with poor PS is a challenging and complex one. To fully contemplate this matter, one must take into account the specificities of this disease, the current knowledge on the field and possible alternatives in order to take the most ethical and supported decision.[2] Let's start by imagining a case of a 60 year-old male with a history of heavy smoking, that was admitted due to extensive-stage SCLC presenting with shortness of breath, superior vena cava syndrome (SVCS), and significant weight loss. The ECOG PS was 3. His serum LDH was 600 U/l, and sodium was 120 mEq/L. A PET-CT showed an infiltrative mediastinal mass causing compression of the superior vena cava, in addition to several liver metastases (TNM stage IVB). No brain metastasis was detected on a brain MRI. This case may seem quite familiar to many attending clinicians that routinely care of lung cancer patients. For instance, this case highlights the early metastatization of SCLC, which presents with extensive stage in around two-thirds of patients. It is also known that approximately 10% of SCLC patients present with SVCS; constitutional symptoms such as weight loss may indicate extrathoracic spread; and hyponatremia may be related to paraneoplastic syndrome of inappropriate antidiuretic hormone (SIADH).[3] The correct frequency of SCLC patients presenting with a poor PS is not fully described, however the literature points that approximately 30-40% of lung cancer patients may present with PS 2-4. In SCLC, it has been described that up to 30% of patients may have a PS of 3 or 4,[1] which is in line with its rapid growth and spread. Given this aggressive nature and the high response rate to systemic therapy, it is recommended that SCLC patients be managed promptly, avoiding delays to diagnose and stage. Most experts recommend initiating specific therapy within 1-2 weeks of diagnosis in order to avoid significant worsening in symptoms and PS.[3] When appreciating a SCLC patient with a poor PS, one can realize the clear lack of evidence to guide therapy decision in this setting.[2] In fact, most clinical trials will only enroll PS 0-1, limiting the representativeness and generalization of their findings. Patients with PS 2 generally derive lower benefit from chemotherapy (CT) in clinical trials, presenting worse response rate and shorter progression-free survival.[2] In regards to PS 3 or 4, these are never represented in clinical trials. The clinical approach is therefore guided based on expert consensus. Guidelines recommend consideration of combination CT when poor PS is due to disease symptoms.[4] In our case, the PS 3 seems to be a constitutional manifestation of advanced SCLC, which could be reversed with CT. Dyspnea caused by SVCS could also be alleviated with CT. SCLC is one of the rare exceptions where oncologists may be willing to offer palliative CT even in poor PS patients. A common routine is to try a couple of CT cycles, hoping that patients will experience an improvement in symptoms and PS.[2] Nevertheless, one should also take into account several other factors that may limit the willingness to start systemic therapy, including the poor prognosis, CT toxicity, and patient/family expectations.[5] In reality, data show that only a limited subset of cases will experience longer survival. In a review of 40 SCLC patients presenting with poor PS, median overall survival was 64 and 7 days in PS 3 and 4, respectively.[6] Thirty-five percent of patients received only one CT cycle, and 30% died prematurely after the first cycle - mostly PS 4.[6] In these situations, palliative measures may be utilized, instead of CT, and help improve quality of life. In general, second-line CT is limited to patients with favorable PS (0-2) since response rate tends to be low. Prophylactic cranial irradiation is not recommended for patients with poor PS.[4] Adding up to this complex therapy decision, one should review the extreme of patients that require admission to an intensive care unit (ICU). A hospital mortality of 72% has been described among 25 consecutive SCLC cases, independently of therapy.[7] In particular, all SCLC patients requiring mechanical ventilation died within 3 months of ICU admission, mostly during the ICU stay.[7] This kind of outcomes may be strongly considered when discussing therapy decisions with patients and families. Novel therapies have revolutionized NSCLC therapy, including small targeted inhibitors and immunotherapy. In SCLC, PD1/PDL-1 inhibitors have shown activity in a subset of cases, especially in combination with CTLA4 inhibitors or CT.[8] Nevertheless, combination immunotherapy may cause significant toxicity that limits its indication in patients with poor PS. Unfortunately, this matter will not be addressed in ongoing clinical trials, leaving oncologists with the difficult task of deciding if immunotherapy – alone or in combination – is appropriate in these settings. One possible approach to be evaluated in clinical trials is to start combination immunotherapy after the best response to induction CT, hence selecting for responding patients that may present a more favorable prognosis. This study concept illustrates the importance of designing specific trials for "real world" patients that often present with limited PS. In summary, SCLC patients may often present with poor PS. These cases should be approached by a multidisciplinary team with expertise to conduct both aggressive and palliative measures with the primary goal of providing symptom relief and, whenever feasible, extend survival. At the end of the day, the Hippocrates quote is more up to date than ever: "To cure sometimes, to relieve often, to comfort always". References 1. Lilenbaum RC, et al: J Thorac Oncol 3:125-9, 2008 2. Gajra A, et al: J Natl Compr Canc Netw 12:1015-25, 2014 3. Pietanza MC et al: In: DeVita 2015 4. NCCN Guidelines 2018 5. 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Keywords: performance status, small cell lung cancer, palliative care

MS18 MANAGEMENT OF SCLC PATIENTS NOT REPRESENTED IN CLINICAL TRIALS
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MS18.02 TREATMENT OF ELDERLY PATIENTS WITH SCLC

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Small cell lung cancer accounts for approximately 30,450 (13%) new cases of lung cancer each year in the United States. The worldwide incidence is unknown. SCLC frequently occurs in elderly patients as defined by ≥70 years of age. A recent analysis of the surveillance, epidemiology and end results (SEER) database showed the incidence of elderly patients diagnosed with SCLC increased from 23% in 1975 to 40% in 2010 with a quarter of patients age 80 or greater (1). Due to comorbidities associated with the aging process resulting in frailty and organ dysfunction, elderly patients (especially patients over the age of 80) may not be offered treatment and are underrepresented in clinical trials. This presentation will review the available retrospective and prospective data. Limited Stage SCLC (LS-SCLC) Concurrent chemoradiation is the standard of care for patients with limited stage disease. Three age-specific retrospective analyses of randomized, North American cooperative group studies evaluating cisplatin-based regimens did not demonstrate significant differences in overall survival or other efficacy endpoints by age (2). However, two of the studies reported significantly increased treatment related toxicity and mortality in the elderly population. To address the toxicity issue, phase II trials evaluated modified chemotherapy and radiotherapy regimens. These studies showed modified regimens were active and less toxic but no definitive trials have been performed. Alternatively, carboplatin is frequently substituted for the more toxic cisplatin in the concurrent regimen. Another approach is to omit the radiation and administer chemotherapy alone. However, a retrospective analysis of elderly LS-SCLC patients from the National Cancer Data Base from 2003 -2011 demonstrated the use of modern chemoradiation was superior to chemotherapy alone

on univariate and multivariate analysis with a 3-year OS of 22% vs 6.3% respectively, P<.001. This effect was seen in patients 80+ years and in patients with comorbidities (3). A subset analysis also showed concurrent treatment significantly improved survival over sequential treatment. Similar findings were observed by the Dutch (4). Extensive Stage SCLC (ES-SCLC) Etoposide and a platinum agent (cisplatin or carboplatin) is the standard of care for upfront treatment of ES-SCLC. Despite the acceptance of etoposide plus carboplatin as a tolerable and equivalent regimen, elderly patients may not receive treatment. A review of the Alberta Cancer Registry revealed that 32% of patients age 75+ did not receive chemotherapy (5). Of the patients who received chemotherapy, 52% completed all cycles and 66% did not require a dose reduction. Patients who completed all cycles with a dose reduction had a decreased risk of death 1.02 (95% CI: 0.57-1.82) compared to a risk of death of 2.72 (95% CI: 1.52-4.87) for patients who did not complete therapy. Four phase II studies evaluating dose modifications of carboplatin and etoposide in the elderly found similar survival outcomes to standard doses (5). In a recent phase II study from China 34 elderly patients or patients with a PS of 2 who received carboplatin and etoposide had a median PFS of 5.8 months and an OS of 14 months (6). Toxicity was acceptable with Grade 3 or greater neutropenia and febrile neutropenia occurring in 40% and 7% of patients, respectively. Prophylactic Cranial Irradiation The role for prophylactic cranial irradiation (PCI) in the elderly population is controversial. Retrospective population based and trial specific analyses have shown that PCI improves survival compared to no PCI but concern over increased neurocognitive dysfunction has resulted in limited uptake of PCI (7-9). Indeed, a comparison of tested and self-reported cognition in two RTOG trials evaluating PCI in patients with LS-SCLC demonstrated higher rates of cognitive decline with advanced age (10). Modern radiation techniques, hippocampal sparing and memantine may reduce the rate of cognitive decline. Recent data also suggests that MRI surveillance may be an option for patients with ES-SCLC (11). Geriatric Assessment Tools Geriatric oncology is addressing the optimal approach to the care of these patients through the development of geriatric assessment tools to better define risks and benefits. Investigators are encouraged to incorporate these tools into their clinical trials. Treating physicians should also consider using validated geriatric assessment tools in their routine practice such as the new ASCO 2018 guideline (12). Overall, elderly patients should be offered standard treatment but they may require dose modifications. Participation in clinical trials and trials that address the unique needs of the elderly are strongly encouraged. REFERENCES Abdel-Rahman O. Changing epidemiology of elderly small cell lung cancer patients over the last 40 years; a SEER database analysis. *Clin Respir J*. 12:1093-9, 2018. Palis AG, et al. Treatment of small-cell lung cancer in elderly patients. *Cancer*. 116:1192-200, 2010. Corso CD, et al. Role of Chemoradiotherapy in Elderly Patients With Limited-Stage Small-Cell Lung Cancer. *J Clin Oncol*. 33:4240-6, 2015. Janssen-Heijnen ML, et al. Tolerance and benefits of treatment for elderly patients with limited small-cell lung cancer. *J Geriatr Oncol*. 5:71-7, 2014. Fisher S, et al. Uptake and tolerance of chemotherapy in elderly patients with small cell lung cancer and impact on survival. *J Cancer Epidemiol*. 2012:708936, 2012. Igawa S, et al. Comparison of carboplatin plus etoposide with amrubicin monotherapy for extensive-disease small cell lung cancer in the elderly and patients with poor performance status. *Thorac Cancer*. 2018, Jun 5 [Epub ahead of print]. Eaton BR, et al. Effect of prophylactic cranial irradiation on survival in elderly patients with limited-stage small cell lung cancer. Cancer. 119:3753-60, 2013. Rule WG, et al. Prophylactic cranial irradiation in elderly patients with small cell lung cancer: findings from a North Central Cancer Treatment Group pooled analysis. J Geriatr Oncol. 6:119-26, 2015. Damhuis RAM, et al. Usage of Prophylactic Cranial Irradiation in Elderly Patients With Small-cell Lung Cancer. *Clin Lung Cancer*. 19:e263-7, 2018. Gondi V, et al. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. *Int J Radiat Oncol Biol Phys*. 86:656-64, 2013. Takahashi T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 18:663-71, 2017.

Keywords: Elderly, Small Cell Lung Cancer, Treatment

MS18 MANAGEMENT OF SCLC PATIENTS NOT REPRESENTED IN CLINICAL TRIALS
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MS18.03 TREATMENT OF SCLC TRANSFORMED FROM EGFR MUTANT ADENOCARCINOMA

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While most molecular findings at time of resistance to EGFR tyrosine kinase inhibitors (TKIs) involve point mutations in the *EGFR* gene or the development of specific signaling bypass tracts, more fundamental changes in cell functioning can occasionally be seen. Indeed, neuroendocrine transformation, specifically to small-cell lung cancer (SCLC), is a relatively rare but recurrent finding at the time of acquired resistance to EGFR TKIs, developing in 3-10% of cases[1],[2],[3]. De novo, EGFR-mutant SCLC has also been reported and represents a subset of the very rare cases of SCLC seen in never-smokers[4]. In both instances, biopsies are histologically indistinguishable from the more frequent, smoking-associated SCLC. Although the transformed tumors maintain the same founder *EGFR* mutation as the initial adenocarcinoma at the DNA level, dependence on EGFR signaling is typically lost through reduced expression of the EGFR protein[5]. Patients with alterations of both TP53 and RB1 at the time of initial diagnosis of adenocarcinoma seem to be at significantly higher risk of transformation[6]. Although this finding was initially described with immunohistochemistry (IHC) assays, it is likely applicable to mutations found by next-generation sequencing (NGS) genotyping panels increasingly used in routine clinical care. Importantly, the percentage of patients with these anomalies that will eventually go on to transform is unknown. The threshold for obtaining tissue biopsy at progression should be lower in patients who are incidentally found to have mutations in *TP53* and *RB1* at initial diagnosis, but no intervention is currently known to decrease transformation risk. Mainly for that reason, specifically obtaining TP53/RB1 IHC or mutational status at diagnosis should be considered investigational. Rather than a linear evolution from NSCLC to SCLC, many experts believe that small-cell transformation occurs in the context of multiple clonal subpopulations evolving dynamically. The cell population that eventually becomes clinically apparent as SCLC has been shown to branch out early from the main adenocarcinoma subpopulation[6], sometimes even prior to initial clinical diagnosis of lung cancer. Clinically, small-cell transformations are usually seen after months to years of TKI therapy (as discussed next), which leads to the hypothesis that the small-cell-prone clonal subpopulation can remain dormant for long periods of time. Although APOBEC-induced hypermutation has been shown to occur in these cells, the specific mechanisms at play during this apparent prolonged period of cell dormancy remain largely unknown. Another proof of the polyclonal nature of these cancers can be seen in the occasional reversal to NSCLC histology at progression after administration of a SCLC-directed therapy such as platinum-etoposide[7]. Due to the rarity of SCLC transformation, published clinical data related to patients' evolution is retrospective and almost exclusively in the form of case reports. However, a retrospective series of 67 EGFR-mutant patients with SCLC transformation treated in 11 high-volume North American centers was recently presented[8]. Demographic characteristics, including age, race and smoking status, were concordant with the general EGFR population and median time between initial diagnosis of metastatic NSCLC and SCLC transformation was 18 months. Almost all patients were actively receiving TKI therapy at time of transformation. Median overall survival from initial diagnosis was 32 months, similar to what is seen in standard EGFR-mutant NSCLC. However, once SCLC was identified (including in 9 patients with de novo EGFR-mutant SCLC), median survival was 11 months, more in line with what is seen in smoking-associated SCLC. While high clinical response rates to platinum etoposide (54%) and taxanes (50%) were noted, these responses were mostly transient, with median progression-free survivals of 3.4 and 2.7 months respectively. Importantly, considering the interest surrounding these therapies, no responses were seen in 17 patients who received checkpoint inhibitors, including the ipilimumab-nivolumab combination. Cytotoxic chemotherapy, especially the classic regimen of platinum-etoposide, thus appears to be the favored initial approach to SCLC-transformation. Potential for reversal to NSCLC, performance status and toxicity profiles must be taken into account for later lines of therapy. Although CNS involvement is frequent, prophylactic cranial irradiation is not recommended. Despite these recent improvements in our understanding of EGFR-mutant small-cell transformation, its rarity makes it challenging to prospectively evaluate novel therapeutic strategies. Prospective identification of patients at high risk of transformation and multicentric collaborative efforts will likely be needed to improve outcomes for this entity. [1]Piotrowska Z, Stirling K, Heist R, et al. OA 07.05 Serial Biopsies in Patients with EGFR-Mutant NSCLC Highlight the Spatial and Temporal Heterogeneity of Resistance Mechanisms. Journal of Thoracic Oncology. 2017 Nov 1;12(11):S1762. [2]Sullivan I, Planchard D. Osimertinib in the treatment of patients with epidermal growth factor receptor T790M mutation-positive metastatic non-small cell lung cancer: clinical trial evidence and experience. Therapeutic advances in respiratory disease. 2016 Dec;10(6):549-65. [3]Yu H, Arcila ME, Rekhtman N, et al. 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Keywords: small-cell transformation, EGFR, SCLC

MS18 MANAGEMENT OF SCLC PATIENTS NOT REPRESENTED IN CLINICAL TRIALS
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MS18.04 RETREATMENT WITH PLATINUM AND ETOPOSIDE AND TREATMENT BEYOND SECOND LINE

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Extensive stage small cell lung cancer (SCLC) is characterized by an initial response to chemotherapy followed by progression usually within 6 months. The clinical approach to second line therapy and beyond depends on patient wishes, performance status (PS), and duration of response to initial therapy or progression free interval (PFI). While some have challenged the importance of PFI in selection of subsequent therapy (1), guidelines by the European Society of Medical Oncologists (ESMO) (2) and the American College of Chest Physicians (ACCP)(3), recommend treatment options based on PFI. This presentation will focus on retreatment with platinum-based chemotherapy and treatment beyond second line. The ACCP guidelines, which have been endorsed by the American Society of Medical Oncology (ASCO) recommend re-challenge with the first line regimen in patients with a PFI of at least 6 months. The ESMO guidelines define sensitive relapse as a PFI of more than 3 months and suggest these patients may derive benefit from re-challenge with the original, usually platinum based, regimen. Genestreti (4) evaluated the benefit of re-challenge with platinum-etoposide in a retrospective, multi-institutional review. In 112 patients who progressed more than 90 days after initial chemotherapy, re-challenge with platinum-etoposide resulted in a response rate (RR) of 45% and a median overall survival (mOS) from re-challenge of 7.9 months. There was no difference in survival using PFI of 90, 120, or 150 days. A second European multicenter study (5) reported outcomes of 161 patients receiving second line therapy. Platinum sensitive patients (PFI 3 months) who were re-challenged had a higher RR and longer mOS. Response to first line therapy and PS were independent predictors of survival. Single institutional series have also supported the importance of sensitivity to first line therapy in determining second line treatment. Nagy-Mignotte (6) defined sensitive disease as PFI of at least 3 months. Of the 300 patients who received first line platinum-etoposide therapy, 48% had sensitive disease and the majority of these (72%) were re-challenged. The RR to re-challenge was 65% (21% complete response) and mOS from second line was 9.3 months. Patients with resistant or refractory disease were primarily treated with taxanes or topotecan. The RR in these patients was 21% with mOS of 5.2 months and 3.8 months. Kim et al (7) found response to initial therapy and PS to be significantly associated with survival after second line therapy in 232 patients from a single institution in Japan. Treatment Beyond Second Line There are currently no approved third line therapies for SCLC and the evidence for benefit from any therapy consists of retrospective reports and phase II trials. In the largest series reported from Japan (8) only 30% of SCLC patients receiving first line therapy went on to receive third line treatment. The majority of patients received single agent therapy in third line with amrubicin being most common (47%). Independent prognostic factors were time to treatment failure of at least 5 months and PS at time of third line therapy. A Dutch study found only 18% of their SCLC patients received at least 3 lines of therapy. The RR to third line was 25% with mOS of 5 months (9). An international multi-center retrospective analysis (10) found that the majority of patients were re-challenged with a regimen previously received in first or second line, with 6% of patients receiving platinum-based chemotherapy in all 3 lines. The RR was modest at 18% with mOS from third line of 4.7 months. Response to second line therapy was predictive of response to third line but only baseline LDH was prognostic for survival. It is clear that few patients with SCLC go on to receive treatment beyond second line. However, carefully selected patients with good PS may derive benefit. There is a need for new, active therapies. The most promising new options for treatment beyond second line include targeted therapy to DLL3 (rovalpituzumab-T) and immunotherapy. Updated results with these agents will be discussed. References Lara P et al Journal of Thoracic Oncology 2015; 10(1):110-115 Fruh M et al Annals of Oncology 2013; 24 (Suppl 6): vi99-vi 105 Jett J et al Chest 2013; 143 (5) (Supp): e4005-e4019 Genestreti G et al Clinical Lung Cancer 2015; 6: 223-8) Garassino MC et al Lung Cancer 2011; 72: 378-83 Nagy-Mignotte H Clinical Lung Cancer 2012; 78: 112-120 Kim YH et al Cancer 2008; 113: 2518-23 Saruwatari K et al Clinical Lung Cancer 2016; 17:581-87 DeJong WK et al, Lung Cancer 2006; 52: 339-42 Simos D et al Clinical Lung Cancer 2014; 15: 110-118

Keywords: retreatment small cell

MS19 PULMONARY DILEMMAS WITH IMMUNOTHERAPY
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MS19.01 DRUG-INDUCED PNEUMONITIS WITH IO: HOW WORRIED SHOULD WE BE FOR OUR LUNG CANCER PATIENTS

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In recent years, indications for the use of immune checkpoint inhibitors (ICI) in the treatment of non-small cell lung cancer (NSCLC) have been rapidly expanding. With the increased use of ICI comes concern about monitoring and managing rare, but serious, side effects including pulmonary toxicities. Pneumonitis is a general term typically used to describe non-infectious causes of focal or diffuse inflammation of the lung parenchyma and may encompass analogous terminology including acute interstitial pneumonitis, interstitial lung disease, and pulmonary fibrosis. Several meta-analyses and larger scale systematic or institutional reviews have illustrated that across clinical trials of ICI in various cancer types, pneumonitis has only been reported at low frequencies and has generally been of low grade [1-6]. Serious cases including death from pneumonitis are rare. ICI-related pneumonitis can be challenging to diagnose as there are no pathognomonic clinical or radiographic findings that define this condition. The symptoms of pneumonitis, including dyspnea and cough, may be subtle and, particularly among lung cancer patients, these symptoms may be difficult to distinguish from other common conditions such as chronic obstructive pulmonary disease, infection or simply the patient's underlying malignancy. Up to one third of cases of pneumonitis are asymptomatic [4] and documented solely on imaging hence a high index of suspicion is required to make the diagnosis. Most commonly pneumonitis has been reported to occur within the first few months of initiating ICI therapy, however pneumonitis can occur as early as the first dose or may even emerge after ICI treatment has been discontinued [4, 6, 8]. Often, the onset of pneumonitis coincides with other immune related adverse events (irAEs) [4]. Concurrent or sequential use of CTLA-4 and PD-1 blockade appears to increase the risk of pneumonitis [1, 2, 4], while age, ethnicity, and chemotherapy do not [9]. The influence of smoking history [4, 9], tumour type [1-2] and radiation [7, 9] on developing ICI-related pneumonitis is less clear as various groups have reported differing observations. There is also considerable variability in radiographic presentation [4, 6, 8] thus bronchoscopy and lung biopsy may be valuable tools to exclude alternate diagnoses. Even on pathology though, there are no definitive findings characterizing pulmonary irAEs [4]; histopathological findings ranging from diffuse alveolar damage to sarcoid granulomas have been described [4, 6]. In small series, a correlation has been noted between anti-tumour activity with ICI and the occurrence of irAEs [3], but this too remains unproven and is not specific to pneumonitis. At present, there are no validated treatment recommendations for pneumonitis resulting from treatment with ICI. Management of ICI pneumonitis follows the same general guidelines as other irAEs namely, withholding ICI, starting steroids, and if needed, using additional immunosuppressants such as mycophenolate mofetil or infliximab [10]. Like most irAEs, pneumonitis is generally steroid-responsive and usually resolves within 4-6 weeks [10]. The prolonged half-life of the antibodies necessitates the protracted period of corticosteroid treatment and slow tapering. Only very limited data is available regarding re-challenge with ICI after development of pneumonitis. Again, in small series - all involving 10 or fewer patients - 25-30% of patients re-challenged with ICIs developed recurrent pneumonitis [1, 4, 9]. In conclusion, immune-related pneumonitis is a rare, but potentially fatal, side effect of ICI for which vigilance in monitoring is required in order to ensure timely diagnosis and treatment. As pneumonitis is usually a diagnosis of exclusion, multidisciplinary input is often required to make the diagnosis. The results from meta-analyses and several large reviews on irAEs provide reassurance that for the vast majority of NSCLC patients, ICIs can safely be administered and are well tolerated treatments. SELECTED REFERENCES: 1. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of programmed cell death 1 inhibitor related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. JAMA Oncol 2016; 2(12):1607-1616. 2. Abdel-Rahman O, Fouad M. Risk of pneumonitis in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Ther Adv Respir Dis 2016; 10(3):183-193. 3. Costa R, Carneiro BA, Agulnik M, et al. 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Keywords: pneumonitis, immune checkpoint inhibitors, non-small-cell lung cancer

MS19 PULMONARY DILEMMAS WITH IMMUNOTHERAPY
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

INVITED SPEAKER
MINI SYMPOSIA

MS19.02 WHAT ARE THE CLINICAL FEATURES OF IO PROGRESSION/ PSEUDOPROGRESSION AND RADIATION FIBROSIS VS RECURRENCE

C. Liam

Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur/ MY

IO Progression vs Pseudoprogression The patterns of response to treatment with immunotherapy differ from those with molecularly targeted agents or cytotoxic chemotherapy where responses can take appreciably longer to become apparent. In addition, a unique response pattern termed "pseudoprogression" may be encountered with immunotherapy with checkpoint inhibitors in which patients appear to have a transient worsening of disease, manifested either by progression of known lesions or the appearance of new lesions, before disease stabilizes or regresses. While pseudoprogression is rare in lung cancer with reported rates of < 5%, it is a worrying situation for both clinicians and patients on immunotherapy.[1,2] It can be difficult to differentiate pseudo-progression from true disease progression, but close monitoring of the following clinical features may help identify pseudoprogression - Pseudoprogression is often asymptomatic, whereas true progression is more likely to be associated with clinical decline. - The patient's performance status remains stable or improves if it is pseudoprogression while the performance status may deteriorate in true disease progression - Systemic symptoms may or may not improve in pseudoprogression while systemic symptoms often worsen in disease progression - Symptoms of tumour enlargement may or may not be present in pseudoprogression whereas true progression may be associated with symptoms of tumour enlargement - There is an initial increase in baseline tumour burden followed by a response in pseudoprogression while there is an increase in baseline tumour burden in true progression. New lesions that appear in pseudoprogression remain stable and/or subsequently respond while in true progression, new lesions appear and increase in size. Biopsy may reveal evidence of immune cell infiltration in pseudoprogression[3,4] and evidence of tumour growth in true progression. However, histological confirmation is not always possible. Smaller deposits of tumour may continue to grow or new lesions appear in the first few months of effective immunotherapy during this period of immune priming and appear as progressive disease on restaging scans. These areas of apparent pseudoprogression should be carefully followed to distinguish nonresponding patients with progressive disease from those with delayed response. Distinguishing treatment-induced imaging changes from progressive disease has important implications to avoid premature and inappropriate discontinuation of a treatment regimen. **Radiation Fibrosis vs Recurrence** Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT), is a recommended treatment for stage 1 non–small-cell lung cancer (NSCLC) in patients who are medically inoperable or refuse surgery. Most patients treated for NSCLC with SABR develop post-treatment radiographic changes due to radiation-induced lung injury (RILI) which can occur in the acute phase (within six months) as radiation pneumonitis and in the late phase (after six months) as radiation fibrosis. With SABR, the incidence of acute- and late-onset RILI is high with acute benign computed tomography (CT) changes in 54-79% of patients and late changes in 80–100% of patients.[5] Radiation pneumonitis may appear as ground-glass opacities, consolidation or both. The late phase of radiation fibrosis frequently appears as a well-defined area of volume loss with a linear scar or consolidation, parenchymal distortion and traction bronchiectasis that conforms to the treatment portals which may either stabilize or evolve up to 24 months. Shrinkage of the region of fibrotic consolidation or a more sharply defined demarcation between normal and irradiated lung parenchyma may occur as the process progresses. Such benign CT changes can mimic tumour recurrence, especially when they develop as mass-like patterns.[6] Distinguishing radiological changes due to radiation-induced fibrosis after SABR and local tumor recurrence can be quite challenging.[7] A systematic review by Huang et al.[7] identified several high-risk radiologic features on CT scan to discriminate between SABR-induced fibrosis and tumor recurrence. These include an enlarging mass-like lesion at the primary site, sequential enlarging opacity, enlarging opacity after 12 months, bulging margins, disappearance (loss) of linear margins, craniocaudal growth, disappearance (loss) of air bronchograms, ipsilateral pleural effusion, or lymph node enlargement. While some sources caution against the use of PET scans to differentiate between post-SBRT fibrosis and recurrence, others have postulated a SUVmax of $\geq$ 5 can be a useful discriminator.[a,b,d] Due to a high number of false-positive findings on PET, patients suitable for salvage therapy should undergo a biopsy, whenever possible.[8] The optimal follow-up schedule for patients treated with SABR for early stage NSCLC is unclear, although clinical practice guidelines of the European Society for Medical Oncology recommend CT imaging every 6 months for a period for at least 3 years in those patients suitable for salvage therapy.[8]The timing of local recurrence after SABR, as well as a persistent risk of second primary lung cancer with an annual rate of 2% to 5%, suggests that long-term radiological follow-up using CT scans is needed, especially in patients fit enough to undergo any radical treatment. Others recommend a post SABR follow-up strategy similar to that of postsurgical cases, i.e. all patients eligible for any type of salvage undergo 6 months follow-up CT scans for a period of 3 years post-SABR, followed by annual CT scans thereafter.[9,10] With suspicion of progressive disease, recommendations include a multidisciplinary team discussion with consideration for biopsy and/or surgical or nonsurgical salvage therapy if safe and when further investigations are non-reassuring.[10] **References** 1. Fehrenbacher L, Spira A, Ballinger M, et al. Lancet. 2016; 387(10030):1837-1846. 2. Borghaei H, Paz-Ares L, Horn L, et al. N Engl J Med. 2015; 373(17): 1627–1639. 3. Wolchok JD, Hoos A, O'Day S, et al. Clin Cancer Res. 2009; 15(23):7412-7420. 4. Ribas A, Chmielowski B, Glaspy JA. Clin Cancer Res. 2009; 15(23):7116-7118. 5. Park KJ, Chung JY, Chun MS, Suh JH. Radiographics 2000; 20:83-98. 6. Linda A, Trovo M, Bradley JD. Eur J Radiol 2011; 79(1):147-154. 7. 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MS19 PULMONARY DILEMMAS WITH IMMUNOTHERAPY
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MS19.03 DIAGNOSTIC APPROACHES SUSPECTED IO PROGRESSION/ PSEUDOPROGRESSION AND WHAT/WHEN TO REBIOSPY FOR TT PROGRESSION

K. Czarnecka-Kujawa

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The 2000's marked the beginning of precision medicine era with treatment of NSCLC becoming increasingly personalized. This was driven by effective therapies in biomarker-defined populations, most notably treatments targeting the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), programmed cell death-1 (PD-1), and programmed cell death ligand-1 (PD-L1) pathways (1) testing for which is now the standard of care for majority of patients with NSCLC, both, at the time of diagnosis and with recurrent disease (2-4). In addition, testing indications emerged for other proto-oncogenes, many of which are actively investigated as therapy targets (3, 5). In addition, given development of effective treatments for recurrent NSCLC in setting of acquired resistance (AR) to targeted therapies (TT), the minimally-invasive tumor sampling to identify resistance mutations has become increasingly attractive, given frailty of population with metastatic lung cancer (4, 6). Imaging and clinical patient status are used to diagnose cancer progression, pseudoprogression and recurrence. Conventional tumor response criteria serve as standardized measures for treatment response in NSCLC. However, given unique tumor behaviour upon exposure to immunotherapy, immune response criteria have been developed to assess treatment response in patients on immunotherapy (7). While preparing to obtain a diagnostic sample in setting of suspected disease recurrence/progression one should consider: 1) procedural safety and convenience; 2) size of tissue sample, 3) proportion of tumor cells in the sample; 4) fixative used to preserve tissue; 5) tumor heterogeneity; 6) difference in genetic make up of the primary and metastatic tumor(4). The choice of diagnostic procedure to confirm disease recurrence/ progression must be guided by the procedure safety and diagnostic yield.

Percutaneous or surgical lung biopsies, are often not possible for patients with advanced lung cancer. The minimally-invasive techniques have become an attractive alternative for tissue acquisition in this setting. The most common, minimally-invasive techniques utilized by interventional pulmonologists are: 1) transbronchial biopsy (TBBx) or transbronchial needle aspiration (TBNA); 2) Endoscopic techniques: Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA) and Esophageal Ultrasound- guided Fine Needle Aspiration (EUS-FNA); 3) and pleural fluid sampling. Studies show that endoscopic techniques provide tissue of comparable quantity and quality material for molecular testing compared to surgical or conventional needle biopsy. Reported adequacy of EBUS-TBNA samples for molecular diagnosis ranges from 77% to 98% (8). EBUS samples have one of the lowest insufficiency rates (4%) for EGFR and KRAS mutational analysis (compared with CT-FNA – 7.5%; ultrasound guided/superficial FNA- 10%) and can provide sufficient tissue quantity for multigene testing (i.e. p53 mutation, BRAF and PIK3CA) (8). EBUS-TBNA samples have been shown to yield a higher number of viable cells with less crush artifact and better concordance with the primary tumor for expression of the PD-L1 than TBBx (9). TBNA has been shown to improve diagnostic yield in NSCLC when added to conventional TBBx. High concordance has been reported for detection of EGFR mutation and PD-L1 expression between primary and metastatic tumors. Some authors suggest that either of the two sites can be used for molecular testing. However, there is a significant heterogeneity in PD-L1 expression within tumors (10). Additionally, AR to Tyrosine Kinase Inhibitors (TKI) develops almost invariably within 8–16 months on TKI use, resulting in disease progression. The T790M mutation is the most common mechanism of AR with TT available for patients baring this EGFR aberration. During workup of recurrence, some of the patients will be diagnosed with transformation into a new primary lung cancer, which warrants different treatment than metastatic NCSLC. For these reasons, an attempt should be made to obtain a fresh tissue sample if disease progression/relapse are suspected. Pleural fluid cytology has been shown to be an excellent source of tumor cells with high yield in detection of both EGFR and ALK mutations(5). In all instances, bronchoscopist should work closely with cytopathologists seeking feedback on tissue quality, quantity for ancillary testing (5). 1. Thai AA, Solomon BJ. Treatment of ALK-positive nonsmall cell lung cancer: recent advances. Current opinion in oncology. 2017. 2. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, et al. 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Keywords: Interventional Pulmonology, Metastatic Lung Cancer, Diagnosis

MS20 INNOVATIVE AND EVOLVING STRATEGIES IN DIAGNOSIS AND MANAGEMENT OF STAGE I NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MS20.01 ROBOTIC AND INNOVATIVE SURGERY

W. Hanna
Thoracic Surgery, McMaster University, Hamilton/ON/CA

In the era of personalized lung cancer treatment, surgery is follwoing the trend of targeted therapy. As lung cancer becomes easier to detect at early stages with low dose computed tomography, innovations in surgery have been developed to make targeted surgery easier and more prevalent. This talk will focus on novel innovations in surgery for small pulmonary nodules. We will discuss targeted robotic surgery, mapping with near-infrared techology, electromagnetic navigation, 3D preoperative mapping and simulation, hybrid operating rooms, and minimally invasive staging. We will also touch on the role of Artificial Intelligence in the future of surgery for lung cancer. The goal of this talk would be to introduce the audience to the future of surgical treatment of early stage lung cancer.

Keywords: Robotic surgery, Targeted Surgery, Surgical Innovation

MS20 INNOVATIVE AND EVOLVING STRATEGIES IN DIAGNOSIS AND MANAGEMENT OF STAGE I NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MS20.02 THE FUTURE OF STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR)

B. Loo
Radiation Oncology, Stanford University, Stanford/CA/US

Stereotactic ablative radiotherapy (SABR) has produced a paradigm shift in the curative treatment of lung cancer over the past two decades. Particularly in stage I lung cancer, systematic clinical investigation through prospective trials has established SABR as the current standard of care for definitive treatment in patients who are medically inoperable or have contraindications to surgery. Optimization of treatment protocols, better understanding of normal tissue tolerance to accelerated radiation, and technological advances have led to progressive improvements in efficacy, safety, and clinical efficiency, and are concomitantly expanding both the clinical adoption and indications for SABR of lung tumors to new and larger patient populations. With recent advances in systemic therapies, including genetically targeted agents and immunotherapies, successful eradication of micrometastatic disease is finally a prospect for a growing proportion of patients. As such, radical radiotherapy approaches including SABR will be increasingly crucial to achieve combined modality cures for many patients with all stages of lung cancer from early to metastatic. This lecture will review the major clinical data underlying the current practice of SABR and the emerging evidence and investigations pointing the way to its future.

Keywords: SABR, Stereotactic ablative radiotherapy

MS20 INNOVATIVE AND EVOLVING STRATEGIES IN DIAGNOSIS AND MANAGEMENT OF STAGE I NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MS20.03 IMMUNOTHERAPY AND SURGERY: NEOADJUVANT OR ADJUVANT? IS IT SAFE?

J. Chaft
Thoracic Oncology, Memorial Sloan Kettering Cancer Center, New York/NY/US

Background: Immune checkpoint blockade (ICB) has become a standard of care for many patients with non-small cell lung cancer, either alone or in combinations with standard chemotherapy. There is also an emerging role of combinations after progression on targeted therapies. The role of ICB in the perioperative setting is yet to be defined. Many large trials have launched to evaluate either neoadjuvant or adjuvant ICB drugs alone or in combination with chemotherapy. Preclinical data: Preclinical data demonstrate a greater efficacy of neoadjuvant versus adjuvant ICB in eliminating distant metastases after resection of the primary triple negative breast cancer tumor in mouse models.[1] This preclinical data has fostered enthusiasm for neoadjuvant studies of ICB in resectable lung cancers, though none of these presently designed studies directly compare neoadjuvant to adjuvant ICB therapy. Clinical data: The TOP1201 study was the first to evaluate ICB with ipilimumab in addition to carboplatin + paclitaxel in early-stage NSCLC. Of 24 patients treated, only 13 were ultimately resected 2 with delays due to diarrhea, 11 were deemed not appropriate for surgery after treatment, 1 because

of toxicity.[2] There was no obvious safety concern posteropatively when compared to non-randomized controls treated with preoperative chemotherapy. There was also no signal of added benefit from addition of ipilimumab in this study in an unselected population, comparable to studies in metastatic disease. The recently published study of neoadjuvant nivolumab was different by design. In this two-institution study resectability was defined pretreatment, and 20 of 21 patients were completely resected without delay. A high rate of major pathologic response was seen after only 2 doses of nivoluamb in this study. There were no safety signals.[3] Preliminary presentations of data from the lung cancer mutation consortium study of neoadjuvant atezolizumab and the single institution study of carboplatin + nab-palictaxel + atezolizumab have met their pre-defined safety and efficacy boundaries for expansion, respectively.[4,5] Ongoing studies: By nature of design, the presenting data is from neoadjuvant studies where efficacy and safety signals are available faster than those in a standard adjuvant study design. This should not negative the huge international efforts ongoing to evaluate the efficacy of adjuvant ICB after resection and standard adjuvant therapy for resected NSCLC. There are 4 ongoing randomized phase 3 studies comparing single agent anti-PD-(L)1 agents versus observation or placebo. In the neoadjuvant space, the phase 2 studies listed above will expand to provide larger datasets anticipated to result in the next year. Other small phase 1 and 2 efforts are ongoing. Additional large phase 3 efforts comparing neoadjuvant chemotherapy to chemotherapy + ICB and some ICB combinations are actively recruiting internationally. These studies will answer important directly comparative questions and investigate the role of potential surrogates of survival, such as pathologic response. Conclusions: The field has embraced the importance of investigating immunotherapy in this potentially curative space, but we are years from being able to draw definitive conclusions from the randomized Phase 3 studies of perioperative ICB. Preclinical data suggest the neoadjuvant approach may be superior to adjuvant ICB and the single small reported study of neoadjuvant nivolumab showed a tremendous efficacy signal that ongoing studies hope to replicate.[3] While the rapidly enrolling adjuvant studies remain extremely important given the high rate of pathologic upstaging at the time of surgical resection, emphasis on appropriate patient identification for neoadjuvant study enrollment will lead to earlier trial readouts, important correlative science, and essential study of potential surrogate efficacy endpoints such as pathologic response. References: 1. Liu J, et al. Improved Efficacy of Neoadjuvant Compared to Adjuvant Immunotherapy to Eradicate Metastatic Disease. Cancer discovery 2016;6:1382-99. 2. Yang CJ, et al. Surgical Outcomes After Neoadjuvant Chemotherapy and Ipilimumab for Non-Small Cell Lung Cancer. Ann Thorac Surg 2018;105:924-9. 3. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. N Engl J Med 2018;378:1976-86. 4. Rusch, et al. Neoadjuvant atezolizumab in resectable non-small cell lung cancer: Initial results from a multicenter study (LCMC3). J Clin Oncol 36, 2018: supple; abstr 8541. 5. Shu C, et al. Neoadjuvant atezolizumab + chemothearpy in resectable non-small cell lung cancer. J Clin Oncol 36, 2018: supple; abstr 8532

Keywords: adjuvant immunotherapy, neoadjuvant immunotherapy, Immune checkpoint blockade

MS20 INNOVATIVE AND EVOLVING STRATEGIES IN DIAGNOSIS AND MANAGEMENT OF STAGE I NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MS20.05 BEYOND SURGERY - SUPPORT OF THE SURGICAL PATIENT

K. Kuhns
Thoracic Surgery, Penn Presbyterian Medical Center, Philadelphia/PA/US

Purpose: Discuss how to optimize patient support and education to achieve improved patient satisfaction, decrease patient anxiety, decrease readmission rates associated with post-operative complications and improve overall outcomes of the thoracic surgical patient. **Introduction:** Lung cancer is the most common cancer worldwide contributing 13% of the total number of new cases diagnosed in 2012. SEERS data shows that the five-year survival for lung cancer patients is only 18.6%. Surgery remains the gold standard of care for Stage I and II non-small cell lung cancer (NSCLC) and for selected patients with locally advanced Stage IIIA disease. Support and education of the thoracic patient is imperative to achieve the best outcomes in terms of physical, emotional, social and spiritual well-being. The support and education not only focus on the surgery but must also embrace the whole patient journey which includes lifestyle modifications, secondary prevention, knowledge and acceptance of their disease and self-empowerment. Thoracic patients undergoing surgery for a known or suspected lung cancer usually have little knowledge of what to expect during the preoperative, postoperative and recovery period. A dedicated multidisciplinary support system which includes physicians, advanced practice providers, nurses, radiologists, oncologists, therapists and nutritionists is needed to help patients navigate through this process to achieve optimal outcomes with minimal complications, decreased hospital stays, high patient satisfaction, low anxiety and lifestyle modifications that last long after recovery. Supporting the thoracic surgical patient begins at the first encounter and continues through the entire process which encompasses the pre-operative work up, surgery, recovery and beyond. During the initial encounter, the patient's support system, level of education, social and economic needs and lifestyle choices need to be identified. Most patients and their families are overwhelmed by the diagnosis of cancer or potential cancer and are not only frightened by the diagnosis, but also of the impact an illness will have on them emotionally and financially. Multiple studies have shown that good quality preoperative teaching increases patient satisfaction, improves patient outcomes, and decreases patient readmission rates following surgery. Although the benefit of preoperative education is widely recognized in the literature, finding the resources available to provide efficient and effective teaching is a challenge. Using multi-format education including written material, video, internet access, support groups and access to health care providers has been found to improve patient outcomes, decrease anxiety and improve patient satisfaction. Furthermore, supporting patients by use of existing programs within a health care system can also help achieve optimal outcomes in patient's undergoing thoracic surgery and reduce the cost. The use of nurse navigators, smoking cessation programs, nutritionists, outpatient rehabilitation, support groups and volunteers is critical. Hospital re-admission rates after major thoracic surgery can run as high as 10-17 percent. Improving the transition from hospital to post-discharge care can be effective in decreasing emergency room visits and re-hospitalizations. Moreover; use of concierge pharmacy services for management of discharge mediations, day after discharge phone calls and easy patient access to a hospital provider all help to support patients and their families during the transition from hospital to home. More studies need to be done to identify which programs and interventions achieve the best outcomes for patient's undergoing thoracic surgery. The utilization of existing programs in combination with newer technologies needs to be reviewed and studied to determine what works best in helping patients to change behaviors and promote optimal outcomes following thoracic surgery.

MS21 GIANTS IN THORACIC ONCOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 15:15-17:00

MS21.01 SURGERY AND ITS EVOLUTION

P. Van Schil
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Slow rise Surgery would not be possible without detailed knowledge of human anatomy. In the 16th century Andreas Vesalius published his "De humani corporis fabrica", providing very detailed anatomy of the human body. He also understood the importance of teaching, already internationally, and performed the first endotracheal intubation in pigs. William Harvey described the anatomy of the cardiovascular circulation. Ambroise Paré rediscovered blood vessel ligation, applied specific wound dressings and already designed rudimentary limb prostheses. General surgical interventions quickly developed (1). Thoracic surgery only developed very late due to the fact that opening of the chest resulted in collapse of the lung and pneumothorax (2). Opposing views ensued whether the thoracic interventions should be performed by "Unterdruck" or "Überdruck" (negative versus positive pressure). Gotthard Bülau introduced closed water seal drainage to re-expand the lung. After experimental studies, Ferdinand Sauerbruch designed a negative pressure chamber to perform thoracic interventions, principle of which was also used in the "iron lungs" during the polio epidemic. However, its use was not quite practical and finally, positive pressure became the preferred option after development of a positive pressure apparatus by Ludolph Bauer. *Tuberculosis: start of thoracic surgery After introduction of endotracheal intubation and intratracheal anesthesia, thoracic surgery developed as a separate specialty from general surgery. Pulmonary tuberculosis became a wide-spread problem and specific tuberculosis centers (sanatoria) were created with multidisciplinary medico-surgical cooperation "avant la lettre". This provided a clear impetus towards further development of thoracic surgery. Devastating infections were encountered necessitating a variety of special procedures as extrapleural dissection, rib resection, cavernostomy with open drainage, and sometimes an extensive thoracoplasty. Théodore Tuffier is credited for performing the first successful lung resection for tuberculosis in 1891, putting a clamp on the apex after extrapleural dissection followed by resection of diseased lung parenchyma and closure of the lung surface by a continuous suture. Lung resection: pneumonectomy* Alexis Carrel who won the Nobel prize In 1912, contributed enormously to further development of surgical techniques by providing detailed description of vascular sutures, organ transplantation and even extracorporeal circulation. Thoracic surgical oncology started to develop with Evarts A. Graham performing the first one-stage pneumonectomy for lung cancer in 1933. Patient was a 48-year-old gynecologist who resumed practice afterwards and died at the age of 78 years. In the era before

computed tomography, pneumonectomy became a standard procedure for lung cancer to obtain a complete resection. *Lung resection: less than pneumonectomy* Surgical principles of lobectomy developed somewhat later, although Arthur Tudor Eduards performed the first lobectomy for tumor in 1928 but this case was only published ten years later. Initially a mass-suture ligation technique was used for which a lobectomy tourniquet was developed. Later on, individual dissection with ligature or suture of hilar structures was introduced. William Rienhof described the modern technique of bronchial suture with interrupted silk sutures. He already advocated an atraumatic dissection, preservation of blood supply and covering of the bronchial stump. *Lung resection: less than lobectomy* Elective resection of pulmonary segments was described by Edward D. Churchill who performed the first anatomical lingulectomy in 1939. Especially for tuberculosis and bronchiectasis, segmentectomies were performed. With the introduction of the new WHO and 8th TNM classifications of lung tumors, there is currently an ongoing discussion whether sublobar resection comprising an anatomical segmentectomy and wide wedge excision for small (< 2 cm) early-stage lung cancer, provides similar results as lobectomy (3). The results of randomized trials are eagerly awaited for. *Bronchoplastic and tracheoplastic surgery* Not only resection of lung parenchyma became common practice but also reconstruction of the bronchus and trachea in selected patients with central lung tumors. Although initially considered "impossible surgery", Paul Gebauer in 1948 described bronchial excision and reconstruction by a wire-supported dermal graft. The first sleeve lobectomy was performed in 1947 by Sir Clement Price Thomas in a Royal Air Force cadet as an alternative to pneumonectomy which would have made an end to his career as military pilot. Tracheal surgery was further developed by Griffith Pearson and Hermes Grillo who both obtained an extensive experience with tracheal resection and reconstruction for non-malignant and malignant diseases. *Minimally invasive surgery* Although generally, the principles of surgical resection of lung, mediastinal and pleural tumors have been well-established, the approach still remains controversial. Initially, for extensive disease posterolateral thoracotomy and sternotomy were routinely used. With better imaging techniques, especially computed tomography and later on, positron emission tomography, and new technical developments, minimally invasive procedures were introduced from 1990 on. There was a slow transition from muscle-sparing thoracotomies to minimally invasive approaches by video-assisted thoracic surgery (VATS) or more recently, to robotic-assisted thoracic surgery (RATS). VATS can be performed by multiple ports, a single port without rib spreading, and more recently, by a subxiphoid approach. The relative contribution of each technique has not been clearly established but medium-term results seem to be similar to open techniques on the condition that oncological principles are not compromised. Complete resection including systematic lymph node dissection for lung cancer still remains the most important prognostic factor. Undoubtedly, minimally invasive techniques will be refined in the near future making thoracic surgery a fascinating specialty. References 1. Naef A. P. The story of thoracic surgery. Hogrefe & Huber Publishers, Toronto, 1990 2. Naef A.P., von Segesser L.K. (eds). Thoracic and Cardio-vascular Surgery. From the magic mountain to rocket science. European Association for Cardio-thoracic Surgery, Windsor, 2010 3. Sihoe A., Van Schil P. Non-Small cell lung cancer: when to offer sublobar resection? Lung Cancer 2014; 86: 115-120

Keywords: History, Thoracic Surgery, evolution

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MS21.02 CHEMOTHERAPY THROUGH THE 21ST CENTURY

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The development of systemic therapies for lung cancer can be divided into three phases starting with the application of cytotoxic agents in the mid-20th century, followed by the arrival of molecularly targeted therapies at the beginning of the 21st century and more recently the emergence (or reemergence) of immunotherapy. The first of these phases dates to 1948 when Karnofsky and colleagues reported on the activity of nitrogen mustard (HN_2) in bronchogenic carcinoma. The impetus for their study derived in part from a *"remarkable temporary remission"* they had observed in a patient with an *"anaplastic carcinoma of the lung"* coupled with prior reports detailing the use of HN_2 in the *"palliative treatment of Hodgkin's disease, lymphosarcoma, leukemia, and allied disorders"*. This seminal study involved 35 patients with a mixture of tumor histologies (mostly squamous carcinomas) all but one of whom were male. Tumor shrinkage was noted in nearly 50% of patients with an average response duration of approximately three weeks. Notably, HN_2 also produced a rapid improvement in tumor-related symptoms in nearly three-quarters of the study population. This symptomatic relief was considered the *"most important and striking effect"* and was *"usually evident within four to seven days"*. Although the authors concluded that HN_2 was a *"feeble therapeutic agent in carcinoma of the lung"*, this proved to be a landmark study for the following reasons: 1) it helped established standards for the rigorous clinical testing of cytotoxic agents in for what was then considered an "untreatable" disease; 2) it pioneered the use of performance status (i.e. Karnofsky scale) as a useful tool for classifying the clinical condition of individual patients, and 3) because it was the first to use of quality of life analysis and assessment of tumor-related symptom control as important endpoints of drug efficacy in lung cancer. Over the ensuing seven decades thoracic oncologists doggedly pursued the development of effective cytotoxic agents in NSCLC with the time-honored goals of improving overall survival, reducing tumor-related symptoms and, where possible, effecting a cure. Though the pace of progress was at times painfully slow, these determined efforts eventually paid off initially with the recognition that cisplatin-based drug combinations could produce higher response rates than non-platinum-containing regimens and later with the recognition that these regimens also improved survival compared to supportive care alone. Today platinum-based doublet therapy is considered standard first-line treatment for patients with advanced stage NSCLC and good performance status lacking an actionable genomic abnormality. The most commonly used regimens appear comparable with respect to toxicities and outcome with the possible exception of platinum-pemetrexed, which is less effective in squamous carcinomas. Maintenance therapy is an option in patients with non-squamous carcinomas whose disease has not progressed after 4-6 six cycles of initial platinum-based chemotherapy. Likewise, the addition of bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), yields a modest improvement in survival in selected patients with non-squamous carcinomas albeit at the cost of additional toxicities. In patients with squamous carcinomas adding necitumumab, an antibody against EGFR, modestly improves overall survival. In the second-line setting, docetaxel (± ramucirumab) yields a modest survival benefit over supportive care. Similar results have been achieved with pemetrexed. Symptom improvement also can be achieved with chemotherapy, usually occurs early in the courses of treatment and may occur in the absence of objective tumor regression. Finally, in early stage and locally advanced disease, chemotherapy modestly increases rates of cure when administered before or after surgery and/or radiotherapy. Enthusiasm for cytotoxic therapy waned in the early 2000s with the recognition that gefitinib, an EGFR tyrosine kinase inhibitor, produced marked tumor regression in selected patients whose tumors harbored either small, in-frame deletions or amino acid substitutions clustered around the ATP-binding pocket of the tyrosine kinase domain. This milestone discovery spurred further studies that identified additional genomic abnormalities that could serve as therapeutic targets (e.g., ALK translocations, HER2 and BRAF mutations, etc.). Drugs that specifically target these genomic abnormalities became the major focus of much of the cancer drug development of the past 15 years and are now considered a cornerstone of genomic or precision medicine. In more recent years much attention has shifted to application of immunotherapeutic agents in solid tumors including NSCLC (and SCLC) seemingly pushing cytotoxic agents further into the background. Indeed, immune checkpoint inhibitors already have changed (& are changing) the treatment paradigm for NSCLC patients with advanced and locally advanced disease. Moreover, we are witnessing dramatic advances in the combined use of immunotherapy and chemotherapy potentially heralding a new phase of systemic therapy for lung cancer – viz. the routine use of chemotherapy integrated with targeted therapy and/or immunotherapy. However, despite the transformational successes of genomic medicine it is important to remember that only a small percentage of NSCLC patients actually derive benefit. Accordingly, further progress in the management of NSCLC will require the use of all the therapeutic tools at our disposal in the most thoughtful manner possible informed by both basic science and clinical observations. In short, in spite of its prosaic nature, chemotherapy will remain a key component of the management of lung cancer for the foreseeable future. Hellmann MD, Li BT, Chaft JE, Kris MG. 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Keywords: non-small cell lung cancer; chemotherapy

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MS21.03 REVOLUTION IN RADIATION

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In the past few decades, there have been many changes in the field of radiotherapy. These include better imaging, better motion management, improvements in treatment planning, better position verification and more precise treatment delivery. This has led to an increased use of radiotherapy and to significant improvements in clinical outcome. Stereotactic body radiotherapy (SBRT, aka SABR) is currently the standard of care for patients with medically inoperable stage I NSCLC. The technique is now safely used for more centrally located, larger and multiple lesions as well. SBRT is increasingly being considered as an alternative to surgery in operable patients. The results of two randomized clinical trials which were closed prematurely due to poor accrual, suggest equivalence between SBRT and surgery. Comparative effectiveness studies point in the same direction. New randomized trials on this topic are currently recruiting. In stage III NSCLC, radiotherapy can also be delivered with increased precision. Although the use of much higher dose has not (yet) led to better outcomes, the newer radiation techniques are associated with less toxicity and over the years, there has been a steady improvement in control and survival rates. The use of immunotherapy in combination with radiotherapy holds many promises. The role of proton therapy is still investigational. For patients with oligometastatic disease or oligoprogression, local treatments including radiotherapy can be highly effective and may lead to long term control and improvements in survival. We are awaiting the results of randomized studies to unequivocally show this benefit. In LS-SCLC, there is still discussion on the schemes for thoracic radiotherapy (BID or QD). The improvement in median survival in both arms of the recent CONVERT trial compared to earlier studies are probably exemplary for the general improvements in radiotherapy techniques. In ES-SCLC patients, thoracic radiotherapy is advocated for those patients with a response after chemotherapy but with residual disease in their chest. In ES-SCLC, prophylactic cranial irradiation is nowadays sometimes replaced with MRI-surveillance. Delayed cranial irradiation is than used in about two out of three patients. An important breakthrough in radiotherapy is the introduction of MRI guidance on the linear accelerator. This not only provides better soft-tissue imaging, but also for the first time, continuous imaging during the delivery of the treatment. The anatomical information from the MRI made daily with the patient on the treatment couch can be used to daily adapt the treatment plan. This allows for the use of smaller margins and early results demonstrate important benefits, especially in high-risk patients.

Keywords: MRI guidance, Radiotherapy, radiation oncology

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MS21.04 TARGETED THERAPY - THE SECOND REVOLUTION

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Over the last 15 years we have witnessed a revolution in the development of molecularly targeted therapy for non-small cell lung cancer (NSCLC). At the same time, there has been an unprecedented evolution in the techniques available to detect molecular changes in tumours. The technology has evolved from single gene assessment in frozen tissues by Sanger sequencing to broad molecular profiling platforms that are able to sequence large panels of mutations using only circulating tumour DNA from peripheral blood samples. The revolution started in the late 1990s when monoclonal antibodies and oral tyrosine kinase inhibiters were being developed to target the epidermal growth factor (EGFR) pathway of NSCLC. At that time, assessment of EGFR was limited to immunohistochemical assessment of EGFR protein, or copy number. However in 2003, dramatic responses seen in a small subset of patients led to deep sequencing of these patients' tumours and the identification of two driver mutations in the tyrosine kinase domain of the *EGFR* gene. Testing for these mutations on Exons 19 and 21, now has become standard of care and should be reflex for all cases of adenocarcinoma of the lung. Several trials comparing first-line chemotherapy to first or second generation EGFR TKIs have now shown conclusively that TKI therapy is superior to chemotherapy, and for a decade now, first or second generation EGFR TKIs, including gefitinib, erlotinib and afatinib are now the standard of care world-wide. However, all patients relapse usually within months to a short number of years, and considerable research has shown that there are several possible mechanisms of resistance. The most frequent (50-60%) is emergence of the T790M resistance mutation, and several TKIs specifically targeting this mutation have been developed. Osimertinib, a third generation TKI has been approved for second-line treatment of T790M mutant NSCLC, and recently a trial comparing osimertinib to gefitinib or erlotinib in the first-line setting has demonstrated its superiority for both progression-free and overall survival. Other mechanisms of resistance include emergence of other mutations, MET amplification, and for a small percentage of patients, small cell transformation. ALK mutations were discovered when a single patient had a dramatic and unexpected response to crizotinib, which was being evaluated at that time as a MET inhibitor; sequencing identified the first ALK fusion in a lung cancer tumour. This led rapidly to focused screening and expansion of the Phase I/II trial specifically for patients with ALK mutated tumours. As was the case with EGFR TKIs, numerous second-line and then first-line studies confirmed the superiority of crizotinib over chemotherapy, and ALK TKIs are now the first-line standard of care. Second and third generation ALK inhibitors have been developed rapidly including ceritinib, alectinib, brigatinib and lorlatinib. While ALK mutations may be comprised of several different fusion partners, for the most part, TKI selection has not been based on the fusion variant. Recently, resistance point mutations in the TK domain also have been reported, of which the G1202R mutation appears to confer the greatest resistance. ROS1 is another fusion variant that has demonstrated excellent response to crizotinib and other ALK TKIs. Less frequent lung cancer mutations for which targeted therapy is available in other cancers include *HER2, BRAF, RET* mutations, The MET exon 14 skipping mutation is seen in sarcomatoid lung cancer variants, and it also is responsive to crizotinib. Mutation testing for lung cancer should now be reflex at the time of diagnosis. In general, at a minimum, all patients should have testing with a multiplexed targeted panel that includes all the mutations for which targeted therapies are available. Screen by immunohistochemistry for ALK and ROS1 (and pDL-1) also are recommended. The next generation hybrid capture platforms are not yet widely in use, but in limited centres have been shown to be a reliable test for fusion variants including ALK and ROS. Molecular testing technology has advanced so much and so rapidly that it is now possible to identify mutations through testing of ctDNA in peripheral blood. Several techniques and platforms have been developed that have shown high sensitivity and specificity in particular for T790M detection. Now in many centres, routine blood testing is now preferred over invasive biopsies to look for this resistance mutation when progression is suspected. Multiplexed targeted panels evaluating many mutations and even tumour mutation burden in peripheral blood also are now available, but the true role of these panels in clinical care has yet to be determined.

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MS21.05 QUALITY OF LIFE - ARE WE PAYING ENOUGH ATTENTION?

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The greatest challenge facing quality of life, symptom and patient reported outcome evaluation in advanced lung cancer is the incorporation of the measurement of these parameters into daily clinical practice. While all oncologists embrace the significant basic science and survival improvements of recent years, we must acknowledge that these benefits are still only measured in months of additional life for the average patient, and treatments continue to have significant risks. Are we meeting the goals and needs of patients receiving systemic therapy? There are several issues key to understanding the practicality and value of PRO evaluation. Recent studies have addressed these questions. How much do patients value and agree with the monitoring of quality of life? Are PRO issues accurately and reproducibly measured? Can we conduct PRO evaluation in clinical research and in daily practice in a practical fashion that can allow inclusion into all clinical settings? Most importantly, beyond demonstrating that oncologists wish to listen to the patient's voice, does the measurement of PROs give guidance in daily practice that results in better patient care, economic benefit, and aids in better decision making? There can be no doubt that patients with advanced lung cancer place aspects of quality of life at the top of their concerns and goals in their management. Over 95% of patients stated that quality of life was a key concept for them in a survey of 660 patients with lung cancer (1), and a similar percentage of 148 patients endorsed serial evaluation of quality of life and lung cancer symptoms (2). Today we have valid measures designed for lung cancer and mesothelioma with tested, published,

and acceptable psychometrics. Such testing establishes feasibility, acceptability, reliability and validity. These measures, including the EORTC-QLQ-30, the FACT-L, the LCSS and the LCSS-meso, all meet high standards and are available in over 50 languages (3). Using electronic assistance makes the evaluation of PROs more practical in both clinical trials and daily practice. A trial using the electronic form of the LCSS placed on a tablet-like device (called the "eLCSS-QL") demonstrated high patient, nurse and physician acceptance. The electronic format correlated very highly with the paper and took only about two minutes to complete (2). Other major advantages of using computer assistance is that results over time can immediately be displayed graphically, the data can be filed without transcription, and the device can interpret the results. All of these features make evaluating PROs easy to incorporate into busy clinical practices and into research trials. To date, the greatest use of quality of life and PRO evaluation in patients with thoracic malignancies has been in clinical trials. Typically, these assessments have been used to determine whether or not a new treatment which influences survival or PFS or response also affects quality of life. These results are generally used as secondary or tertiary endpoints in new agent approval. Shortcomings in PRO assessment are common in these trials, most frequently seen as failure to include all patients and in low percentages of patients with sufficient follow up. With high patient acceptance and available feasible questionnaires, the fault lies with the study design or the conduct of the investigators, and not with the patients. We recently completed a study which investigated several endpoints through the use of electronically conducted PRO evaluation, with the eLCSS-QL. 164 patients completed the eLCSS-QL every 3 weeks; all endpoints were evaluable in over 90% of patients. Specifically, we evaluated whether just 3 items (quality of life, distress, activity level, called the 3-Item Global Index or "3-IGI") of the 9 included in the LCSS could: 1) more accurately predict survival at baseline than performance status; 2) could predict risk groups for hospitalization; 3) identify those at greater risk for regret; and most importantly 4) indicate by change in the 3-IGI after just 2 treatment cycles which patients are likely or unlikely to benefit from treatment. The findings from this study, are presented at the 2018 WCLC (4,5). In brief, we found that assessing change from baseline (20% decline) with the 3-IGI after only 2 cycles of systemic treatment identifies those patients who have poor response and survival outcomes if continued on the same therapy. Patients with this decline continued to receive more than two additional treatment cycles on average, even though PRO assessment showed meaningful declines at a much earlier point. The economic cost of this additional treatment was an average of almost $11,000 per patient. Additionally, nearly all patients who at 3 months after starting treatment regretted having received treatment were those who had this 20% decline of the 3-IGI at 6 weeks. This PRO assessment is rapid, easy, and inexpensive. Reports to physicians need to include analysis of the impact in that even when physicians were aware of the PRO worsening, they often did not act on the findings. The 3-IGI at baseline provided a better indication of the burden of the cancer experienced by the patient. This resulted in better prediction of survival, which could aid in better design of clinical trials. Quality of life, symptom assessment, and PRO evaluation has become practical for both research trials and clinical practice. Responding to PRO changes can result in better decisions concerning continuing treatment, changing treatment, lessening toxicity, and savings in cost of unhelpful treatment. References: 1) Gralla RJ, et al. Journal of Thoracic Oncology. 2014. 9: 1243-8. 2) Hollen PJ, et al. Supportive Care in Cancer. 2013. 21: 165 – 172. 3) Hollen PJ, et al. Seminars in Oncology 1996. 23: 31-40. 4) Hollen PJ, et al. Proceedings of WCLC 2018. 5) Gralla RJ, et al. Proceedings of WCLC 2018. Supported by: NIH/NCI R01 CA157409

Keywords: Quality of life, PRO, LCSS

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MS21.06 IMMUNOTHERAPY - SEQUENCE OR COMBINATION?

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Despite advances in the treatment of cancer, with novel molecularly targeted therapies and drug combinations, lung cancer continues to be one of the leading causes of cancer death worldwide. For this reason, significant efforts have been made to examine the interaction between cancer and the immune system. This has led to the discovery of the programmed death 1 (PD1) and ligand (PDL1) pathway, which was found to play a key role in immune evasion by cancer cells and the formation of a tumor microenvironment. Blockade of this pathway enables the ability of the innate immune system to activate their anticancer responses and to reverse the tumor microenvironment. Newly approved drugs, such as nivolumab and pembrolizumab, have mechanisms of action that inhibit PD1, while others like atezolizumab, block PDL1. Although, responses with these drugs have shown significant activity in some patients, only 20-30% of patients respond overall. In this talk, mechanistic studies to identify predictive markers of response will be discussed along with markers of resistance (both primary and acquired). In addition, novel combinations of immunotherapy with chemotherapy, targeted therapy and even chemotherapy will be explored including their use in sequence or combination.

Keywords: Immunotherapy, biomarkers, targeted therapy

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MS21.07 THE GROWING ROLE OF BIOMARKERS IN TREATMENT SELECTION: "THE TISSUE IS THE ISSUE"

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Much progress has occurred in the treatment of lung cancer over the last decades. A main reason for this progress is due to technology developments, which make it possible to identify new targets and develop new active drugs targeting the molecular abnormalities. However, developing predictive biomarkers for selection of the right group of patients to the right treatment has been crucial in this progress. The detection of *EGFR* mutations as predictive biomarkers for EGFR TKIs paved the way for biomarker development and was shortly followed by the detection of Anaplastic Lymphoma Kinase fusions and the development of ALK-inhibitors. Later, many other targets have been identified (i.e. *ROS1, BRAF, RET, TRAKS*) and specific targeted drugs developed with impressive clinical effect in biomarker defined subgroups, particularly of NSCLC (1). The International Association for the Study of Lung Cancer (IASLC) has together with the College of American Pathologists (CAP) and the Association for Molecular Pathology (AMP) developed guidelines for molecular testing of patients with advanced NSCLC, which second edition has recently been published (2). Those guidelines have been the role model for several other guidelines globally. Assay developments have been crucial in the biomarker development. While traditional immunohistochemistry (IHC) is still relevant for selection of patients to certain targeted therapies, e.g. ALK- inhibitors, more technological advanced assays based on DNA or RNA have become more" relevant" as multiplexed marker analysis seems in many cases "mandatory" as (sparse) "Tissue is the Issue" (3). The last revision of the CAP/IASLC/AMP guidelines recommend the use of Next Generation Sequencing (NGS) if possible, as this assay gives more information and detect mutations as well as fusions. Today only a limited number of targets are linked to FDA approved drugs for treatment of lung cancer and the use of NGS gives a broad molecular profiling of the patients' tumor. This knowledge gives the patient opportunity to seek clinical trials, of which many are ongoing, including a broad range of molecular targets. Many molecular targets have seen several generations of specific targeted drugs, e.g. EGFR and ALK and more knowledge has emerged on resistance mechanisms, a knowledge, which in some cases, leads to targeted agents specifically targeting the resistance mechanisms. The third generation EGFR TKI represented by osimertinib targeting T790 M mutation is the best example. This development has paved the way for the need for biopsy at progression, which is a change in the current "culture". However, acquiring tissue at this stage can often be challenging, and the development of liquid biopsy is rapidly emerging. The IASLC has just published a consensus report on the role of liquid biopsy in the management of patients with NSCLC (4). The liquid biopsy technology has the capability to be applied to NGS and several other DNA and RNA assays with high specificity (90-100%) and increasing high sensitivity (70-90%). The progress with immunotherapy has been remarkable for patients with lung cancer; however, the role of predictive biomarkers in immunotherapy has been challenging. PD-L1 has been pursued by the relevant pharmaceutical companies, but, unfortunately, with the development of their own proprietary assays that differ with regard to antibodies, processing platforms, and with different cut-off points for definition of "high'- versus "low" PD-L1 expression in the clinical trials. IASLC has compared the analytical performances of the different assays in order to see if harmonization is possible, and the results of the "Blueprint Project" indicate that three assays (Dako's 28-8 and 22C3 and Ventana's SP 263) perform very similar and seem to be interchangeable when the same clinical cut-offs for the different categories are used (5,6). Tumor mutation burden has also emerged as a predictive biomarker for immunotherapies (7); however, the tumor mutation burden assays need to be compared and standardized as well. Much research today is devoted to try to identify new and better predictive biomarker(s) for immunotherapy. While we have primarily focused on "single" biomarker assays for immunotherapy thus far, it might be time to look into the role of "combined" biomarkers or assays for the most optimal selection of patients, who benefit from immunotherapy. In conclusion, a tremendous development of biomarkers and assays have been seen over the last decade(s), which has made it possible to identify subgroups of patients

with dramatic effect of new targeted therapies. Future drug development needs to ensure the biomarker development occurs simultaneously in the clinical development to ensure validation and proper selection of subgroups of patients, who will benefit from the new agents. Development of "masterprotocols" seems to be one mechanism for speeding up this development (8). REFERENCES: 1.Hirsch FR, Scagliotti GV, Mulshine JL et al: Lung Cancer: Current Therapies and New Targeted Treatments. Lancet 389 (10016); 299-331, 2017. 2.Lindeman NI, Cagle PT, Aisner DL et al: Updated Molecular Testing Guidelines for Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors. Guideline from the College of American Pathologists, The International Association for the Study of Lung Cancer and the Association for Molecular Pathology. J Thorac Oncol 142(3); 321-346, 2018. 3.Hirsch FR, Wynes MW, Gandara DG, Bunn PA: "The Tissue is the Issue". Clin Cancer Res 16 (20); 4909-4911. 2010 4.Rolfo C, Mack PC, Scagliotti GV et al: IASLC Statement Paper: Liquid Biopsy for Advanced Non-Small Cell Lung Cancer. J Thorac Oncol , June 6th, 2018 (E-pub ahead of time). 5.Hirsch FR, McElhinny A, Stanforth D et al; PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase1 of the Blueprint PD-L1 Comparison Project. J Thorac Oncol 12(2); 208-222, 2017. 6.Tsao MS, Kerr KM, Kockx M et al: PD-L1 Immunohistochemistry Comparison Study in Real-Life Samples; Results from Blueprint Phase 2 Project. J Thorac Oncol , May 22, 2018 (Epub ahead of time). 7.Hellman MD, Callahan MK, Awad MM: Tumor Mutation Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilumumab in Small Cell Lung Cancer. Cancer Cell 14(33): 853-861, 2018. 8.Malik SM, Pazdur R, Abrams JS et al: Consensus Report from a Joint NCI Thoracic Malignancy Steering Committee- FDA workshop on strategies for integration of biomarkers into clinical development of new therapies for lung cancer leading to inception of "Masterprotocols" in lung cancer. J Thorac Oncol 9 (10); 1443-1448. 2014

Keywords: lung cancer, Biomarkers

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MS21.08 WHERE WILL WE BE IN 10 YEARS?

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Lung cancer is the leading cause of cancer death in the world, accounting for as many as one fourth of all cancer deaths. Mortality rates for lung cancer in the US and the world have been declining, albeit in varying amounts around the world. The decline is due mostly to decreasing tobacco consumption and early detection through CT screening. Improvements in therapy have also contributed and therapeutic improvements have come mostly in recent years. In the US, annual lung cancer deaths in males have decreased from 90/100,000 to 45/100,000 in males and from 45 to 35/100,000 in females from 1960-2018. Over this period 5 year survival rates have increased from 5% to 18%. However, the annual number of US deaths has remained about 160,000 per year due to increasing population and aging of the population. Social pressures and new agents to assist in smoking cessation should continue to reduce the incidence of lung cancer although some of these gains may be offset by increased air pollution. We should see agents that can reduce lung cancer incidence through prevention in high risk populations including the potential of low dose aspirin, eicosanoid, and immunotherapeutics including IL1beta inhibitors and checkpoint inhibitors. New biomarkers of early progression including circulating tumor DNA may markedly improve early detection. For early stage therapy in resectable patients, adjuvant chemotherapy improved 5 year survival by about 5%. For locally unresectable stage III lung cancer, the addition of chemotherapy (CT) to radiation therapy (RT) improved 5 year survival by 5-10%. More recently, the addition of immunotherapy to CT/RT for unresectable stage III disease has further improved survival. The use of immunotherapy for resectable lung cancer has produced considerably higher response rates than chemotherapy but its effects on survival remain to be determined. For stage 4 disease, the 5-year survival rates have increased from 1% to as much as 15%. Molecularly targeted therapy for patients with a driver alteration have improved outcomes considerably with 4 year survivals of over 50%. At present, tyrosine kinase inhibitors (TKIs) are approved for EGFR and BRAF v600E mutations and for ALK and ROS1 rearrangements. It is likely that TKIs for MET and HER2 mutations and for RET and NTRK rearrangements will be approved in the near future. The most common molecular driver is KRAS mutation but at present no KRAS inhibitors have been approved, although it is likely that KRAS inhibitors will be approved in the next decade. Immunotherapies with anti-PD-1 antibodies have improved 5 year survival rates for advanced disease to about 15% and the combination of chemotherapy and immunotherapy seems to produce even higher long term survival rates. Approved immunotherapies include the anti-PD-1 antibodies pembrolizumab and nivolumab, and the anti-PD-L1 antibodies atezolizumab and durvalumab. Other checkpoint inhibitor antibodies are in late clinical development and will likely be approved in the future. Combinations of checkpoint inhibitor antibodies with anti-CTLA antibodies are in advanced clinical development and will likely be approved in the near future. Agonists and antagonists to multiple other immunotherapeutic targets have been developed and are in early phase clinical trials alone and in combination with checkpoint inhibitor antibodies. Therapies for other targets such DNA repair enzymes, stem cell pathways inhibitors, antibody drug conjugates are in development and should become available in the next decade. Over the next decade we can anticipate further lowering of death rates and improved survival rates which will be attributed to declining smoking rates, improved adherence to screening recommendations and to improved therapy. Wide-spread molecular testing and treatment and understanding the immune system with novel immune therapies should lead the improvements over this next decade.

MS22 BIOLOGY OF THE LUNG AND LUNG CANCER
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MS22.01 LUNG DEVELOPMENT AND STEM CELLS

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Our laboratory has pioneered the use of stem cell biology approaches for the study of adult lung progenitor cells and lung cancer. Through a combination of mouse genetics and cell biology, we have developed tools to identify and characterize cells with progenitor cell activity in adult lung tissue. We have also applied our expertise to the study of lung cancer, which resulted in our definition of the cancer stem cell populations in the two most common types of lung cancer. We have examined the mechanisms that regulate lung progenitor cell self-renewal and differentiation in the normal lung and in the context of lung cancer. One major focus in our lab has been the creation of three-dimensional co-culture and co-transplantation organoid systems that have begun to define the cell-cell crosstalk between epithelial progenitors, endothelial cells and mesenchymal cells in the lung. I will discuss how we have recently used our organoid system to define lung mesenchymal cell types that specifically regulate airway or alveolar epithelial cells. I will also present new studies in which we have examined how epigenetic factors, particularly H3K9 methyltransferases and demethylases, affect lung injury repair, lung tumorigenesis and response to therapy in lung cancer.

Keywords: Tumor Models, stem cells, epigenetics

MS22 BIOLOGY OF THE LUNG AND LUNG CANCER
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MS22.03 NON-CODING RNA IN LUNG CANCER

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Lung cancer is a disease of the genome caused by the aberrant activation of oncogenes and inhibition of tumor suppressor genes. However, the vast majority of the human genome is only transcribed into RNA and not translated into proteins. Hence, one major class of products derived from the genome are long non-coding RNAs (lncRNAs). These recently discovered class of molecules can execute a wide range of functions in the cell. Their versatility is based on their capability of specifically interacting with DNA, RNA or proteins, while often their molecular mechanisms of action are unknown. The role of lncRNAs in lung cancer is only beginning to emerge. As one of the first lncRNAs linked to cancer at all, we identified the conserved transcript MALAT1 as a marker significantly associated with development of distant metastasis and overall survival in early stages of lung adenocarcinoma (1). Although MALAT1 has been found deregulated in a plethora of pathological conditions after its discovery (reviewed in 2), it remained unknown whether it would only be a molecular marker or an active player in lung cancer metastasis. Hence, we generated a genetic loss-of-function model in human lung cancer cells using a then innovative approach combining gene editing and RNA degradation (3). Employing this model, we showed that MALAT1 was essential for tumor cell migration *in vitro* and metastasis formation *in vivo* in a mouse xenograft model. Moreover, an inhibitor for MALAT1 could also pharmacologically suppress metastasis formation in a mouse model (4). Thereby, the nuclear lncRNA MALAT1 acts as an epigenetic regulator of a signature of multiple genes associated with migration, invasion and metastasis mediating the aggressive cellular phenotype (4). Beyond MALAT1, we have screened for additional lncRNAs relevant for lung adenocarcinoma using gene expression profiling as well as RNAi screening with a customized library of

3200 siRNA targeting cancer-associated lncRNAs. Thereby, we identified the important role of linc00673 / LUCAIR1 for the suppression of p53-mediated senescence in lung cancer cells. Moreover, we discovered the lncRNA VELUCT which is essential for lung cancer cell viability despite its extremely low abundance (5). In summary, non-coding RNAs can play important roles in lung carcinogenesis and metastasis (reviewed in 6-8) **References**: (1) P Ji*, S Diederichs* et al.: MALAT-1, a novel non-coding RNA, and Thymosin b4 predict Metastasis and Survival in early-stage Non-Small Cell Lung Cancer. Oncogene (2003) (2) T Gutschner et al.: MALAT1 - A paradigm for long non-coding RNA function in cancer. Journal of Molecular Medicine (2013) (3) T Gutschner et al.: Non-coding RNA Gene Silencing through genomic integration of RNA destabilizing elements using Zinc Finger Nucleases. Genome Research (2011) (4) T Gutschner et al.: The non-coding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Research (2013) (5) J Seiler et al.: The lncRNA VELUCT strongly regulates viability of lung cancer cells despite its extremely low abundance. Nucleic Acids Research (2017) (6) T Gutschner et al.: The Hallmarks of Cancer: A long non-coding RNA point of view. RNA Biology (2012) (7) A Roth et al.: Long Noncoding RNAs in Lung Cancer. Current Topics in Microbiology & Immunology (2016) (8) S Dhamija et al.: From junk to master regulators of invasion: lncRNA functions in migration, EMT and metastasis. International Journal of Cancer (2016)

Keywords: metastasis, MALAT1, long non-coding RNA

MS23 WHAT'S NEW IN TARGETED THERAPY?
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MS23.03 MANAGEMENT OF CNS METS IN THE ERA OF CNS-PENETRANT TKIS (MED ONC AND RAD ONCO PERSPECTIVES)

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Central nervous system metastases (CNSMs) are common in non small cell lung cancer (NSCLC). Their incidence is particularly high in presence of driver mutations (25-30% of *EGFR* mutated NSCLCs, 30-40% of ALK rearranged NSCLCs). CNSMs are associated with short survival and dismal quality of life [1]. The treatment of CNSMs has traditionally been a challenge for medical oncologists. In fact, most of cytotoxic drugs do not cross the blood-brain barrier (BBB), rendering it difficult to control disease with medical therapy. An integration with radiotherapy (RT) is usually needed, either stereotactic, in presence of a limited number of small lesions, or whole brain (WBRT), in case of disseminated or large metastases. Surgery is generally considered only for single symptomatic lesions [2]. The introduction of immune checkpoint inhibitors (ICIs) has not radically changed the therapeutic approach to CNSMs, as most of ICIs have a limited intra-cranial activity due to high molecular weight. Potential synergy between ICIs and RT, based on BBB permealization and antigen unmasking, is object of debate [3]. The major advances have been observed in the field of NSCLC with "druggable" genetic alterations. Recent years have seen the development of many tyrosine kinase inhibitors (TKIs) against *EGFR* mutations and ALK rearrangements, which are active against a wider range of molecular alterations and often show a significant intra-cranial activity. Clinical trials with first and second generation *EGFR* TKIs (gefitinib, erlotinib, afatinib) showed that their intra-cranial concentration is negligible. As a consequence, brain is the most common site of treatment failure [4]. Third generation *EGFR* TKI osimertinib completely changed the perspective. A pooled analyses of patients with CNSMs enrolled in phase II trials showed an intra-cranial objective response rate (IC-ORR) of 54% and a disease control rate (IC-DCR) of 92%, irrespective of RT. Median time to brain progression (B-TTP) was not reached. Brain response was rapid, being evidenced at first evaluation in 80% of patients. A phase I trial investigated the activity and safety of osimertinib 160 mg qd (instead of 80 mg qd) in patients with brain and/or leptomeningeal disease, showing promising activity and manageable toxicity [5]. First generation ALK TKI crizotinib proved some intra-cranial activity in regulatory trials. However, brain disease control was better in case of previous RT (IC-ORR 33% vs 18%; IC-DCR 62% vs 56%; TTP 13 vs 7 months) [6] Ceritinib, the oldest second generation ALK TKI, showed a superior activity on CNSMs (IC-ORR 63% and IC-DCR 63% in ALK-inhibitor-naïve patients). Most of the cases had previously received RT and that the outcome of the remaining patients has not been separately analyzed. However, this result is consistent with the preclinical evidence that ceritinib is transported across the BBB by specific carriers. The ongoing trial ASCEND-7 is addressing the efficacy of ceritinib in a population of patients with brain and/or leptomeningeal disease [7]. Alectinib, another second generation ALK TKI, has an even higher BBB penetration, with a linear correlation between plasma and brain concentrations. After encouraging data from phase I and II trials, the phase III study ALEX demonstrated a higher IC-ORR for alectinib than for crizotinib in first line (59% vs 26%), with an evident benefit in terms of complete responses (45% vs 9%). About 2/3 of the patients had received RT, but the proportion was balanced between treatment arms [8]. A higher intra-cranial activity has emerged for brigatinib, one of the newest ALK TKIs. A pooled analyses from 2 clinical trials in both crizotinib-treated and -naïve patients showed an IC-ORR of 46% with 90 mg qd and 67% with 180 mg qd. Median B-TTP was 18.4 months in this last cohort. Interestingly, IC-DCR with brigatinib did not differ according to RT [9]. Lorlatinib, the last ALK inhibitor, has a broader spectrum of activity on ALK alterations. In a phase I trial on heavily pre-treated patients, IC-ORR was 42%, with 17% of complete responses. Spinal punctures showed that drug concentration in cerebrospinal fluid is 75% of the plasmatic one [10]. In conclusion, new TKIs have deeply changed the management of CNSMs from NSCLC with driver mutations. Thanks to their intra-cranial activity, rapid and durable brain responses can be seen without RT. The omission of RT allows patients to be spared by the cognitive impairment associated to radiations. Indeed, the optimal tolerability of these molecules favours their upfront administration to patients with CNSMs. [1] Rangachari D, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Can* 2015; 88(1):108-111. [2] Tsao MN, et al. 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Keywords: Radiotherapy, non small cell lung cancer, Target therapy

MS24 GLOBAL PERSPECTIVES ON TOBACCO CONTROL
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MS24.02 LEGAL ACTION AGAINST THE TOBACCO INDUSTRY IN EUROPE

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A growing coalition of individual patients and anti-tobacco and health organizations in the Netherlands has pressed charges against four tobacco companies active in the Netherlands: Philip Morris International, British American Tobacco, Japan Tobacco International and Imperial Tobacco Benelux. The tobacco manufacturers are accused of attempted murder and manslaughter and/or premeditated attempts to cause grievous bodily harm and/or premeditated attempts to cause damage to health. Another accusation concerns the falsification of documents. Currently, a court of appeal is considering whether it will order the Public Prosecution Service to bring this case to court after the Service earlier had decided it could not do so. If the case eventually is brought to court it would be the first criminal case against the tobacco industry in the world. **Deliberate addiction** In September 2016 criminal lawyer Bénédicte Ficq (Ficq & Partners) filed a criminal complaint against the tobacco industry on behalf of two lung patients and the Youth Smoking Prevention Foundation[1]. The complaint documentation[2] filed argues that the tobacco industry deliberately makes cigarettes more addictive by adding hundreds of additives, which makes new smokers addicted quickly and makes existing smokers more addicted. Furthermore, the accusation focusses on the fact that cigarette companies make tiny holes in the filters of cigarettes in order to sabotage the official measurements of harmful substances. The holes in the filters, almost invisible to the naked eye, draw extra air into the measurement machines. As a result, those machines measure lower values than those actually inhaled by smokers, who block the holes with their lips and fingers as they smoke. Because of this, smokers inhale 2 to 3 times the recorded

and maximum allowed levels of harmful substances. **Additives** Lawyer Bénédicte Ficq commented: 'When I began to study all the additives that cause, enhance and maintain addiction, I nearly fell off my chair in shock at all the manipulated additives in cigarettes. The industry just one goal, and that is to get people addicted. People do not realize just how manipulated a cigarette is today. We want to make that clear to the Public Prosecutors Office, and we are convinced that when, like us, it understands what tobacco manufacturers put on the market, it too will conclude that it amounts to "causing grievous bodily harm".' **No free will** The case submitted demonstrates the various ways the tobacco industry can be held legally responsible for the health damage caused to smokers. By knowingly and intentionally getting smokers addicted, the tobacco industry denies them their free will to smoke or not. The fact that cigarettes are a legal product according to the Tobacco Act does not relieve the tobacco industry of its obligation to respect other laws. According to the submission made, the tobacco industry fails to comply with a number of criminal law provisions. It therefore has a case to answer before a criminal court. **Growing coalition** In the months that followed the initial complaint, more and more organizations joined, including the Dutch Cancer Society (DCS), the Dutch Journal of Medicine (NTvG), the Federation of Cancer Patients, the Netherlands Cancer Institute (NKI-AVL), the combined Academic Medical Centers in the Netherlands, and most of the professional organizations of medical specialists and health care workers. Together these organizations represent the better part of the medical profession in the Netherlands as well as many thousands of patients. **Appeal after rejection** Last February, the Dutch Public Prosecution Service concluded 'that it is not possible to bring a successful prosecution against the tobacco industry under the current legal and regulatory frameworks'.[3] Lawyer Bénédicte Ficq has an entirely different view and in May on behalf of her clients made use of the possibility to appeal the decision with the court of appeal. The court currently assesses whether a prosecution would be feasible and whether this prosecution is expedient. If the court judges that both criteria have been met, it will order the prosecution. **Press coverage** The case against the tobacco companies from the start has got a lot of attention in both national and international media. All major moments in the case caused extensive press coverage with peaks when the case was first announced, when the Dutch Cancer Institute decided to join the case, and when the Public Prosecution Service announced not bring the case to court. Internationally the case was covered by leading media including The Guardian, The Independent, The Washington Post, Japan Times, ABC, NBC, Fox, and Channel New Asia. Der Spiegel[4] published an extensive double interview with Bénédicte Ficq and Wanda de Kanter. All the press coverage added to the public awareness of the addictive nature of tobacco and the manipulative nature of the tobacco manufacturers. A publicity campaign of the same size would be worth millions. **International followers** The Dutch team met in Geneva with lawyers and anti-smoking organizations from different countries to give them backgrounds to the Dutch case and share their research findings and legal approach. Many consider to follow the Dutch example. In France the National Committee to Counter Tobacco use already pressed charges against tobacco companies operating in France[5] generally on the same accusations as in the Netherlands. It is due to two brave lung patients that the criminal case is on the agenda in the Netherlands and internationally, opening the eyes of the public for the despicable practices of the tobacco industry. It is time that these practices are considered where they belong: in criminal court. *Drs. Wanda de Kanter is lung physician in the Dutch Cancer Institute (NKI-AVL), chair of the Dutch Youth Smoking Prevention Foundation and member of the IASLC Tobacco and Prevention Team. She was awarded twice (in 2014 and 2015) the Woman in the Media Award for women who are most visible in media.* [1] www.stichtingrookpreventiejeugd.nl [2] https://sickofsmoking.nl/wp-content/uploads/2017/03/Complaint-Tobacco-Industry.pdf [3] https://www.om.nl/algemeen/english/@102217/no-further/ [4] http://www.spiegel.de/spiegel/tabak-und-sucht-was-sie-noch-nicht-ueber-zigaretten-wissen-a-1195389.html [5] http://www.cnct.fr/communiques-de-presse-44/le-scandale-du-filtergate-177.html

Keywords: Criminal law tobacco

MS24 GLOBAL PERSPECTIVES ON TOBACCO CONTROL
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MS24.03 THE IMPORTANCE OF PHYSICIAN INVOLVEMENT IN TOBACCO CONTROL

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Tobacco remains the most important preventable cause of premature mortality in the world. WHO, based on Framework Convention on Tobacco Control (WHO-FCTC), recommends the implementation of comprehensive tobacco control measures, including tobacco price policies, bans on tobacco advertising, promotion and sponsorship, health education, access to tobacco dependence treatment, strict regulation of tobacco products and other interventions. Physicians remain among the most respected and trusted community voices on health matters and should play a key role in all tobacco control measures. Their activities may be accomplished at both individual, institutional, community and society levels. In the everyday health-care setting physicians should counsel patients and their families against smoking and exposure to second-hand smoke and assist them to overcome tobacco addiction (1). Successful intervention begins with identifying users and appropriate interventions based upon the patient's willingness to quit. To motivate patients to quit they should be informed about the health, economic and social benefits of quitting (2). The activities that can help patients ready to quit are summarized in the "5 A's" model developed by The United States Department of Health and Human Services (3). This minimal intervention that may be accomplished within 3-5 minutes, includes asking about tobacco use, advising users all users to quit, assessing willingness to quit, advising quitting, and further referring and arranging for cessation services. To perform properly these roles, all physicians should be provided a basic training on brief interventions for smoking cessation and on evidence-based tobacco cessation measures. An indispensable condition for the effective physicians' cessation counseling are their own behaviors and practices. Physicians should serve as role models in not smoking or quitting smoking for the general public. Compared to smokers, physicians who do not smoke are far more likely to engage in cessation advice and counselling (4, 5). Indeed, greater tobacco control progress has been shown in countries with lower smoking rates among physicians (6) Tobacco control activities at the community level, apart from those described above, may include speaking out publicly and lobbying for comprehensive public policies to control tobacco use, visiting schools to promote tobacco-free lifestyles and cultures, organizing campaigns to extend tobacco-free public places or disseminating evidence-based information and materials about tobacco related problems through local media. Professionals that have leadership positions should engage in the policy-making process at the community and national level. This may include promoting WHO-FCTC, developing tobacco-control strategies, participation in legislation processes and supporting comprehensive tobacco control measures, such as increased taxation and prices of tobacco products or lobbying for funding of tobacco control programs. An example of a bottom-up initiative undertaken by health professionals was the development of policy recommendations of a tobacco control bill and the legislation that banned smoking in public places in Poland (7). A similar initiative was undertaken by the British Medical Association that prompted the development of the legislation to smoking ban in enclosed public places in the United Kingdom (8). Medical societies should encourage their members to become engaged in tobacco control advocacy, organize plenary sessions and panel discussions at society conferences and workshops, adopt resolutions and issue ethical opinions on members, advocate for health care systems to reimburse for cessation counseling and treatment, issue press releases, hold press or organize direct lobbying by medical society leaders (9). In conclusion, the professional responsibility of physicians extends beyond the treatment of tobacco-related disease to include prevention, cessation counseling and policy advocacy, in the fight to eradicate tobacco use as an international public health pandemic. References 1. Richmond R. Physicians can make a difference with smokers: Evidence-based clinical approaches. Int J Tubercul Lung Dis 1999; 3: 100–12. 2. A guide for tobacco users to quit. 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Keywords: tobacco control, physician role

MS24.04 CHALLENGES OF TOBACCO CONTROL IN CHINA

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Tobacco use remains a serious threat to global health and has killed almost 100 million individuals during the 20th century, and if current trends continue, approximately 1 billion people will die from tobacco use during the 21st century[1]. The rates of smoking prevalence are still increasing in many low- and middle-income countries, although decreasing in most high-income countries, thus, the number of tobacco-related deaths will continue to increase in the future years. China, the largest populous country in the world with a population of more than 1.3 billion individuals, is also facing this rigorous public health challenge. Owning to the large population base, China remains the largest tobacco producer and consumer in the world[2, 3]. According to the report of World Health Organization (WHO) in the year of 2009, China consumed more than 2.2 trillion cigarettes, which account for 38% of the world's cigarettes and more than the other top four tobacco-consuming countries combined[2]. Each year, more than 1.2 million people have been killed as a result of tobacco use in China and by the year 2030, the number of tobacco-related deaths will go up approximately 300%, resulting 3.0 million tobacco-related deaths annually[1]. Even to this day, the situation of tobacco control in China is still increasing serious, accompanying with high smoking prevalence, low and affordable price of cigarettes, poor knowledge of tobacco harms, and heavy economic burden of tobacco-related diseases etc. The WHO Framework Convention on Tobacco Control (FCTC), which covers 87.4% of the world's population and consists of more than 170 countries as signatories, is the first ever international treaty devoted to tobacco control in the world. Despite ratifying the FCTC in the year of 2005, the pace of tobacco control in China has lagged behind of most of the eligible signatories, which rank in the bottom 20% in WHO's ranking of the success of countries in tobacco control and FCTC compliance[4, 5]. With an effort to assist eligible signatories to reduce tobacco use, the WHO FCTC introduced the MPOWER measures (**M**onitoring tobacco use and prevention policies**; P**rotecting people from the harms of tobacco smoke; **O**ffering help to quit tobacco use**; W**arning about the dangers of tobacco**; E**nforce bans on tobacco advertising, promotion and sponsorship; **R**aising taxes on tobacco)[6]. However, the implement of MPOWER measures needs to be largely improved in China at present. The health professionals also play a critical role in smoking cessation and even brief smoking cessation interventions are effective. However, the awareness of adverse health effects of smoking in health professionals is relatively poor in China[7, 8]. Cigarette gifting culture is another concern. Rarely seen in other cultures, the practices of gifting and sharing cigarettes are well accepted and pervasive across China. In Chinese culture, cigarette sharing or gifting is a bridge for establishing and maintaining interpersonal relationships, as well as a gesture to show respect and welcome guests. As a result, cigarette sharing or gifting is not only a contributor to individuals initiating smoking process, but also a major barrier to smoking cessation, especially in rural China[9]. In addition, it is worth noting that China's State Tobacco Monopoly Administration is not only a governmental agency responsible for all aspects of tobacco industry, including tobacco growing, processing, product manufacturing and distribution and also material and machinery supplies, it is also in charge of tobacco control affairs in China, which presents a serious conflict of interest and is another significant obstacle for tobacco control in China[10]. In summary, several impediments for tobacco control in China need be overcome, including poor awareness of harm of tobacco use and high smoking prevalence among physicians, cigarettes gifting and sharing culture, and conflict of interest in government agency. Therefore, it is very important to improve the awareness of the harms of tobacco use, decrease the smoking prevalence among physicians, and training standard anti-tobacco skills for health professionals. Furthermore, additional cultural-specific measures also should be taken to discourage sharing or gifting cigarettes to reduce tobacco use through sharing or gifting, especially in rural China. More importantly, to separate the functions of the government from the tobacco industry may be the most critical step to eliminate the contradictions in China's tobacco policies and to fulfill the WHO FCTC goals in China. **Reference** 1. World Health Organization. WHO Global Report: Mortality Attributable to Tobacco. Geneva: World Health Organization. http://www.who.int/tobacco/publications/surveillance/rep_mortality_attibutable/en/index.html. . 2. World Health Organization. 2008–2013 action plan for the global strategy for the prevention and control of noncommunicable diseases. http://whqlibdoc.who.int/publications/2009/9789241597418_eng.pdf. 3. China Health Statistics Yearbook. . http://wsb.moh.gov.cn/htmlfiles/zwgkzt/ptjnj/year2011/index2011.html. 4. World Health Organization. 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Keywords: Challenge, Tobacco Control, Chinese

MS25.01 IMPACT OF TUMOR VOLUME ON OUTCOME: WHAT ARE THE LIMITATIONS?

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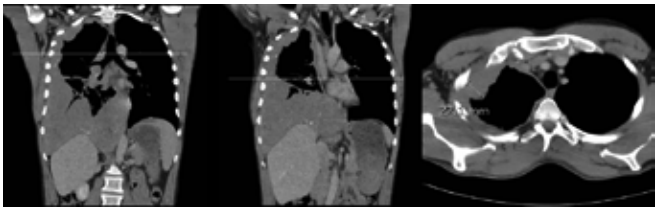
A key goal of cancer staging is to stratify patient survival using anatomical tumour characteristics identified on imaging at presentation. The relationship between burden of cancer and patient outcomes is an established tenet of oncology, and most staging and prognostic systems incorporate surrogates or estimates of total tumour burden. Nevertheless, malignant pleural mesothelioma has long posed challenges in quantifying tumour burden for staging and prognostication. Many cancers grow outward from a nidus to form a mass of tumour cells which can be measured in three dimensions and volume of tumour quantified. However, the unique morphology of mesothelioma, growing as a sheet of tumour around the pleural cavity, adds complexity to the routine quantification of tumour burden. Furthermore, CT imaging, at least using human interpretation, may have difficulty distinguishing between pleural tumour and atelectasis, pleural fluid, and pleural scarring or plaques, confounding the accurate measurement of tumour volume. The relationship between tumour burden and outcomes in mesothelioma was first reported in 1997, noting that tumour size as measured using 3-D reconstructions of chest CT was prognostic in patients undergoing surgical resection, with a tumour volume <100cc predicting better survival[1]. These findings have been reproduced in a number of studies, both using CT imaging in the context of extrapleural pneumonectomy[2] and using FDG-PET to estimate pleural tumour volume in non-surgically treated patients[3]. However, the technical challenges of accurately and reproducibly measuring tumour volume have remained barriers to routinely incorporating this metric into clinical practice prognostication, staging systems, and clinical trial stratification. In practical terms, what do we need to be able to apply an estimate of tumour volume in everyday clinical practice? Centres of excellence and radiology research laboratories may be able to use computerised estimates of volume as measured by CT scan or FDG-PET scan, however a sound prognostic indicator which can be applied to the population as a whole must also be applicable in a less resource-rich environment. Currently, there are numerous commercial and research tools for measuring tumour volume, however each requires a different level of clinician or radiographer input, and those which require manual oversight or contouring are also prone to inter-observer variability. Furthermore, it is not clear whether there is consistency between platforms. The most recent iteration of the IASLC staging database collected information on unidimensional measurements of pleural tumour thickness from 472 patients as a surrogate measure of tumour bulk, attempting to approach the semi-quantification of tumour bulk using a technique which could be rapidly applied in any setting, including community practice or low resource settings. In brief, measurements of pleural tumour were taken perpendicular to the chest wall or mediastinum at the point of maximum tumour thickness, one each in the upper, middle and lower thirds of the thorax[4] (Figure 1a and b). As published in the recent update of the AJCC/IUCC staging system for mesothelioma, these measurements could be analysed in a number of ways, but were consistently identified as prognostic indicators and may even provide better discrimination between patient outcomes than existing T stages, which classify by the extent of anatomical organ involvement or invasion, rather than tumour bulk. Whether these measurements were summated, or dichotomised by maximal thickness, or ranked by quartile, these findings were consistent and predicted for overall survival. Another recent publication supports the relationship between unidimensional tumour measurements of thickness, and both tumour volume and survival[5]. Taking three structured measurements from the mediastinum, chest wall, and diaphragm, nine measurements were determined, which correlated significantly ($p<0.0001$) with total tumour volume as estimated by gross tumour volume from a radiation boost volume calculation. Diaphragmatic tumour thickness was more strongly associated with time to recurrence ($p<0.0001$) and survival ($p=0.001$) than mediastinal or chest wall tumour

thickness. In conclusion, whilst tumour volume is clearly a prognostic indicator in mesothelioma, the question of how to best incorporate this metric into routine staging and clinical practice remains open. The IASLC Mesothelioma Staging Database will shortly open to further data collection, and will again incorporate unidimensional measurements of tumour thickness, in an effort to further define a simple and readily applied surrogate of volume. Automated measurement of volume continues to be refined by multiple investigators, and concordance between platforms will be needed to move the field forward. 1. Pass HI, Temeck BK, Kranda K, Steinberg SM, Feuerstein IR. Preoperative tumor volume is associated with outcome in malignant pleural mesothelioma. J Thorac Cardiovasc Surg 1998;115:310-7; discussion 7-8. 2. Gill RR, Richards WG, Yeap BY, et al. Epithelial malignant pleural mesothelioma after extrapleural pneumonectomy: stratification of survival with CT-derived tumor volume. AJR Am J Roentgenol 2012;198:359-63. 3. Nowak AK, Francis RJ, Phillips MJ, et al. A Novel Prognostic Model for Malignant Mesothelioma Incorporating Quantitative FDG-PET Imaging with Clinical Parameters. Clin Cancer Res 2010;16:2409-17. 4. Nowak AK, Chansky K, Rice DC, et al. The IASLC Mesothelioma Staging Project: Proposals for Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma. J Thorac Oncol 2016;11:2089-99. 5. de Perrot M, Dong Z, Bradbury P, et al. Impact of tumour thickness on survival after radical radiation and surgery in malignant pleural mesothelioma. The European respiratory journal 2017;49. Figure 1: In the IASLC T staging database, tumour bulk was estimated by measuring the thickest tumour at the upper, middle and lower hemithorax bounded by structures shown above and below lines in (a), (b). Tumour is measured perpendicular to the chest wall or mediastinum (c).



Keywords: Tumour volume, Cancer Staging

MS25 GENETIC AND PROGNOSTIC MARKERS IN MESOTHELIOMA; GOING BEYOND THE HISTOLOGY SUBTYPES
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MS25.02 HOW SHOULD P16, BAP1, AND NF2 MUTATIONS BE INTEGRATED IN THERAPEUTIC ALGORITHMS?

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Malignant mesothelioma (MM) is a rare cancer with a natural history of 7–9 months if untreated and a 5-year survival rate of less than 5% for the epithelioid and 0% for the biphasic and sarcomatoid types. MPM aggressiveness is strongly associated with histological differentiation (2017 -MESOPATH data). Up to now there are no curable available therapeutic options but patients treated with avastin, cisplatin, pemetrexed, or targeting angiogenesis (bevacizumab) may present a median longer survival by few months. However for epithelioid type depending of the TNM stage of the disease surgery remains a therapeutic option that may increase overall survival depending on the radiological volume and tumor thickness. Additionally, in 2017 the immune checkpoints inhibitors have been evaluated in unresectable malignant pleural mesothelioma [MPM] and recent preliminary data using immunotherapy combination have demonstrated a potential efficacy for second line therapy. Moreover, recent trials using drug that target the epigenome such as the enhancer of zest homolog 2(EZH2) was expected to bring the promise of a better survival for patient harboring BAP1 mutations. These data showed the extreme importance of an accurate histopathological diagnosis in the management of the patient and the urgent need of more effective treatments. The 2015 WHO classification have upgraded the histological diagnosis of MPM in separating the epithelioid from the non-epithelioid types for a better prognostication. The second most important challenge is the separation of benign reactive mesothelial hyperplasia and malignant epithelioid mesothelioma and the need of molecular markers to select the best treatment strategy at an early stage when the treatment can prevent the spread of the disease. In 2018, a recent IASLC-EURACAN multidisciplinary meeting in Lyon, France, reported the most common genomic advances in MPM that may change routine practice and management of patient. Development of genomic analysis has reported the most frequent genomic alterations observed in malignant pleural mesothelioma and new advances for diagnosis and prognostication. The genomic landscape of MPM rest on inactivating mutations in several tumor suppressors genes. CDKN2A (p16), BAP1 and NF2 are the three most frequent genomic alterations observed in MPM. BAP1 is a tumor suppressor gene located in chromosome band 3p2.1 that encodes BRCA1 -associated protein 1 which belongs to the ubiquitin C-terminal hydrolase subfamily of deubiquitinating enzymes removing ubiquitin from proteins and also from histone H2A which is important for coordination of cell proliferation. Moreover BAP1 enzymes bind to the BRCA1 protein via its RING finger domain and are involved in regulation of the cell cycle, cellular growth, regulation of DNA transcription, response to DNA damage and chromatin remodeling. BAP1 alterations follow the classic two hit paradigm so one mutant allele which is present in all cells just need the other mutant allele by somatic inactivation to trigger transformation. The mutational status of BAP1 can be very easily assessed by immunohistochemistry on biopsy tissue and cytology samples by showing a lack of nuclear staining with a positive control observed on the adjacent normal cells is very easy and accurate to perform. BAP1 loss of expression is observed in approximately 60% of MPM, mostly on the epithelioid type. BAP1 is one of the most important tumor suppressor genes which inactivation will contribute in treatment decision; first as a molecular marker for separating chronic pleuritis, or benign reactive atypical mesothelial hyperplasia from malignant pleural epithelioid mesothelioma allowing a diagnosis of in situ mesothelioma which may favor early treatment to prevent the spread of the disease; second, BAP1 loss which results from increased trimethylated histone H3 lysine 27 (H3K27me3, increased enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) expression and enhanced repression of polycomb repressive complex2 (PCR) targets. Preclinical models of EZH2 inhibition have showed a benefit in malignant pleural mesothelioma presenting BAP1 loss. A phase II clinical trials evaluating the EZH2 inhibitor tazemetostat in MPM is ongoing. Additionally, a new alternative splice isoform of BAP1 has been reported to regulate DNA damage response and to influence drug sensitivity. BAP1 loss play also a role in prognostication, these patients having a much better prognosis. Another driver mutation is the CDKN2A gene located in chromosome 9p21 encoding $p14^{ARF}$ and $p16^{INK4a}$ which through $p14^{ARF}$ interacts with MDM2 leading to MDM2 degradation and activation of p53 . In consequence loss of $p14^{ARF}$ favor cell survival. On the other way loss of $p16^{INK4a}$ leads to inhibition of the retinoblastoma pathway and to cell progression. CDKN2A(p16) is observed by FISH analysis in nearly 50% of malignant pleural mesothelioma to more than 80% in sarcomatoid and desmoplastic mesothelioma A large number of publications have confirmed that CDKN2A(P16) homozygous deletion by FISH testing is an accurate marker of malignancy playing a major role in the separation of benign reactive mesothelial hyperplasia versus epithelioid malignant pleural mesothelioma and more interestingly in the separation of diffuse chronic pleural fibrosis from sarcomatoid MPM. Finally the last more common driver mutation, the neurofibromin 2 gene (*NF2)* located at chromosome 22q12 encodes the merlin protein which regulates the hippo pathway. Next generation sequencing has showed alterations in *NF2* in 20 to 50% of MPLM and In consequence the loss of NF2 results in cell proliferation and survival. The potential utility of NF2 loss was evaluated using immunohistochemistry by Sheffield et al, showing that the incidence of *NF2* immunohistochemical staining was not helpful for the diagnosis of mesothelioma with a sensitivity of 4%. However, recent investigation has showed that defactinib a focal adhesion kinase (FAK) inhibitor may have a potential action on the NF2 pathway for blocking cell survival. The diverse molecular events are not exclusive and it should be expected that additional mutations may play a role in treatment sensitivity. BAP1, *NF2* and p16 are the main tumor suppressor genes involve in mesothelioma important to evaluate for diagnosis, prognostication and treatment decision. Therapeutic algorithms will be presented during the session. References Ladanyi M, Zauderer MG, Krug LM, Ito T, McMillan R, Bott M, Giancotti F. New strategies in pleural mesothelioma: BAP1 and NF2 as novel targets for therapeutic development and risk assessment.Clin Cancer Res. 2012 Sep 1;18(17):4485-90 McCambridge AJ, Napolitano A, Mansfield AS, Fennell DA, Sekido Y, Nowak AK, Reungwetwattana T, Mao W, Pass HI, Carbone M, Yang H, Peikert T. Progress in the Management of Malignant Pleural Mesothelioma in 2017. J Thorac Oncol. 2018 May;13(5):606-623 Churg A, Sheffield BS, Galateau-Salle F. New markers for separating benign from malignant mesothelial proliferations: are we there yet?*Arch Pathol Lab Med*. 2016;140(4):318–321. Sheffield BS, Hwang HC, Lee AF, et al. 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MS25 GENETIC AND PROGNOSTIC MARKERS IN MESOTHELIOMA; GOING BEYOND THE HISTOLOGY SUBTYPES
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MS25.05 TARGETING THE MICRO-RNA: A NEW THERAPEUTIC VENTURE

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Malignant pleural mesothelioma (MPM) has remained a therapeutically challenging condition since the establishment of cisplatin and pemetrexed chemotherapy (chemo) as the standard of care in suitably fit patients (1). Approaches to drug development in MPM as in cancer in general have traditionally focused on identifying specific cellular or biologic "targets" considered of importance in the cancer pathogenesis in the hope of obtaining large therapeutic impact. Unfortunately successful "targeted" therapy of advanced MPM has to date remained elusive. The arguments for these failures in MPM emphasize the complexity of the pathogenesis of MPM, characterized by alterations in multiple cellular pathways and the absence of landmark "drivers". The search for therapy by targeting fundamental pathologic processes in MPM has seen greater success. An example of this has been vascular endothelial growth factor (VEGF) signaling which has been shown to play a pivotal role in MPM pathogenesis. Targeting VEGF with the addition of the anti-VEGF monoclonal antibody bevacizumab to standard chemo in patients (pts) with advanced MPM was shown to improve survival compared with standard chemo (2). Another such approach of interest in MPM is that focusing on non-coding RNAs with their deregulation seen in MPM as in many other human cancers. MicroRNAs (miRNAs), are a subclass of non-coding RNAs with short sequences (18–24 nucleotides) that target messenger RNAs (mRNAs) through partial base pairing to sites found in their 3´ untranslated region (3). They regulate gene expression post-transcriptionally by blocking the translation of target mRNAs. Over 1000 human miRNAs have been identified with roles in the control of gene and protein expression (4). In MPM several miRNA expression profiles have been identified in tissue and in blood (serum or plasma) as potential biomarkers of MPM, with possible a role in diagnosis and prognosis (5, 6). Several dysregulated miRNAs have also been associated with the pathogenesis of MPM affecting many of the hallmarks of cancer, by being downregulated and thus losing their tumour suppressor functions (5). Thus, developing a therapeutic approach to MPM by targeting miRNAs has focused on restoring the levels of deficient miRNA. Therapeutic miRNA replacement to date has mainly focused on the use of synthetic miRNA mimics to restore lost tumor suppressor expression (7). The miRNA-15/16 family specifically has been shown to be downregulated and to have a tumour suppressor function in MPM , targeting the mRNAs of BCL2, CDK1, ETS1, and JUN, which are all involved in cancer progression (7,8). Based on this finding Reid et al focused on developing a therapeutic strategy targeting miRNA-16 (miR-16). Firstly they showed in vitro that restoring miR-15 and -16 expression inhibited MPM cell growth and that systemic delivery of a miR-16 mimic inhibits tumour growth in vivo (8). Furthermore, in vitro, miR-16 restoration increased the sensitivity of cells to gemcitabine and pemetrexed chemo (8).Reid et al used an alternative to the liposomal or nanoparticle basedmethods frequently used to deliver miRNAs, by employing EnGeneIC Dream Vectors (EDV™) nanocells (EDVs)(7, 8, 9). This is a bacterially derived delivery system developed by EnGeneIC Ltd (Sydney, Australia) and comprises nonviable minicells 400 +/- 20 nm in diameter, which were loaded with a miR-16 mimic, and coated with bispecific antibody to EGFR (panitumumab), as EGFR is known to be expressed in a high proportion of mesothelioma patients (7, 8, 9). These pre-clinical experiments were followed by a first in man open label, phase 1, dose-escalation escalation study in patients with refractory advanced MPM aimed to assess the safety, optimal dosing, and activity of TargomiRs (the aforementioned EDV minicells loaded with miR-16-based miRNA targeted to EGFR (10)). Patients were given TargomiRs via 20 min intravenous IV) infusion either once or twice a week (3 days apart) in a traditional 3 + 3 dose-escalation design in five dose cohorts. Several dose-escalation steps were planned either once or twice weekly, but after analysis of data from the first eight pts, all subsequent patients started protocol treatment at 1 x 10^9 TargomiRs. The primary endpoints were to establish the maximum tolerated dose (MTD), defined by dose-limiting toxicity, to define the optimal administration schedule and to explore anti-tumour activity (10). Twenty six enrolled pts received at least one TargomiR dose. Overall, 5 DLTs were noted: infusion-related inflammatory symptoms and coronary ischaemia, respectively, in 2 pts given 5 x 10^9 TargomiRs twice weekly; anaphylaxis and cardiomyopathy, respectively, in two pts given 5 x 10^9 TargomiRs once weekly but who received reduced dexamethasone prophylaxis; and non-cardiac pain in one pt who received 5 x 10^9 TargomiRs once weekly. MTD was 5 x 10^9 TargomiRs once weekly. TargomiR infusions were accompanied by transient lymphopenia (25 /26 pts), temporal hypophosphataemia (17/26 [65%] pts), increased aspartate aminotransferase or alanine aminotranferase (6/26 [23%] pts), and increased alkaline phosphatase blood concentrations (2/26 [8%]). Cardiac events occurred in 5 pts: 3 with ECG changes, one pt had ischaemia, one pt had Takotsubo cardiomyopathy. 22 pts were evaluable for response: one (5%) partial response, 15 (68%) stable disease, six (27%) progressive disease. The duration of response in the responding pt was 32 weeks. Median overall survival was 200 days (95% CI 94–358)(10). This phase I study demonstrated acceptable safety and signs of activity of TargomiRs acting as proof of concept supporting further development in pts with refractory MPM. The optimal next step is not clear. Possibilities include a formal Phase II study evaluating TargomiRs in the weekly or alternative schedules or combination studies with chemo or immune checkpoint inhibitors. Another novel combination option has been suggested by the recently identified link between the fibroblast growth factor axis and the miR-16 family (11). 1. J Clin Oncol 2003;21: 2636–44 2. Lancet.2016 Apr 2;387(10026):1405-1414. 3. Cell 2009; 136: 215–33. 4. Nat Rev Mol Cell Biol 2013; 14: 475–88. 5. Int J Mol Sci. 2018 Feb 17;19(2) pii: E595. 6. Sci Rep. 2017 Jun 9;7(1):3140. 7. Epigenomics 2016 8(8),1079–1085 8. Ann Oncol 2013 24: 3128–3135 9. Cancer Cell 2007 11(5), 431–445 10. Lancet Oncol. 2017 Oct;18(10):1386-1396. 11. Mol Oncol. 2018 Jan;12(1):58-73

MS26 FROM TEXTBOOK TO PRACTICE AROUND THE WORLD
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MS26.01 TRANSLATION OF CLINICAL DATA TO REAL WORLD - ASIA

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Real world evidence (RWE) research becomes more important than before since data about real-world effectiveness and safety might impact the reimbursement and utilization of new but pretty expensive drugs or medical devices in precision medicine and immune-oncology era. The data are requested more by regulators, public and private payers as well as patients and physicians, all of whom seek to better understand the impact or usefulness of the drugs or medical devices either already approved for the indication or under approval process for the expansion of the indication in a real-world setting. Ministry of Food and Drug Safety (MFDS) formerly known as Korean Food and Drug Administration requires post-approval research or post-market surveillance to determine real world safety due to concerns about unexpected safety and complications in a larger population while it does not require the data about real world efficacy and cost-effectiveness after approval. However, National Health Insurance Service (NHIS) and Health Insurance Review and Assessment Service (HIRA), only one governmental payer in Korea, may need real world clinical effectiveness and cost-effectiveness of both drugs, especially molecular-targeted agents and immune checkpoint inhibitors, and medical devices, such as next generation-sequencing, after the coverage. Actually, the decision whether to approve or reimburse a drug or medical device is usually made based on a prior large clinical trial(s) which have already given both clinical efficacy and safety profile but not cost-effectiveness and/or budget impact on the healthcare system. Cost-effectiveness can often be addressed in a longer time or from assumptions based on the results of prior clinical trials. Nevertheless, the Korean reimbursement system has to decide whether to cover drugs or medical devices for patient's request as well as company's one without solid cost-effectiveness data. In addition, most of the trials were conducted outside Korea or included a few Korean patients, requiring more information from a larger Korean population who might different age groups, different genders and different molecular backgrounds in the real world from the population included in the clinical trials. Therefore, the data about real-world Korean patient experience have the potential to improve the quality and delivery of medical care in Korea but also reduce overall costs by reducing or fixing gaps between clinical trials and real clinical practice. Especially, as some immune checkpoint inhibitors or next generation sequencing has been reimbursed since 2017, the NHIS and HIRA recognizes the importance of RWE and need of RWE research or comparative effectiveness research. However, there are some barriers to be overcome for the research. First of all, all of clinical data which are needed for the research should be collected well. All claims from providers in Korea are submitted electronically to the NHIS using a computer with software that meets electronic filling requirements, which are later reviewed by the HIRA. Fortunately, since there is only one insurance system run by government in Korea, therefore the claims seem good as clinical data. However, the requirement is rather optimized to or fitted more in with billing service while personally identifiable information on beneficiaries is obtained as little as possible, which, makes electronic data captured less useful for real world evidence research. Some clinical data, such as demographic or survival related data, are also collected by another governmental organization, Statics Korea, but electronic data interchange between the organizations is rather difficult due to enforced domestic laws, personal information protection act. Merging clinical data already electronically obtained has one of the barriers to be overcome. Sometimes more data should be captured separately or in addition to those from the current electronic health claims or

governmental organization. Therefore, we have to overcome barriers related to collection of clinical data. Fortunately, all providers in Korea use electronic medical records. Secondly, resources for the research including research personnel, funding process and supporting infrastructures, are also a big issue. Most of clinical trials for developing drugs or medical devices are initiated or sponsored by companies which are very familiar to clinical trials from designing through conducting to analyzing and reporting steps. However, real world evidence research is usually initiated, sponsored or supported by the organizations running health care reimbursement system which are not familiar as much as companies. The research itself are not familiar to most investigators or contract research organizations as well. The research budget is not also easily estimated and therefore funding for each research becomes another problem. In addition, the funding source is also debatable. Thirdly, generation of a high level of trust from stakeholders is another issue. Due to the nature of real world evidence research such as data collection and research design, studies in general could not yield definitive conclusions because of the many confounding factors. Therefore, a framework should be in place to facilitate the development of trust and to reduce the uncertainty. Establishment of independent organizations, such as Patient-Centered Outcomes Research Institute (PCORI), can be considered. A kind of credit or incentive can considered as well for stakeholders The participation of all stakeholders mght be important for a high level of traust. The governmental organizations in Korea, NHIS and HIRA as well as Ministry of Health and Welfare, have already started consultation to and discussion with healthcare sector stakeholders including academic researchers and product developers as well as patient advocacy groups to develop draft guidance of the use of RWE and then to embed the evidence in the reimbursement and regulations. Although there still remain many challenges or barriers to be overcome at many different levels, it is kept in our mind that quality and transparency at each stage of RWE generation will be critical for all stakeholders.

Keywords: Clinical Data, Barriers, Real World Evidence

MS26 FROM TEXTBOOK TO PRACTICE AROUND THE WORLD
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MS26.02 TRANSLATION OF CLINICAL DATA TO REAL WORLD - NORTH AMERICA

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Clinical trials assist oncologic treatments in moving forward; enabling the creation of new benchmarks for quality care for lung cancer patients. Beyond the demonstration of efficacy however, is the implementation of change in the real world. For some nations, the health care structure is responsive and for others there are multiple steps required to introduce new treatments into standard practice. Within North America there are three dominant countries; Canada, the United States and Mexico. Each has a unique health care system with many complexities that influence access to oncologic care. The Canada Health Act governs the delivery of all medical care in Canada.It emphasizes five key aspects; public administration, comprehensiveness, universality, portability and accessibility. The federal government provides transfer payments to the respective provinces and the provinces manage local administration of health care services. The medical system is funded through provincial and federal general tax revenue. As a result, there is a centralized system for health care that involves no direct payment by the patient for care. The provision of care in the US is multi-faceted. Government sponsored programs include Medicaid, aimed at individuals with low income or certain medical conditions and Medicare for people aged >= 65. The Affordable Health Care Act, introduced in 2010, aimed to expand Medicaid coverage, make affordable health insurance available through subsidies based on income and ensure that insurance premiums were reasonable regardless of pre-existing health care conditions. The current US administration has eroded the initial goals of the program. Employed individuals may opt for private health care insurance however, there is a significant proportion of the population that do not have insurance. The different health care coverage options result in multiple tiers of access to care. The Mexican medical system has three public health care delivery programs; Instituto Mexicano del Seguro Social (IMSS) for employed citizens of private companies, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE) for civil servants and the Seguro Popular for the remainder of the population. The former two programs have tripartite funding from the employee, employer and government, the latter relies on the individual and government support. The health care systems employed by the respective countries have a significant impact on the adoption of new therapies for thoracic malignancies. The translation of clinical trials evidence to the real world is hampered by the practicalities of administration and funding of the specified therapies. The introduction of immunotherapy into the treatment algorithm for NSCLC provides some insight into the process involved in each country. In Canada, the introduction of new cancer therapies involves Health Canada approval, a national health technology assessment (HTA) through the pan Canadian Oncology Drug Review (pCODR) process and national price negotiations through pan Canadian Pharmaceutical Alliance (pCPA). Once a therapy has been deemed clinically and cost effective, the individual provinces are able to negotiate local contracts and add new oncologic agents to their respective formularies. This national process, while ensuring cost effectiveness and a degree of drug price negotiation power, results in significant delays in access to new therapies. The advantage however, is that in a universal health care system, all Canadians have access to approved oncologic drugs regardless of their employment status or income. The disadvantage lies with the therapies that do not meet the bar for approval due to evidence or cost effectiveness issues and that the system is not nimble and responsive. In the example of immunotherapy, nivolumab was first approved by Health Canada in the post-platinum metastatic setting in February 2016. The review by pCODR was completed with approval provided that it was cost effective in June 2016. The longest aspect of the funding for nivolumab was the national price negotiations that took 9 months to reach an agreement that was agreeable to pCPA and the company in March 2017. Subsequently, nivolumab has been funded for all Canadians who meet the listed Health Canada indication. Medicaid/Medicare and private insurance decisions regarding funding of cancer therapies in the US are based on guidelines provided by the National Comprehensive Cancer Network (NCCN). Unlike Canada, the US oncology drug funding model operates on a free market basis and the price of therapy is determined by what the market will bear. Furthermore, the 2003 Medicare law prohibits Medicare from negotiating drug prices which presents significant challenges for patients with a co-pay or those that pay fee for service. Despite the financial hurdles posed by immunotherapy, the US system is responsive to clinical trials evidence. The Food and Drug Administration (FDA) promptly approved nivolumab in the platinum treated second line setting for squamous and non squamous NSCLC in March and October 2015 respectively based on data presented in that year. The NCCN issued revised treatment algorithms incorporating nivolumab for squamous in May 2015 and non squamous disease in October 2015, the result being government and private insurance coverage within 1-2 months of FDA approval. In Mexico, COFEPRIS, the Comisión Federal para la Protección contra Riesgos Sanitarios, similar to Health Canada and the FDA, approved nivolumab for NSCLC in September 2016. However, as of September 2017 nivolumab was not listed on the Basic Table of Drugs covered by IMSS. For Seguro Popular, the Federal Fund for Protection against Catastrophic Health Expenditures (FPCHE) covers high-cost health interventions. This program covers six types of malignant conditions; breast cancer, cervical cancer, prostate cancer, testicular cancer, non- Hodgkin's lymphoma, and childhood cancers. Unfortunately, lung cancer treatment is not covered by this plan as of 2015. While immunotherapy is approved for use in Mexico, there is no government funded mechanism to access therapy rendering it outside the reach of many of the citizens of the country. The practicalities of the transition of clinical trials data to the real world can be challenging at many levels. Depending on the national infrastructure, patients are faced with affordability and timely access issues. Navigating the health care system is the first, critical step of treatment adoption which subsequently enable an understanding of the efficacy and toxicity of providing new therapies to our real-world lung cancer patients.

MS27 THERAPEUTIC IMPLICATIONS OF STAGING ISSUES
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MS27.01 STAGING OF LYMPH NODES IN EARLY STAGE NSCLC: THERAPEUTIC IMPLICATIONS

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For patients with potentially curable non-small cell lung cancer (NSCLC), typically those without evidence of distant metastasis, the status of lymph node involvement is one of the most powerful prognostic factors: 5-year survival for patients with clinical N0, N1, N2 and N3 is estimated at 60%, 37%, 23% and 9%, respectively. Because clinical nodal status also determines optimal treatment modality, clinical nodal staging, performed with the combination of radiologic studies (CT and PET/CT scans) and invasive nodal biopsy techniques (bronchoscopy, endobronchial ultrasound/endoscopic ultrasound, mediastinoscopy, and other minimally invasive surgical methods which extend access to the mediastinum), is highly recommended for most patients being considered for curative-intent therapy. The minority of patients who undergo curative-intent surgical resection for NSCLC provide the vast majority of long-term survivors of lung cancer. Patients with amenable primary tumors, clinical N0 and N1 and adequate physiologic function typically undergo primary surgical resection or definitive radiation therapy (with use of chemotherapy in the setting of node-positivity), those with N2 or N3 typically undergo combined-modality chemotherapy

and radiation therapy. Irrespective of the clinical staging approach, because of the residual inaccuracy of clinical staging even when adequately applied, thorough pathologic nodal staging is also strongly recommended as the most accurate determinant of stage in patients who undergo attempted resection. Estimated 5-year survival rates are 75%, 49%, 36% and 20%, for patients with pathologic N0, N1, N2 and N3 respectively. The pathologic nodal stage also has therapeutic implications: patients with pN1-3 benefit from adjuvant chemotherapy; those with pN2 or 3 may also benefit from radiation therapy (which is harmful to patients with pN0 or pN1). Accurate pathologic nodal staging requires surgical retrieval of lymph nodes from certain specific hilar and mediastinal stations depending on the location of the primary tumor (the pathologist has no access to these nodes without surgical retrieval) and examination of all lymph nodes provided in the resection specimen (including intrapulmonary lymph nodes which are present within the anatomic resection specimen and therefore available to the pathologist, irrespective of surgical practice). ***Gaps in the quality of nodal staging.*** Although there is no universal definition of clinical or pathologic nodal staging quality, multiple organizations have made recommendations for nodal staging. The American College of Surgeons Oncology Group provided an anatomically-precise definition of 'systematic sampling' and 'mediastinal lymph node dissection' which was used in the landmark Z0030 trial. Although this trial revealed survival equivalence between the two extents of surgical nodal retrieval in patients undergoing resection for clinical T1 or T2 and N0 or non-hilar N1 NSCLC, the quality of nodal staging in 'real world practice' falls well short of these definitions. The use of PET/CT scans has increased in the US with greater willingness of insurers to cover testing, but invasive mediastinal nodal staging remains severely underused, with penetration rates below 20% in many institutions. Large US database analyses reveal that up to 18% of 'node-negative' resections have no lymph nodes (pNX); 40-60% of pN0 or pN1 resections have no mediastinal lymph nodes; and less than 20% of pN0 resections have up to 10 lymph nodes, despite multiple studies showing that a minimum of 14 to 20 lymph nodes are associated with the lowest hazard for death. In a population-based cohort of over 2300 resections within a high lung cancer mortality region of the US, only 15% of patients had the combination of preoperative PET/CT scan, invasive mediastinal nodal staging and pathologic examination of any mediastinal lymph nodes; 17% had no attempted histologic examination of mediastinal lymph nodes before, during or after surgical resection. ***Survival implications.*** The nodal staging quality gap has profound survival impact. For example, the survival of patients with pNX resections mirrors that of patients with pN1, not pN0; pN0 and pN1 patients without pathologic mediastinal nodal examination have a 5% lower 5-year survival rate than those with any mediastinal nodes; patients without attempted histologic examination of mediastinal lymph nodes (lacking both invasive preoperative biopsy and mediastinal nodal examination in the resection specimen) have 14% to 37% higher hazard for death within 5 years, compared to those who do. Unsurprisingly, eligibility for adjuvant therapy is significantly more likely when histologic examination of mediastinal lymph nodes is attempted. Furthermore, when large sets of surgically resected NSCLC patients are ordered according to stringency of pathologic nodal staging quality, a strong direct association with survival is revealed. ***Quality improvement.*** The near-universality of the nodal staging quality gap, its profound survival impact, and the negative impact on clinical trial eligibility, accrual, balanced randomization and accurate determination of intervention-related outcomes, suggest the need for corrective intervention. The urgency of this need is heightened by the predicted increase in the proportion of candidates for curative-intent treatment with deeper penetration of low dose CT screening and more organized management of patients with incidentally-detected lung nodules; the widening array of candidate novel adjuvant treatments; the opportunity to develop stage-independent biologic prognostic markers; and the intensifying interest in comparative effectiveness studies of surgical versus non-surgical treatment modalities. Sustainable quality improvement will require simple, rationally-designed and empirically-proven interventions because of the complexity of lung cancer care and the multiplicity of providers involved. We can conceptualize accurate pathologic nodal staging as involving a chain of responsibility from surgical retrieval during the operation (surgeon and scrubbed assistants), accurate specimen labeling (nodal mapping by members of the operating team, often the 'circulating nurse'), secure specimen transfer from the operating room to the pathology laboratory, complete retrieval of all provided lymph node material (pathologic specimen gross dissector, often a pathology technician), thorough examination of all material (pathologist) and accurate reporting in a standardized format (pathologist and transcriptionist). A breach in quality at any of these steps in the chain of responsibility could, in theory, impair the accuracy of pathologic nodal staging. To be sustainably successful, corrective interventions must secure quality across all links in the chain of responsibility, which is only as strong as its weakest link.

Keywords: Outcomes improvement, quality, survival

MS27.02 INVASIVE STAGING IN MEDICALLY INOPERABLE PATIENTS TREATED WITH SBRT: IS IT NECESSARY?

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Patients with stage I, medically inoperable non-small cell lung cancer (NSCLC) who are treated with stereotactic body radiation therapy (SBRT) are typically not routinely subjected to invasive mediastinal or hilar staging. In an era of combined positron emission tomography (PET) and computed tomography (CT) staging, the presence of clinically node negative disease in a patient ineligible for surgery usually justifies use of SBRT, although there are a proportion of patients who harbor subclinical nodal disease. For instance, in large SBRT series (with long followup) using PET/CT clinical staging only, the rates of regional recurrence (defined as hilar or mediastinal failure) were estimated at up to 15%[1,2], with other smaller prospective and retrospective series suggesting higher or lower regional rates. Yet all of this occurs in the face of excellent long term local control that is consistently high among studies using SBRT. Therefore, there exists a double- edged sword in answering the question of whether there is a strong desire to consider routine invasive mediastinal staging in this population. On one hand, there is the possibility of undertreating patients who already harbor occult regional nodal disease; on the other hand the chances of detecting nodal failure appear modest at best, and implications exist with respect to use of potentially more prolonged courses of radiotherapy and/ or systemic therapy in a medically frail population where significant competing risks for survival exist. To put things in perspective, rates of regional nodal failure following surgical resection in medically operable patients appear similar - in the ACOSOG Z0030 trial, 18% of patients with resected clinical stage I disease were found to have regional nodal upstaging, with the majority (13%) having occult N1 disease[3]. Other comparative retrospective studies of SBRT and surgery have shown varying differences in rates of regional nodal failure; however these sorts of studies are fraught with bias in terms of definitions of regional failure, rates of histological diagnosis (in the case of SBRT), patient selection, and duration of follow-up. Within SBRT series themselves, there is less data available, but some indication may exist that at least local control and survival is unchanged in patients who have invasive mediastinal staging versus those who do not[4], likely largely owing to competing risks of mortality. Other series have shown that incidental low SBRT dose to the hilum may or may not reduce the chance of regional nodal recurrence[5,6], and so at this time at least should not be considered a factor in determining whether to consider invasive nodal staging upfront. Other important factors such as tumor size and location however have been fairly consistently reported in both surgical and SBRT series as indications to consider invasive mediastinal staging. In fact, the high false negative rates of CT and PET/CT in detecting nodal disease in central (defined as within the inner third of the hemithorax) tumors would lend argument to the fact that all patients (whether treated with SBRT or surgery) should undergo invasive staging[7,8]. To attempt to answer this question further, the STAGE trial was a prospective study that evaluated the role of endobronchial ultrasound (EBUS) nodal staging in patients with high risk (T2 lesion, centrally located via RTOG definition, and/or suspicion of N1/2 disease on PET/CT) NSCLC suitable for SBRT. Initial results suggested that in patients with cN0 disease on PET/CT, the rate of upstaging using EBUS was approximately 11%[9]. Therefore there are a small but significant proportion of patients who do have occult nodal disease in high risk subgroups that may warrant routine evaluation of the hilum/mediastinum, however long term outcome data is required. Until we have definitive answers from STAGE and other ongoing prospective trials (NCT02719847, NCT01786590), the decision to consider invasive mediastinal staging in a medically inoperable stage I NSCLC patient will largely be an individualized one; yet we are at least fortunate to know that even in a clinical N0 scenario, the chances of nodal failure appear modest at best, and that perhaps with appropriate patient selection (at least for the time being), we can slowly begin to avoid the harm of the double-edged sword that we wield. 1. Marwaha G, Stephans KL, Woody NM, Reddy CA, Videtic GM. Lung stereotactic body radiation therapy: regional nodal failure is not predicted by tumor size. *J Thorac Oncol*. 2014;9(11):1693-1697. 2. 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MS27 THERAPEUTIC IMPLICATIONS OF STAGING ISSUES
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MS27.04 THERAPEUTIC IMPLICATIONS OF AJCC 8TH EDITION T1 SUBSETS

L. Donahoe

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In January 2018, the American Joint Committee on Cancer (AJCC)/ International Union for Cancer Control (UICC) introduced the 8thedition of the tumor, node, and metastasis (TNM) staging system for lung cancer. In the 7thedition, T1a tumors were defined as <2cm and T1b tumors were defined as 2-3cm. In preparation for the 8thedition, an analysis was done of the International Association for the Study of Lung Cancer (IASLC) database and statistically significant differences in survival based on tumor size in increments of 1cm were found (1). Thus, the 8thEdition T-stage was divided into three subgroups: T1a, tumor 1cm or less; T1b, tumor more than 1cm but not larger than 2cm; T1c, tumor more than 2cm but not larger than 3cm. Currently, the standard of care for early stage lung cancer is surgical resection by lobectomy, based on the results of the 1995 Lung Cancer Study Group trial showing improved survival compared with sublobar resection (2). With improvements in imaging technology and clinical staging, the question of whether sublobar resection, in the form of wedge resection or segmentectomy, can provide an oncologically equivalent treatment remains to be answered (3). In a comparison of survival between lobectomy and sublobar resection, it was found that the survival benefit from lobectomy was only present for patients before 1997 and not for the newer cohorts (4). This suggests that early stage lung cancer patients of the present era are different from the era by which our current standards of care were established. Similarly, in comparing outcomes after lobectomy with sublobar resection using the T-stage from the AJCC/UICC 7thedition, there was no difference in survival based on the type of resection for T1a and T1b ground glass-predominant nodule groups, although there was a higher rate of lymph node metastases in the T1b group (5). Additionally, Okada et al found that there was no difference in survival between lobectomy or segmentectomy for T1a tumors based on the AJCC/UICC 7thedition classification (6). Thus, even when using the prior classification of T-stage, there is evidence to suggest that these early tumors should be managed differently than larger, more advanced non-metastatic tumors. With the introduction of the AJCC/UIC 8thedition of the staging system, further studies will be able to better delineate the question of whether sublobar resection is appropriate for early stage lung cancer and whether a specific size cutoff within the T1 stage can guide the extent of resection. 1. Rami-Porta R, Bolejack V, Crowley J, Ball D, Kim J, Lyons G, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015;10(7):990-1003. 2. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg. 1995;60(3):615-22; discussion 22-3. 3. Van Schil PE. Non-small cell lung cancer: the new T1 categories. F1000Res. 2017;6:174. 4. Yendamuri S, Sharma R, Demmy M, Groman A, Hennon M, Dexter E, et al. Temporal trends in outcomes following sublobar and lobar resections for small (≤ 2 cm) non-small cell lung cancers--a Surveillance Epidemiology End Results database analysis. J Surg Res. 2013;183(1):27-32. 5. Tsutani Y, Miyata Y, Nakayama H, Okumura S, Adachi S, Yoshimura M, et al. Appropriate sublobar resection choice for ground glass opacity-dominant clinical stage IA lung adenocarcinoma: wedge resection or segmentectomy. Chest. 2014;145(1):66-71. 6. Okada M, Mimae T, Tsutani Y, Nakayama H, Okumura S, Yoshimura M, et al. Segmentectomy versus lobectomy for clinical stage IA lung adenocarcinoma. Ann Cardiothorac Surg. 2014;3(2):153-9.

Keywords: lung cancer, Surgical resection, TNM 8th Edition

MS28 IO COMBINATIONS IN ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MS28.02 COMBINATION IO+IO

M. Ahn

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Immune checkpoint inhibitors (CPIs) such as anti-cytotoxic T lymphocyte antigen-4 (CTLA-4), anti-programmed death-1 (PD-1), or PD-L1 demonstrated durable response rates across broad range of solid tumors including non-small cell lung cancer (NSCLC), which has revolutionized treatment of solid tumors. In NSCLC, Pembrolizumab monotherapy in patients with high PD-L1 expression showed significant improvement of overall survival (OS) compared with platinum doublets as first-line therapy. For further improvement of efficacy and durable response, several randomized phase III studies of CPIs combined with chemotherapy also demonstrated significant improvement of OS regardless of PD-L1 expression. Given that combination of CTLA-4 inhibitor, ipilimumab with anti-PD1, nivolumab led to significant increase of response rate and survival in malignant melanoma, similar approach has been applied to the treatment of NSCLC. The Checkmate 227 study, a randomized phase 3 trial comparing nivolumab plus ipilimumab (Ipi-Nivo) with standard platinum-based chemotherapy in NSCLC has been conducted. Preplanned co-primary analysis demonstrated significant improvement of progression free survival (PFS) with nivolumab plus ipilimumab in patients with high tumor mutation burden (TMB) of at least 10 mutations per megabase, tested by FoundationOne CDx assay. The median PFS was 7.2 months (95% CI 5.5 to 13.2) versus 5.5 months (HR 0.58, 95% CI 4.4 to 5.8, p<0.001). The objective response rate was 45.3% with nivolumab plus ipilimumab and 26.9% with chemotherapy. The incidence of grade 3 or 4 treatment related adverse events was similar between two arms (31.2% with nivolumab plus ipilimumab vs 36.1% with chemotherapy), however, the incidence of discontinuation of drugs is more common in nivolumab plus ipilimumab combination (17% vs 9%). Although overall survival data are not yet mature, these results indicate that TMB is considered an independent predictive marker for selected patients who most likely benefit from the combination of nivolumab and ipilimumab. Recent update of CheckMate 227 study (Part 2) in patients with < 1% of PD-L1 expression was presented. The PFS was significantly improved with combination of nivolumab plus ipilimumab compared with chemotherapy alone (HR=0.74, 95% CI;0.58-0.94), but the benefit from nivolumab plus ipilimumab combination was confined only in patients with TMB 10 mut/Mb suggesting TMB can be considered predictive biomarker for combination of nivolumab plus ipilimumab. In contrast, the MYSTIC study, which compared durvalumab plus tremelimumab with platinum-based chemotherapy, did not meet the primary endpoint of PFS. Final analysis of overall survival is pending. Actually, achievement of 45% of PFS at 1 yr in patients with <1% of PD-L1 expression with combination of nivolumab plus ipilimumab is quite encouraging. However, several issues still remain for use of TMB as a biomarker in clinical practice. TMB can be analyzed by whole exome sequencing, targeted sequencing from tissue or liquid biopsy, where the study platforms are not standardized. Further, the cut-off value of high TMB is quite variable among studies. The tissue availability for TBM test might be another issue and turn-around time also should be improved. Immune checkpoints are orchestrated by a set of co-stimulatory and co-inhibitory molecules that regulate the activation and effector functions of T lymphocytes. Until now, combination of ipilimumab with nivolumab showed promising results in NSCLC, but other combination approach of anti-PD1 or anti-PD-L1 with antibodies targeting other co-inhibitory molecules, such TIM-3, BTLA, VISTA, LAG-3, or TIGIT is actively involved in early clinical trial. Similarly, antibodies targeting co-inhibitory molecules, such CD28, OX40, GITR, CD137 or CD27 combined with anti-PD1 or anti-PDL1 are also underway for early clinical trial (Table 1). Most of these combinational approaches have demonstrated synergistic effect in preclinical model, however, it should be further investigated whether these results can be translated into clinical trial, even though several early clinical studies of combination showed tolerable safety profile and response even CPIs refractory patients. Further, it will be long way to go to determine which combination is the most effective among others. Moreover, continuous efforts to search for predictive biomarker for combination approach of CPIs should be elaborated. References Hellmann, M.D., et al., Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med, 2018 Pardoll, D.M., *The blockade of immune checkpoints in cancer immunotherapy.* Nat Rev Cancer, 2012. **12**(4): p. 252-64 Borghaei H.,

et al. Nivolumab (Nivo) + platinum-doublet chemotherapy (Chemo) vs chemo as first-line (1L) treatment (Tx) for advanced non-small cell lung cancer with <1% tumor PD-L1 expression: Results from CheckMate 227. J Clin Oncol 36,2018 (suppl;abstr 9001) Table 1. Ongoing early clinical trials of co-stimulatory of co-inhibitory molecules alone or in combination with anti-PD1 or anti-PD-L1.

Molecules	Agents (Company)	ClinicalTrials.gov identifier
Co-inhibitory molecules		
CTLA-4	**Ipilimumab (BMS) Tremelimumab (AZ) MK1308 (Merck)**	**Phase III Phase III NCT03179436**
TIM3-	**MGB453 (Novartis) TSR-022 (Tesaro) LY3321367 (Lilly)**	**NCT02608268 NCT02817633 NCT03099109**
VISTA	**JNJ-61610588 (Janssen) ***	**NCT02671955**
LAG-3	**BMS986016 (BMS) IMP321 (Primo BioMed) LAG525 (Novartis) TSR033 (Tesaro) MGD013 (MacroGenics)**	**NCT02966548 NCT02614833 NCT03365791 NCT03250832 NCT03219268**
TIGIT	**BMS986207 (BMS) OMP313M32 (OncoMed) MITIG7192A (Genentech) MK7684 (Merck)**	**NCT02913313 NCT03119428 NCT02794571 NCT02964013**
Co-stimulatory molecules		
OX40	**GSK3174998 (GSK) MOXR0916 (Genentech) MEDI0562 (Medimmune) PF-04518600 (Pfizer)**	**NCT02528357 NCT02219724 NCT02318394 NCT02315066**
GITR	**TRX518 (Leap Therapeutics) MEDI1873 (Medimmune) BMS986156 (BMS)**	**NCT01239134 NCT02583165 NCT02598960**
CD137	**Urelumab (BMS) Utolimumab (Pfizer)**	**NCT01471210 NCT01307267**
CD27	**Varilumab (Celidex Therapeutics)**	**NCT01460134**

*terminated

Keywords: non-small cell lung cancer, combination, immune check point inhibitors

MS28 IO COMBINATIONS IN ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MS28.04 COMBINATION WITH TARGETED THERAPIES

R. Soo

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Molecular targeted therapy and immunotherapy have transformed the treatment of lung cancer. In oncogene driven lung cancer such as *EGFR* mutant or *EML4-ALK* rearranged NSCLC, molecular targeted therapy is associated with high response rates but are usually not durable. Lately, the use of immune checkpoint inhibitors targeting programmed death receptor-1 (PD-1) and programmed death receptor ligand-1 (PD-L1) have generated regulatory approvals in the first line and pre-treated setting for advanced NSCLC. Single agent immune checkpoint inhibitors are associated with lower responses but responses are more durable. The combination of targeted therapy and immunotherapy can potentially deliver new opportunities to improve anti-cancer treatments. In this presentation, PD1/PD-L1 inhibitors in combination with targeted therapies will be discussed with a focus on EGFR mutant/ ALK rearranged NSCLC. The areas to be reviewed include: (1) oncogene signalling pathways and PD-L1 expression, (2) the reduced effectiveness of immune checkpoint inhibitors in pre-treated *EGFR/ALK* +ve NSCLC, (3) mechanisms for an impaired response to immune checkpoint inhibitors, (4) the relationship between PD-L1 expression and response to targeted therapy, (5) the immunological effects of molecular targeted therapy and (6) the efficacy and toxicity outcomes in studies of combination targeted therapy and immune checkpoint inhibitors in oncogene driven tumors. In addition, the role of immunotherapy in combination with antiangiogenic agents and EGFR monoclonal antibodies in oncogene negative NSCLC will also be presented. A better understanding of the integration of targeted therapies with immunotherapies will be required to inform on the design of combination strategies and improve outcomes and reduce toxicities in patients.

Keywords: Molecular targeted therapy, oncogene driven lung cancer, combination therapy

MS28 IO COMBINATIONS IN ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MS28.05 COMBINING IO WITH RADIATION

C. Faivre-Finn

Clinical Oncology, The University of Manchester and the Christie NHS F'Dation Trust, Manchester/GB

Lung cancer remains the leading cause of cancer-related death worldwide, with non-small cell lung cancer accounting for 85% of the disease. Over 70% of patients present with locally advanced, non-resectable or metastatic disease and despite improvements in chemo-radiotherapy regimens and the development of molecularly targeted agents, 5 year survival rates remain poor, with acquired resistance to novel targeted therapies becoming a growing concern. Currently there remains an unmet need in effectively treating and inducing durable responses in advanced disease. Targeting the immune system has, however, recently given hope of improving therapeutic outcomes for these patients. The notion that the immune system is capable of recognising and eliminating cancer cells is now a widely accepted phenomenon and growing evidence suggests lung cancer is an attractive target for such intervention. Recent success targeting the programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) axis of immune checkpoint inhibition in stage IV non-small cell lung cancer suggests a major immunotherapeutic advance in treating lung cancer and unheralded opportunity for such approaches to further improve outcome for patients. Currently there is considerable interest in combining anti-PD-1 or PD-L1 monoclonal antibodies with established standard of care therapies such as radiotherapy. Radiotherapy is known to be immunostimulatory and efforts are underway to combine and augment the efficacy of the immune checkpoint inhibitors further. The combination of radiotherapy with immunotherapy has the potential to augment anti-tumour immune responses. This talk will outline the interaction between lung cancer and the immune system, summarises current evidence supporting the use of monoclonal antibodies targeting the PD-1 axis in lung cancer (including the PACIFIC trial) and will summarise ongoing clinical trials.

Keywords: radiotherapy, immunotherapy

MS29 SELECTION INTO SCREENING PROGRAMS: INTERPLAY OF RISK ALGORITHMS, GENETIC MARKERS AND BIOMARKERS
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MS29.02 DEFINING SCREENING FREQUENCY & DURATION USING RISK PREDICTION ALGORITHMS AND CT IMAGE FINDINGS

K. Ten Haaf

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Lung cancer screening guidelines generally recommend annual screening, similar to the design of the National Lung Screening Trial.[1, 2] However, results from European trials indicate that longer time-intervals between screenings can still yield a stage-shift.[3, 4] This has led to discussion on the feasibility of screening programs with longer time-intervals between screenings. Findings from trials has led to improvements in interpreting and managing nodules found on CT screens. These findings have been essential in improving nodule management protocols and reducing the number of false-positive results.[5, 6] But, the results of CT screens have also been shown to inform an individual's future lung cancer risk.[5, 7, 8] The NLST showed that individuals with a negative baseline screen had a lower risk of developing lung cancer compared to participants with a positive baseline screen.[8] Analyses of the ongoing Dutch-Belgian Lung Cancer Screening Trial (NELSON) indicate that the results of the first three screening rounds were indicative for detection of lung cancer in the fourth screening round.[7] In addition, NELSON showed that the characteristics of screen-detected nodules can be used to estimate the two-year risk for developing lung cancer.[5] Risk prediction models have been suggested for selecting individuals for lung cancer screening. Analyses of different risk prediction models have been shown to be superior compared to participant selection based on age and pack-years.[9] Combining these models with the information provided by CT screens may allow the personalization of an individual's screening regimen. This session will consider the evidence on the effects of varying time-intervals between screenings. In addition, it will discuss the potential for personalizing the screening regimen based on screening results and

other risk factors. **References** 1. Aberle DR, Adams AM, Berg CD, et al. Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening. *New England Journal of Medicine* 2011;365:395-409. 2. Moyer VA, on behalf of the USPSTF. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine* 2014;160:330-338. 3. Yousaf-Khan U, van der Aalst C, de Jong PA, et al. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. *Thorax* 2016. 4. Sverzellati N, Silva M, Calareso G, et al. Low-dose computed tomography for lung cancer screening: comparison of performance between annual and biennial screen. *Eur Radiol* 2016;26:3821-3829. 5. Horeweg N, van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. *The Lancet Oncology*;15:1332-1341. 6. Callister MEJ, Baldwin DR, Akram AR, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules: accredited by NICE. *Thorax* 2015;70:ii1. 7. Yousaf-Khan U, van der Aalst C, de Jong PA, et al. Risk stratification based on screening history: the NELSON lung cancer screening study. *Thorax* 2017. 8. Patz Jr EF, Greco E, Gatsonis C, et al. Lung cancer incidence and mortality in National Lung Screening Trial participants who underwent low-dose CT prevalence screening: a retrospective cohort analysis of a randomised, multicentre, diagnostic screening trial. *The Lancet Oncology* 2016;17:590-599. 9. ten Haaf K, Jeon J, Tammemägi MC, et al. Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. *PLOS Medicine* 2017;14:e1002277.

Keywords: Screening interval, lung cancer screening, Risk stratification

MS29.03 POLYGENIC RISK SCORE FOR RISK ASSESSMENT

R. Hung[1], Y. Brhane[2], N. Chatterjie[3], D. Christiani[4], N. Caporaso[5], M. Landi[5], L. Le Marchand[6], G. Liu[7], S. Lam[8], J. Field[9], P. Brennan[10], C. Amos[11]

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Background: Genome-wide association studies uncovered multiple lung cancer susceptibility genes, and consortium efforts greatly increased our ability to investigate the genetic architecture of histological subtypes. However the clinical utility of these genomic discoveries remains unclear. **Method:** We therefore constructed a risk prediction model with polygenic risk score (PRS) based on 18,316 lung cancer patients and 14,025 controls with European ancestry, via 10-fold cross-validation with elastic net penalized regression. Model calibration was assessed, and was validated with UK biobank data (N=336,911 unrelated participants with European ancestry). To evaluate its potential clinical utility, the PRS distribution was simulated in the National Lung Screening Trial (NLST, N=50,772 participants). Absolute risk was estimated based on age-specific lung cancer incidence and all-cause mortality as competing risk. Added value of PRS to the risk prediction model was assessed by Net Reclassification Index. **Results:** A PRS was constructed based on 128 independent lung cancer variants using regularized penalized regression. The lung cancer ORs for individuals at the bottom 5% and top 5% of the PRS distribution were 0.49 (95%CI=0.43-0.56, P=2.7e-26) and 2.23 (95%CI=1.93-2.58, P=2.3e-27) in the training set, and 0.46 (95%CI=0.34-0.64, P=2.50e-6) and 1.33 (95%CI=1.08-1.64, P=7.10e-3) in the testing set, versus those at 40 to 60% as the referent group. The OR per standard deviation of PRS was 1.43 (95%CI=1.39-1.47. P=7.8e-138) for overall lung cancer risk in the training set and 1.24 (95%CI=1.18-1.30, P=2.59-e19) in the testing set. When considering age as the time scale, PRS separated out the curve of 5-year absolute risk and cumulative risk. When simulating the PRS distribution in the NLST population, we estimated 47.4% of cases occurred in the top 20% of the individuals with highest lifetime cumulative risk. **Discussion:** Including well-established genomic information in the risk model can contribute to the risk stratification of the population.

Keywords: polygenic model, Risk prediction, Early Detection

MS29 SELECTION INTO SCREENING PROGRAMS: INTERPLAY OF RISK ALGORITHMS, GENETIC MARKERS AND BIOMARKERS
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MS29.04 LUCID EXHALED BREATH ANALYSIS

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The Breath Biopsy platform enables the collection and analysis of breath samples, in order to look for volatile organic compound (VOC) biomarkers of disease. The LuCID (lung cancer indicator detection) project is one of the first major deployments of the platform in a research setting, and is currently the largest breath-based trial in the world, recruiting up to 4000 patients. The aim of the LuCID project is to discover VOC biomarkers in breath for early detection of lung cancer, which could improve patient outcomes and save lives. In this talk, we will give an introduction to the LuCID program, then go on to describe the biology underlying the VOC biomarkers, before discussing the inherent challenges associated with breath sampling and analysis. We will conclude by giving an update on the progress of the LuCID trial to date. The LuCID Study LuCID is an international multi-centre prospective case-control cohort study (ClinicalTrials.gov ID NCT02612532) currently in progress, evaluating breath VOCs in patients with a clinical suspicion of lung cancer. A clinical suspicion is based on symptoms and/or suspicious finding on incidental imaging. Using tidal breathing, patients breathe into the ReCIVA Breath Sampler to collect breath samples on stable sorbent tubes for later analysis by Gas Chromatography-Mass Spectrometry and Field Asymmetric Ion Mobility Spectrometry (FAIMS, Owlstone Medical Ltd). One arm of the study is focused on early detection of lung cancer, with the aim of increasing the number of cases diagnosed at Stages 1 and 2, while an additional arm is currently being initiated looking at differences in breath profiles pre- and post-surgery which has the advantage of allowing the patient to act as their own control. The Biology of VOCs So why would we believe that VOC biomarkers for lung cancer could be discovered during LuCID? Cancer cells undergo profound changes of their metabolism in order to support high energetic demands of uncontrolled proliferation. Several oncogenic mutations have been shown to affect metabolism of cancer cells by converging to common metabolic pathways linked to cell cycle and anabolic growth. The Warburg effect is among well-established cancer metabolic hallmarks and entails the activation of aerobic glycolysis as main pathway for biosynthetic purposes, as opposed to normal cells that exploit mitochondrial metabolism for their energetic needs. These changes in cellular metabolism favor survival in an oxygen deprived environment and result in altered metabolic intermediates that function as the building blocks for new cells, both enabling the growth of rapidly dividing cancer cells, and also altering the profile of VOCs in breath. As these processes are fundamental to cancer cell survival, such altered metabolism occurs as one of the earliest stages of tumorigenesis, hence VOCs are excellent candidate biomarkers for early detection of cancer. Breath Sampling: Challenges and Solutions The potential of using breath sampling to identify markers of disease has long been recognised, but has to date seen almost no adoption into clinical practice, with only FeNO and H. pylori breath tests in widespread use. This has largely been due to practical considerations that have made large-scale clinical trials impractical to carry out. Most previous tests have involved collecting breath in bags, which - suffer from chemical losses over time - are vulnerable to contamination from ambient air if they are reused incorrectly - are difficult to transport and store. - only allow the collection of smaller volumes, limiting the sensitivity of the analysis. In this section, we will discuss how the ReCIVA breath sampler, a key part of the Breath Biopsy platform, allows these problems to be overcome, and we will present data, including VOC washout curves monitoring changes in VOC levels over time following ingestion of a peppermint capsule, that demonstrate how the ReCIVA performs in practice.

Image 1: The ReCIVA breath sampler Current Status of the LuCID trial In the concluding section, we will provide an update on the LuCID trial. We have identified some VOCs for which we have observed associations with certain disease processes in our biomarker discovery phase, and we are currently investigating what the mechanisms associating these VOCs with lung cancer initiation and progression might be.

Keywords: Biomarkers, Early Detection, breath analysis

MS29 SELECTION INTO SCREENING PROGRAMS: INTERPLAY OF RISK ALGORITHMS, GENETIC MARKERS AND BIOMARKERS
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MS29.05 EARLY DETECTION BIOMARKER DEVELOPMENT: IS SUCCESS ON THE HORIZON?

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There is a recognized need for biomarkers capable of assisting with the early diagnosis of lung cancer. We need tools to improve our ability to identify patients at risk of developing cancer; to identify patients with asymptomatic early stage lung cancer; to identify patients who are more likely to die of causes other than lung cancer; to help us characterize the nature of a patient's lung cancer; and to improve our management of lung nodules (expedite diagnosis, reduce the risks of evaluation, reduce the cost of evaluation). To have clinical utility a biomarker result must affect a clinical decision in a manner that leads to improved patient care. Both the benefit of clinical decisions influenced by true positive and negative results and the harms of clinical decisions influenced by false positive and negative results must be considered. In the screening setting a biomarker should lead to fewer lung cancer deaths without substantially increasing harms or expense, or a similar number of lung cancer deaths with fewer harms or less expense. When used to characterize a lung nodule a biomarker should lead to earlier diagnosis of malignant nodules without substantially increasing the number of procedures performed on patients with benign nodules or fewer procedures for patients with benign nodules without substantially delaying the diagnosis of cancer in patients with malignant nodules.(1) Biomarker development moves through a series of phases. In the discovery phase, a molecule or pattern of molecules are found to be associated with the presence or absence of the condition in question. If the association appears to be strong enough the biomarker may be taken to validation stages. Technical validation refers to the assessment of the accuracy (precision, reproducibility) of the assay that will measure the biomarker. Clinical validation refers to determining the accuracy (sensitivity, specificity, AUC, NRI) of a biomarker, with a fixed threshold for result interpretation, when applied to the intended use population. Through each phase of development standard operating procedures that include pre-analytical, analytical, and post-analytical processes, must be in place. Even accurate biomarkers may not be clinically useful. Prior to clinical use, it is important that the validated biomarker move through the clinical utility phase of assessment. To determine if the accuracy of a validated biomarker is high enough to invest in a clinical utility study one must consider the potential impact of true and false positive and negative results. In a screening context true positive results may lead to individuals with lung cancer being identified at curable stages while false positive results may lead to individuals without lung cancer (or at low risk of developing lung cancer) being enrolled in screening programs where they will be exposed to the associated harms of screening. True negative results could lead to individuals without lung cancer (or at low risk of developing lung cancer) avoiding the harms associated with low-dose CT screening while false negative results could prevent individuals with (or who will develop) lung cancer from being enrolled in a low-dose CT based lung cancer screening program, and thus not have an opportunity to benefit. A judgment about an acceptable tradeoff of benefit and harm from using the biomarker will have to be made. The biomarker should be more accurate at identifying patients with (or who will develop) potentially curable lung cancer than current eligibility criteria and available clinical risk prediction calculators, alone or in combination. What is considered an acceptable tradeoff in a screening context is likely to vary based on whether the biomarker is being applied to a cohort already eligible for LDCT screening or to a cohort that is currently not eligible for LDCT screening. In the former it is most important that patients with lung cancer are not excluded from being screened (rule out test) while in the latter it may be more important not to screen individuals without lung cancer (rule in test). Calculations exist that use currently accepted benefit:harm ratios when available (e.g. the currently eligible cohort for screening had an incidence of lung cancer of 0.83% in the NLST trial) to help determine if the validated accuracy supports pursuit of clinical utility studies.(2) Biomarker-stratified, enrichment, and biomarker-strategy study designs are acceptable approaches to determine clinical utility. Ongoing research trials are moving potential biomarkers through the phases of development. A handful of biomarkers have completed discovery level work and are working on, or have published or presented clinical validation study results. Others continue discovery level work. Few have entered formal clinical utility testing. Oncimmune's panel of autodantibodies, the EarlyCDT-Lung test, is being assessed as part of a 12,000 person randomized controlled screening study (the ECLS study). An exciting amount of high quality discovery and clinical validation work is ongoing. Some companies are in the process of planning true clinical utility studies for early lung cancer detection (Table).

Company	Biomarker	Target	Completed	Ongoing	Plans
ANCON	VOC – NBT	N/A	N/A	Discovery	N/A
bioAffinity	Sputum flow cytometry	N/A	N/A	Discovery	N/A
Exact Sciences	DNA methylation	Nodule	N/A	Discovery	Clinical Validation
Genesys	Antigens, Auto-antibody	Screening	Clinical Validation	N/A	N/A
GRAIL	cfDNA assays	Screening	N/A	Discovery	Clinical Validation
InDi	2 proteins + clinical	Nodule	Clinical Validation	N/A	Clinical Utility
MagArray	Antigens and Auto-antibodies	Nodule	Discovery	Clinical Validation	Clinical Utility
Nucleix	DNA methylation	Screening	Discovery	N/A	Clinical Validation
Oncimmune	Autoantibodies	Nodule, Screening	Clinical Validation	ECLS study	Clinical Utility
Onco-cyte	mRNA + size	Nodule	Discovery	Clinical Validation	Clinical Utility
Owlstone	VOC - FAIMS	N/A	N/A	Discovery	N/A
Synergenz	SNPs + clinical	Screening	Clinical Validation	N/A	N/A
Veracyte	Airway genome signature	Nodule	Clinical Validation	Registry study	Discovery

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MS30 MODERN DAY RT IN LA NSCLC: WHERE IS THE EVIDENCE?
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MS30.01 OVERVIEW OF RT TECHNOLOGY IN LA NSCLC (IMRT, VMAT, IGRT)

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External bean radiotherapy remains the key treatment modality for the radical treatment of inoperable locally advanced non-small cell lung cancer (LA-NSCLC). Outcomes remain poor with a median overall survival of approximately 25–29 months in those patients who have received combined modality therapy [1,2]. In radiotherapy treatment the aim of radical treatment is to achieve an optimal therapeutic benefit with the highest probability of tumour control but with minimal associated toxicity. The Radiation Therapy Oncology Group (RTOG) randomised phase III 0617 study comparing standard dose (60 Gy) to dose escalated radiotherapy (74 Gy) given with concomitant systemic therapy has highlighted in the modern era the importance of the dose received

by normal tissues and toxicity in relation to overall survival. In this study the maximum grade of oesophageal toxicity and the proportion of heart receiving radiation dose were both factors associated with poorer survival [2]. The last two decades have seen many technical advances in radiotherapy delivery techniques. For treatment planning, the objective is to attain conformity of the planned dose to the target volume within minimal dose to adjacent normal tissues. There have been significant advances in radiotherapy treatment planning with improved accuracy of modelling how radiotherapy treatment beams interact with inhomogeneous structures such as the lung. This coupled with improved computing power, permits the accurate and fast generation of intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) plans. Both IMRT and VMAT delivery improves of the sparing of normal tissues but may increase low dose radiotherapy exposures to the lung. The impact of this low dose exposure remains uncertain. There have been important advances in assessment and management of target and organ motion within the thorax and use of techniques to individualise treatment based on the motion to improve the treatment accuracy [3,4]. For radiotherapy delivery over the course of treatment, the objective is consistency between the planned and delivered dose distributions. With recent widespread availability of cone-beam computerised tomography (CBCT) it is now possible to use these images to assess of the shape and position of the radiotherapy target in relation to the planned dose delivery prior to treatment, image guided radiotherapy (IGRT), to improve accuracy of treatment delivery and where necessary to use this information to adapt treatment based, image guided adaptive radiotherapy (IGART) [5]. It is hoped that emerging technologies such MR-Linac, which combines a magnetic reasonance imaging unit with linear accelerator, will further develop IGRT and IGART delivery. Establishing the clinical benefit and cost-effectiveness of these technological advances is challenging. The improved median survival in the standard arm of recent randomised trials [1,2] compared to historical trials suggests that technical advances may improve survival outcomes. Additionally, there are retrospective data from a large series that suggest IMRT in particular may be associated with improved outcome in stage III NSCLC with T3 and T4 tumours [6] and a recent secondary analysis of the RTOG 0617 trial suggests use of IMRT compared to 3D conformal techniques is associated with lower severe lung toxicity and lower cardiac doses [7]. Finally, it is hoped that the use of these advanced techniques will permit radiotherapy treatment intensification either through alter radiotherapy dose delivery or the combination with systemic therapy.

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Keywords: IGRT, IMRT, Radiotherapy

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MS30.04 PERSPECTIVE

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Radiation therapy (RT) in locally advanced non-small cell lung cancer (LA-NSCLC) has not changed in its essence over many decades. The refinements in "standard-of-care" RT followed the general advancements applicable to many other malignancies, such as introduction of IMRT (including VMAT) and IGRT. Tumor motion appears more relevant in lung tumors than in other disease sites, and lung-tumor interface allows for a measurable and intuitively observable movement, therefore enabling motion management in the lung to be more advanced, such as 4D CT for planning and tumor tracking (CyberKnife) or gating in daily practice. Nevertheless, the median survival time (MST) for good performance unresectable Stage II/III patients with NSCLC, treated with concurrent chemoradiotherapy (chemo-RT) has improved significantly over last quarter century, from MST of 17.1 mo (RTOG 9410) to MST of 28.7 mo (RTOG 0617). Since the agents used in concurrent chemotherapy are not significantly different, other causes, mostly widespread use of PET scans for staging, as well as improved RT techniques, likely play a role. Use of CT simulation is associated with improved MST, even when adjusted for other variables, such as chemotherapy use, comorbidities or urban location. Volumetric (rather than 2D) dose prescription; use of lower energy photons and heterogeneity correction; accounting for tumor motion with a 4D CT simulation and IGRT; better understanding of normal tissue tolerance (lung V20) and of the need to limit RT course breaks, all add incremental benefits for a more favorable outcome. In addition, factors such as RT center's experience and volume of treated patients, as well as any protocol deviations in clinical trials, have been found to have a major impact in clinical practice, raising the possibility that strict adherence to RT planning guidelines might benefit all cancer patients treated with RT. Those factors have not yet been accounted for as eligibility/stratification factors in studies. Some much touted newer technologies, as particle RT (protons) have not so far demonstrated a verifiable superiority over photons. The Phase II randomized MDACC trial of photon vs. proton-based chemoradiotherapy for patients with Stage III or oligometastatic NSCLC did not show a difference in radiation pneumonitis rates between the arms and no improvement in local control in the proton arm. However, a steep learning curve in using proton RT was discovered, with lower pneumonitis rates in those patients in the proton group who were treated in the latter half of the study vs. those treated in its early phase. The ongoing NRG Oncology/RTOG 1308 Phase III randomized trial of photon vs. proton chemo-RT (70 Gy, but not lower than 60 Gy) has had a slow accrual, partially due to the paucity of participating centers, since proton technology is not widespread yet; also, a high percentage of patients not being able to enroll due to medical insurance coverage denial for protons, as well as possible perceptions of the superiority of protons. That study's design has been modified recently to allow for a faster study's completion. The original primary endpoint was overall survival, in contrast to the MDACC trial, where pneumonitis and local failure rate were co-endpoints. In order to complete the RTOG 1308 trial sooner by lowering its target accrual, the current primary hypothesis is that the MST in the proton arm is non-inferior to the photon arm (i.e. 28 mo), and major cardiac toxicity and grade 4 or higher lymphopenia is better in the proton vs. photon arm. Additionally, the Quality of Life hypothesis is that, compared with patients receiving photon therapy, patients on the proton arm will have less severe shortness of breath 6 months after the end of concurrent chemor-RT (representing late adverse response to therapy), and that the differences in symptom ratings (based on MDASI shortness of breath item) between arms will be clinically meaningful. The recent availability of Magnetic Resonance (MR)-Guided RT may open a new era in lung cancer RT, allowing for the real-time intrafractional tumor tracking and "on the fly" adaptive RT, both likely to allow smaller tumor target volumes and a rigorous evaluation of doses delivered to the normal structures, therefore lowering toxicity and potentially opening the door to reassessment of RT dose intensification. Finally, with the explosion of evidence-based applications of immunotherapy in metastatic lung cancer and the demonstration of an impressive survival prolongation in the Phase III randomized PACIFIC trial with the addition of maintenance durvalumab following chemo-RT, the role of chemotherapy may be eventually challenged and reevaluated in Stage III NSCLC, to be possibly replaced by concurrent immunotherapy or a chemo-immunotherapy combination.

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Keywords: radiation therapy, lung cancer, immunotherapy

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MS30.05 NUTRITIONAL MANAGEMENT DURING RADICAL RADIOTHERAPY

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Curative intent fractionated external beam radiotherapy (RT) with or without chemotherapy is used to treat locally advanced non-small cell cancer (NSCLC) and common side effects include anorexia, oesophagitis and fatigue, all of which can all impact on nutritional status. Previous

research has shown that up to one third of lung cancer patients treated with RT experience clinically significant weight loss[1] while one third of lung cancer patients present with malnutrition prior to even commencing RT [2]. The negative impact of weight loss and malnutrition on patient and clinical outcomes is well established across all modes of cancer treatment including chemoradiotherpy[3]. There is limited evidence available relating to effective nutritional support strategies to prevent or treat weight loss and malnutrition in lung cancer[4]. There may be a role for enteral feeding where severe oesophagitis occurs in order to support patients through radical radiotherapy and its recovery[1]. The nutrition intervention demonstrated to be most effective in other tumours undergoing radiotherapy treatment is intensive individualised dietary counselling[5] and the presence of dedicated dietetic services to head and neck and oesophageal cancer patients is well established in the U.K with dietitians identified as core members of the multi-disciplinary team. This session will explore the impact of a worsening nutritional status on clinical and patient outcomes and discuss the nutritional interventions that may be of benefit. It will also consider the role of a dedicated lung cancer dietitian and the impact this can have on patients with lung cancer. References: 1. Kiss, N., Isenring, E., Gough, K. et al (2014) The prevalence of weight loss during (chemo)radiotherapy treatment for lung cancer associated patient- and treatment-related factors. Clin Nutr, 33: 1074-1080 2. Unsal, D., Bulent, M., Akmansu, M. et al (2006) Evaluation of nutritional status in cancer patients receiving radiotherapy. Am J Clin Oncol 29: 183-188 3. Sanders, K., Hendricks, L., Troost. et al. (2016) Early weight loss during chemoradiotherapy has a detrimental impact on outcome in NSCLC. J Thor Oncol, 11: 873-879 4. Kiss, N., Krishnasamy, M. and Iserning, E. (2013) The effects of nutrition intervention in lung cancer patients undergoing chemotherapy and/or radiotherapy: a systematic review. Nutr Cancer, 66: 47-56 5. Lee, J., Leong L. and Lim, S. (2016) Nutrition intervention approaches to reduce malnutrition in oncology patients: a systematic review. Support Care Cancer, 24: 469-480

Keywords: radical radiotherapy, NSCLC, nutrition

MS31 CLINICAL SCIENCE IN MESOTHELIOMA
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MS31.02 CLINICAL IMPLEMENTATION OF BAP1 INHIBITORS

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Over the last few years BRCA associated protein 1 (BAP1) has attracted attention in the development of cancer[1-2]. BAP1 is one of the molecular targets that has been identified as a novel target in this disease. The function of BAP1 is mainly regulatory, including its function as deubiquitinating enzyme (DUB) of H2A. Through its deubiquitinase activity and the effects on transcription, BAP1 functions as a tumor suppressor gene. It regulates transcription, cell cycle control, DNA damage repair and cellular differentiation [1-4]. Patients with a BAP1 germline mutation often presents with skin disorders including skin tumors and uveal melanomas and are often diagnosed at an early age. BAP1 germline mutation in patients with mesothelioma was first reported in 2011 [5]. In these cases, prognosis seems to be better with a 5-year survival rate of 47%, as compared to 6,7% for patients who did not have the mutation [6]. Although germline mutations are rare in mesothelioma [7], somatic BAP1 aberrations are more common in mesothelioma tumors. Studies showed that 47-67% of the mesothelioma tumors contain a BAP1 genetic aberration. BAP1 somatic mutations are more frequent in the epithelioid subtype than in the sarcomatoid subtype. Besides single point mutations in the BAP1 gene, copy number loss, rearrangements and multiple alterations have been reported. The somatic BAP1 mutation can easily be identified with immunohistochemistry. **BAP1 as a drug target in mesothelioma** The regulation of histones by BAP1 suggests that an interaction with *histone deacetylase (HDAC) inhibitors* could be beneficial. In mesothelioma, the effect of HDAC inhibitors on H2A is not known, but BAP1 knockdown in mesothelioma cell lines increases the sensitivity for HDAC inhibitors leading to cell death, a process known as synthetic lethality. In the VANTAGE 014 study, a phase III trial including 661 patients, the HDAC inhibitor vorinostat did not improve overall survival in an unselected group of patients compared to placebo [8]. *Enhancer of zeste homolog 2* (EZH2) is upregulated in mesothelioma and preclinical models have identified a possible association between BAP1 loss and EZH2 upregulation. Specific EZH2 inhibitors decreased cell proliferation, reduced invasion and reduced clonogenicity in mesothelioma cell lines and tumor bearing mice. Importantly, BAP1 mutant mice were more responsive to the EZH2 treatment compared to wild type mice. In different tumor types, phase I studies with EZH2 inhibitors showed promising results [9]. Currently a study in mesothelioma patients with the EZH2 inhibitor tazemetostat is ongoing (NCT02860286). Another interaction partner of BAP1 is *host cell factor 1* (HCF1). This protein has a role in cell cycle progression by activating transcription of promotors bound by the E2F (transcription) family. BAP1 deubiquitinates HCF1 and recently multiple groups showed that BAP1 mutation results in increased HCF1 ubiquitination, impairing E2F activation. Decreased activation of E2F causes problems in cell cycle progression and results in the inhibition of cell growth. Although there are no drugs yet available to inhibit E2F, these interaction partners may provide options for new therapeutic interventions. *Synthetic lethality.* Due to its regulatory function in DNA repair damage, it is expected that in BAP1 mutated cases the homologous recombination (HR) DNA repair system is impaired. The use of PARP1 inhibitors could therefore be promising as is shown in ovarian and mammary carcinoma. Preclinical studies of nirapanib and olaparib in mesothelioma cell lines proved to inhibit the cell growth, but this effect was independent of the BAP1 mutation status [10]. Therefore it is expected that other pathways are more important in this approach. **Conclusions.** For the treatment of tumors with BAP1 protein loss, it is important to identify therapeutic agents that reverse the phenotypic effects. Multiple interaction partners and proteins under influence of BAP1 are reported and (pre)clinical data of new inhibitors targeting these partners is promising. Further research on BAP1 action is required before we define an optimal treatment plan. Due to the many interaction partners and different functions of BAP1 the future we will probably end up with a combination of agents to reverse the phenotypic effect of BAP1 protein loss. **Reference** 1. Wang, A., et al., *Gene of the month: BAP1.* J Clin Pathol, 2016. **69**(9): p. 750-3. 2. Bononi, A., et al., *Latest developments in our understanding of the pathogenesis of mesothelioma and the design of targeted therapies.* Expert Rev Respir Med, 2015. **9**(5): p. 633-54. 3. 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Keywords: BAP1, Mesothelioma, EZH2

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MS31.03 TARGETING THE HIPPO PATHWAY

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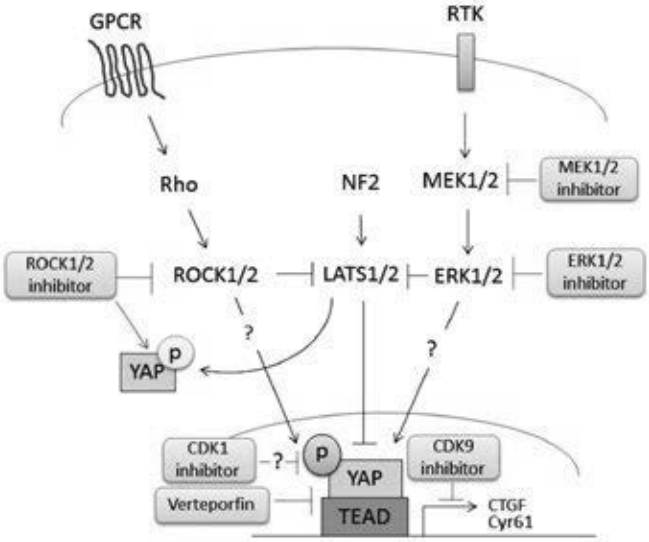
The prognosis for malignant pleural mesothelioma (MPM) remains poor and many anticipated advances in MPM treatment have been disappointing. One reason for the failure of conventional cytotoxic drugs is that they do not address the cancer stem cell population or the stem cell pathways that drive tumor resistance and resurgence following treatment. Cancer stem cells are defined by their properties of self-renewal, pluripotency, a high proliferative capacity and the ability to resist standard chemotherapy and radiation. Among the stem cell pathways, Hippo has proven to be critical to driving growth in MPM with mutations along this pathway implicated in the majority of MPM tumors. The Hippo pathway is a highly conserved regulator of organ size by regulating contact inhibition and of stem cell proliferation and maintenance.(1) The largest and most comprehensive genomic analysis to date of transcriptomes, whole exomes and targeted exomes from 216 MPM samples found Hippo pathway signaling to be the number one most significantly mutated pathway in mesothelioma with a Q-value of 1.70E-17, driven by mutations, copy number variations and fusions in NF2, LATS1, LATS2 and MST1.(2) One of the most frequently mutated genes in MPM is Neurofibromatosis type 2 (NF2) tumor suppressor, located at chromosome 22q12, and is detected in 40% to 50% of MPM tumors.(3) Large tumor suppressor homolog 2 (LAST2) gene, which is located at chromosome 13q12, is another frequently inactivated gene that is detected in 13% of MPM tumors. (3, 4) Inactivation of NF2 and LATS2 by deletion and/or mutation often contribute to dysregulation of Hippo pathway.(5) In addition to LATS2, its closest gene family member LATS1 another Hippo pathway gene, has also recently been identified to be dysregulated in MPM, though less commonly than LATS2. LATS1 is located on chromosome 6 and changes in copy number variation and

fusions to Presenilin 1 (PSEN1) on chromosome 14 have been observed in MPM.(2, 3) Mammalian sterile-20 like kinase 1 (MST1) is an important upstream kinase in the Hippo pathway that has also been found to be dysregulated in MPM.(2) Given the high frequency of mutations and dysregulation in the Hippo pathway, it is a promising potential area of drug development. One specific target along the Hippo pathway is blocking Yes-associated protein (YAP) activity. In normal cells, Merlin, a protein encoded by NF2, and LATS2 contribute to the phosphorylation of the transcription factor YAP at S127,(6) resulting in YAP ubiquitination and activation of Hippo pathway to control cell proliferation. In MPM tumor cells, inactivation of NF2 and LATS2 prevent the phosphorylation of YAP at S127, which results in YAP relocation from the cytosol to nucleus where it interacts with TEA domain transcription factors (TEAD). In addition, constitutively activation of YAP has been identified in over 70% of primary MPM tumors, (3, 5, 7) and YAP activation leads to Hippo signaling attenuation and transcription of downstream target genes, such as connective tissue growth factor (CTGF) and Cyr61.(8) Low Merlin expression (NF2), results in YAP1 activation, and has been shown to be associated with worse clinical outcomes with shorter times to recurrence and shorter overall survival times in patients with MPM.(9) Blocking YAP activity, either via upstream inhibition of one of the several pathways that regulate YAP and Hippo or via direct YAP/TEAD inhibition is an area of active interest.(10) Several novel small molecule YAP inhibitors are in preclinical development with promising results and may enter clinical trials in the near future. FIGURE: Hippo Pathway Potential Drug Targets



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MS31.04 CAR-T AND ADC'S IN MPM

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Novel immunotherapies for malignant pleural mesothelioma (MPM) include Antibody-drug conjugates (ADCs) and Chimeric antigen receptor (CAR) T cells, both of which are in early-phase clinical trials with promising results. CAR T cells are patient T cells that are transduced with genetically engineered synthetic receptors to target a cancer cell surface antigen. The remarkable clinical response rates achieved by adoptive transfer of T cells that target CD19 in patients with leukemia and lymphoma have led to a growing number of clinical trials exploring CAR T-cell therapy for solid tumors including in MPM. Herein, I will review the evolution of ADCs and adoptive T-cell therapy; highlight advances in CAR T-cell therapy for MPM; and summarize the antigen targets being investigated in clinical trials. I will further discuss the barriers to successfully translating ADCs and CAR T-cell therapy for solid tumors and present strategies that have been investigated to overcome these hurdles.

Keywords: Chimeric antigen receptor (CAR) T-cell therapy, Antibody-drug conjugate (ADC), Antigen-targeted immunotherapy

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MS31.05 VACCINATION AND ANTIBODY-BASED THERAPY IN MESOTHELIOMA

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The concept of antibody based therapy hints on two concepts, on the one hand precluding the function of the ligand it binds to, which is for instance the case in VEGF targeting antibodies. And on the other hand the induction of antibody dependent cellular toxicity (ADCC) which may be induced by these antibodies. The latter is caused by activation of the immune system after an antibody binds to its ligand. Here I will focus on the role of antibodies targeting the immune checkpoints. Immunotherapy is now considered a standard treatment in many malignancies. Also in mesothelioma, different antibodies are now being explored [Yap 2017]. The most clinically used type of immunotherapy in oncology are checkpoint inhibitors, mostly PD-(l)1 and CTLA-4 directed antibodies. Concerning the latter, a recently published randomised trial failed to show an benefit of the anti-CTLA-4 antibody tremilimumab, compared to placebo in second and third line treatment in mesothelioma [Maio 2017]. Small and single arm studies on PD-(l)1 have been presented and did show clinical meaningful responses in patients. However this was only present in a minority of patients [Lievense 2017]. The role of ADCC in the functioning of the antibodies is not well established nor investigated, but for instance a regulatory T-cell depletion due to CTLA-4 antibodies has been described. The lack of benefit in the majority of patients is ascribed to the absence of a tumor directed T-cell response present in the majority of mesothelioma patients [Aerts 2013, Yap 2017]. This lack of tumor directed T-cells is related to the immunosuppressive environment caused by mesothelioma. One way of increasing the tumor directed T-cell responses is via vaccination. However in thoracic malignancies the effects of peptide vaccinations were found to be rather limited again due to the immunosuppressive environment created by the tumor. Cellular vaccinations were found to be more effective in this setting [Dammeijer 2016]. In mesothelioma studies on cellular vaccination with dendritic cell vaccination have indeed shown that an increase in tumor directed T-cells can be achieved with clinically relevant responses [Le 2012, Peikert 2016, Aerts 2018]. This concept is now taken forward in a large randomised trial comparing dendritic cell vaccination with best supportive care as maintenance treatment after chemotherapy in patients with mesothelioma. In conclusion antibody based therapy and vaccination hold promise in mesothelioma, and given the dismal prognosis of these patients these options should be investigated and explored further.

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Keywords: Mesothelioma, vaccination, dendritic cell

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MS32.01 GENETIC MOUSE MODELS (GEMMS)

G. Mollaoglu[1], M. Chalishazar[1], F. Huang[2], M. Guthrie[1], S. Bohm[3], J. Breagelmann[3], T. Sen[4], L. Byers[4], J. Johnson[2], R. Wechsler-Reya[5], A. Gazdar[2], R. Deberardinis[2], M. Sos[3], T. Oliver[1]

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Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine lung tumor that has historically been treated as a single disease. Loss of the tumor suppressors RB1 and TP53, and amplifications in*MYC*family members, are frequent events in SCLC. We show that Myc expression cooperates with*Rb1* and*Trp53*loss in the mouse lung to promote aggressive, highly metastatic tumors, that are initially sensitive to chemotherapy followed by relapse, similar to human SCLC. Importantly, MYC drives a neuroendocrine-low ''variant'' subset of SCLC with low ASCL1 and high NEUROD1 expression corresponding to transcriptional profiles of human SCLC. Targeted drug screening reveals that SCLC with high MYC expression is vulnerable to Aurora kinase inhibition, which, combined with chemotherapy, strongly suppresses tumor progression and increases survival (Mollaoglu et al, *Cancer Cell*, 2017; Cardnell et al, *Oncotarget*, 2017). These findings were recently recapitulated in clinical trials where patients with relapsed SCLC exhibited significantly longer survival when treated with an Aurora kinase inhibitor specifically if tumors were high for MYC. More recently, our work and others suggests that MYC-high SCLC is also vulnerable to CHK1 inhibition. These data identify molecular features for patient stratification of SCLC and uncover a potential targeted treatment approach for MYC-driven SCLC. More recently, we have performed unbiased metabolic profiling of MYC-driven SCLC cell lines and murine tumors compared to MYCL and MYCN-driven samples. We find that MYC-driven SCLC is metabolically distinct in vitro and in vivo.Our findings reveal that guanosine nucleotides and biosynthetic enzyme Inosine Monophosphate Dehydrogenase-1 and -2 (IMPDH1 and IMPDH2) are elevated in MYC-high/ASCL1-low tumors and cell lines. IMPDH inhibition using Mizoribine selectively impeded the growth of MYC-high/ASCL1-low xenografts, and combined with chemotherapy to improve survival in MYC-driven genetically engineered mouse models (Huang et al, *Cell Metabolism*, In Press). These data strongly suggest that SCLC is composed of unique molecular subtypes with specific vulnerabilities to targeted therapy that should be considered in basic studies and clinical trial design. References: Cardnell RJ, Li L, Sen T, Bara R, Tong P, Fujimoto J, Ireland AS, Guthrie MR, Bheddah S, Banerjee U, Kalu NN, Fan YH, Dylla SJ, Johnson FM, Wistuba II, **Oliver TG**, Heymach JV, Glisson BS, Wang J, Byers LA (2017). Protein expression of TTF1 and cMYC define distinct molecular subgroups of small cell lung cancer with unique vulnerabilities to aurora kinase inhibition, DLL3 targeting, and other targeted therapies. *Oncotarget*, *8*(43), 73419-73432. Huang F, Ni M, Chalishazar MD, Huffman KE, Kim J, Cai L, Shi X, Zacharias LG, Cai F, Gu W, Ireland AS, Gazdar AF, **Oliver TG**, Minna JD, Hu Z, and DeBerardinis RJ (In Press). Inosine monophosphate dehydrogenase dependence in a subset of small cell lung cancers. *Cell Metab*, *2018*. Mollaoglu G, Guthrie MR, Bohm S, Bragelmann J, Can I, Ballieu PM, Marx A, George J, Heinen C, Chalishazar MD, Cheng H, Ireland AS, Denning KE, Mukhopadhyay A, Vahrenkamp JM, Berrett KC, Mosbruger TL, Wang J, Kohan JL, Salama ME, Witt BL, Peifer M, Thomas RK, Gertz J, Johnson JE, Gazdar AF, Wechsler-Reya RJ, Sos ML, **Oliver TG** (2017). MYC Drives Progression of Small Cell Lung Cancer to a Variant Neuroendocrine Subtype with Vulnerability to Aurora Kinase Inhibition. *Cancer Cell*, *31*(2), 270-285.

Keywords: MYC, Aurora kinase, small cell lung cancer

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MS32.02 PATIENT[1] DERIVED MODELS (PDX & CTC-DERIVED)

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Patient-derived xenograft (PDX) models are a powerful preclinical tool for studying small cell lung cancer (SCLC) biology and therapeutic vulnerabilities. SCLC PDX models can be generated from biopsies or circulating tumor cells (CTCs), though these approaches can be limited by scarcity of tissue and low efficiency of tumor growth. Applying an established clinical-translational pipeline for tissue collection and an automated microfluidic platform for CTC-enrichment, we have generated over 40 PDX models. In a 24-month period, we initiated 17 biopsy-derived PDXs and 17 CTC-derived PDXs, at 89% and 38% efficiency, respectively (Drapkin et al., Cancer Discovery 2018). Whole exome sequencing showed that somatic alterations are stably maintained between patient tumors and PDXs. Early-passage PDXs maintain the genomic and transcriptional profiles of the founder PDX. We have standardized quantitative measurements of efficacy of *in vivo* treatments, utilizing both depth of tumor shrinkage (response) and time to tumor volume doubling (time to progression). With these approaches, we have assessed responses to both standard of care and experimental therapies across a large panel of mice. We find that sensitivity to etoposide and platinum (EP) corresponds with the treatment history of patients, and that resistance to EP corresponded to increased expression of a *MYC* gene signature. Similarly, responses of the PDXs to an experimental combination, olaparib and temozolomide, mirrors the responses seen in patients treated on a clinical trial (Farago et al., ASCO 2018). Biomarker analysis in this panel reveals that basal PARylation is a highly sensitive and specific predictor of response to olaparib and temozolomide. Collectively, this experience highlights the utility of PDX models in SCLC for biomarker discovery and assessment of novel therapeutic strategies. References: 1. Drapkin BJ, George J, Christensen CL, Mino-Kenudson M, Dries R, Sundaresan T, Phat S, Myers DT, Zong J, Igo P, Hazar-Rethinam MH, Licausi JA, Gomez-Caraballo M, Kem M, Jani KN, Azimi R, Abedpour N, Menon R, Lakis S, Heist RS, Buttner R, Haas S, Sequist LV, Shaw AT, Wong K-K, Hata A, Toner M, Maheswaran S, Haber DA, Peifer M, Dyson N, Thomas RK, Farago AF. Genomic and functional fidelity of small cell lung cancer patient-derived xenografts. Cancer Discovery 2018 May 8(5):600-615. PMID: 29483136 2. **Farago AF**, Drapkin BJ, Charles A, Yeap B, Heist RS, Azzoli CG, Jackman D, Marcoux P, Barbie D, Myers DT, Phat S, Zhong J, Grinnell JB, Sequist LV, Mino-Kenudson M, Maheswaran S, Haber D, Hata A, Dyson N, Shaw AT. Safety and efficacy of combination olaparib (O) and temozolomide (T) in small cell lung cancer (SCLC). American Society of Clinical Oncology Annual Meeting, June 1-5 2018. Poster presentation

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MS32.03 LIQUID BIOPSIES FOR DRUG DEVELOPMENT IN SCLC

C. Dive[1], G. Brady[1], D. Rothwell[1], K. Frese[1], K. Simpson[1], J. Pierce[1], E. Kilgour[1], F. Blackhall[2]

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The progress in recent years in understanding SCLC biology and phenotypic heterogeneity has led to a number of rational drug development opportunities being evaluated in early clinical trials. Historically clinical trials in SCLC have not included predictive or pharmacodynamics biomarkers because of a lack of understanding of what to measure and the difficulty of obtaining tumour specimens in which to evaluate them, particularly longitudinally. SCLC patients have prevalent circulating tumour cells (CTCs) that express EpCAM and are thus detectable using the CellSearch (CS) platform. CS CTC number is prognostic at baseline, has a wide dynamic range making it useful as a pharmacodynamic biomarker, and also acts as a surrogate of tumour response to chemotherapy (1). The prevalence of CS CTCs also allows CTC-based predictive biomarker assay development. In this regard we showed that a single CTC-based copy number alteration (CNA) signature can predict pre-treatment whether a SCLC patient will be chemorefractory (progress within 90 days of chemotherapy treatment) or initially chemosensitive (2). We have also recently shown using global

CNA metrics and a panel of 110 SCLC associated genes that ctDNA was detectable in >90% of a cohort of both limited and extensive stage SCLC patients making it a highly suitable tool for patient monitoring. In 2014 we pioneered the development of CTC derived patient explant (CDX) models in immune compromised mice (3) which faithfully recapitulate the donor patients' tumour morphology and genomic landscape, and mimic their response to cisplatin-based chemotherapy. The models also display patient-relevant metastatic tissue tropism and cell subpopulations are competent for vasculogenic mimicry (4). We are currently interrogating phenotypic heterogeneity in our panel of 45 CDX models and using them to test novel drug combinations including DNA damage repair and cell cycle checkpoint inhibitors (5). CDX cells can be cultured *ex vivo* for short periods, genetically manipulated and re-implanted *in vivo* for hypothesis testing studies (6) and most recently we have witnessed progress in culturing CTCs directly from patients' blood samples. These *ex vivo* approaches allow therapy screening (CDX cultures) or real time viability assays tailored to small cell numbers (CTC cultures) that ultimately may be able to inform patient treatment. All of the aforementioned applications of liquid biopsies in SCLC will be discussed and reviewed. References 1. Hou JM, Krebs MG, Lancashire L, Sloane R, Backen A, Swain RK, et al. Clinical significance and molecular characteristics of circulating tumor cells and circulating tumor microemboli in patients with small-cell lung cancer. J Clin Oncol. 2012;30(5):525-32. 2. Carter L, Rothwell DG, Mesquita B, Smowton C, Leong HS, Fernandez-Gutierrez F, et al. Molecular analysis of circulating tumor cells identifies distinct copy-number profiles in patients with chemosensitive and chemorefractory small-cell lung cancer. Nat Med. 2017;23(1):114-9. 3. Hodgkinson CL, Morrow CJ, Li Y, Metcalf RL, Rothwell DG, Trapani F, et al. Tumorigenicity and genetic profiling of circulating tumor cells in small-cell lung cancer. Nat Med. 2014;20(8):897-903. 4. Williamson SC, Metcalf RL, Trapani F, Mohan S, Antonello J, Abbott B, et al. Vasculogenic mimicry in small cell lung cancer. Nat Commun. 2016;7:13322. 5. Lallo A, Frese KK, Morrow CJ, Sloane R, Gulati S, Schenk MW, et al. The combination of the PARP inhibitor olaparib and the Wee1 inhibitor AZD1775 as a new therapeutic option for small cell lung cancer Clin Cancer Res. in press. 6. Lallo A, Warpman Berglund U, Frese KK, Potter DS, Helleday T, Dive C. Ex vivo culture of circulating tumour cell derived explants to facilitate rapid therapy testing in small cell lung cancer. European Association for Cancer Research Annual Conference; Manchester, U.K.2016.

Keywords: SCLC, CDX, liquid biopsies

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MS32.04 MOLECULAR PHENOTYPES OF SCLC

A. Gazdar
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Heterogeneity of neuroendocrine (NE) differentiation in small cell lung cancer (SCLC) determines very different molecular phenotypes Background and Purpose: SCLC is usually regarded as a homogenous tumor treated in a standard fashion. We have established and validated a 50 gene expression quantitative scoring system for NE lung tumors, consisting of both positive and negative scores [1]. While almost all carcinoid tumors have positive scores, SCLC and large cell neuroendocrine carcinomas have positive and negative subpopulations. Methodology: We utilized the NE gene expression score to demonstrate intertumor heterogeneity of gene expression patterns and their relationship to signaling pathways and to immune and inflammatory response. We used cluster analysis to divide the SCLC samples into high and low NE subtypes. We studied two public SCLC tumor data sets (n = 140) as well as 70 cell lines established by us and a pair of high/low sublines established from a single SCLC cell line. Results: The NE score cluster analysis indicated that ~10% of cell lines and ~20 of SCLC tumors were of the low NE subtype. The low NE subtype samples had RB1 mutations or low or absent RB1 expression, confirming their SCLC origin. Differences between the high and low subtypes were divided into those common to tumors and cell lines and those largely or entirely limited to tumors. Differences common to tumors and cell lines. At least three different lineage specific transcription factors were expressed by SCLC tumors and cell lines. Most NE high cells expressed ASCL1 in conjunction with NKX2-1. NEUROD1, occasionally with ASCL1, was expressed by a smaller subset of NE high and occasionally by NE low cells. POU2F3 was expressed by most of the NE low subtypes, and about half of these also expressed ASCL2. However, about 4% of tumors and cell lines (all belonging to the NE low subtype) lacked an identified lineage specific transcription factor. The NE high subtype expressed all of the classic NE markers, as well as numerous neural markers covering neural and glial differentiation. In addition they selectively expressed markers for DNA damage, the FGFR pathway, calcium signaling and Notch inhibitors. The NE low subtype lacked all or most of the NE cell program, NKX2-1 and DLL3 expression, while MYC and REST expression, the Hippo, TGFb and Notch pathways and EMT were greatly upregulated. These and other findings were predicted to impact on the potential responses of the two subtypes to chemotherapy, radiotherapy, and multiple targeted therapies. Differences limited to tumors and absent in cell lines: Despite having a high mutational burden, SCLC is considered to be an "immunological desert", with few infiltrating immune or inflammatory cells, low or absent PDL-1 expression, and modest responses to PD-1 blockade. While the high NE tumors fitted this description most of the low NE tumors had strands of fibrosis encircling tumor islets, with varying numbers of inflammatory cells in the fibrous strands. Major differences at multiple steps were present in the low NE subtype involving the over 200 genes regulating the Cancer-Immunity Cycle, including the major cytokine families, toll like receptors, the inflammasome pathway, the JAK/STAT pathway, HLA antigens, CD47 antigen, perforin and granzymes. These changes were accompanied by highly significant increases in the relative numbers of multiple types of infiltrating immune and inflammatory cells. In addition, the low NE subtype had increased expression of PDL-1 and the interferon gamma signature, suggesting enhanced responses to immunotherapy. Conclusions: SCLC tumors and cell lines can be divided into high and low NE subtypes and these subtypes have major differences in lineage specific transcription factors, expression of the NE program, as well as some oncogenes and pathways, predicting them to respond very differently to conventional and targeted therapies. In addition, very different infiltrating cellular and gene expression patterns of immune responses were present in the low NE tumors, involving multiple aspects of Innate and Adaptive Immunity, and predicting that the low NE subtype tumors are more likely to respond to immunotherapy. In addition, several possibilities of combining cytotoxic, targeted and immunotherapies are suggested from our findings. I thank my collaborators for their invaluable contributions: Ling Cai, Tao Wang, Guanghua Xiao, Luc Girard and John Minna. 1. Zhang W, Girard L, Zhang YA, *et al.* Small cell lung cancer tumors and preclinical models display heterogeneity of neuroendocrine phenotypes. Transl Lung Cancer Res 2018;7(1):32-49.

Keywords: Small cell lung cancer, Heterogeneity, Neuroendocrine differentiation

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MS32.05 TARGETING DNA DAMAGE AND REPAIR

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Small cell lung cancer (SCLC) remains one of the most recalcitrant cancer types, with a 5 year survival less than 10% across all stages. At the genomic level, SCLC is characterized by loss of p53 and RB1 function and frequent amplification or overexpression of MYC family members[1]. These molecular hallmarks of SCLC contribute to high rates of replication stress and genomic instability which, in turn, may make SCLC tumors more susceptible to drugs targeting DNA damage response (DDR). Previously, we found that PARP1, Chk1, Wee1, and other proteins regulating DNA repair are highly expressed in SCLC, as compared to other lung cancers[2]. Based on this finding, several DDR inhibitors have now been tested in SCLC models as single agents or in combination with other DDR inhibitors or chemotherapy. Pharmacologic inhibitors of PARP, Chk1, Wee1, and ATR (alone or in combination) have shown promising activity in SCLC cell lines and mouse models (as reviewed in Sen, Gay, and Byers, TLCR 2018)[3]. Interestingly, in SCLC, response to PARP inhibitors and other DDR inhibitors has not been associated with mutations in BRCA1/2, other gene defects in homologous recombination (HR), or with higher HR deficiency scores. Rather, several novel biomarkers have been identified that define subsets of SCLC with enhanced sensitivity to specific DDR inhibitors. These include high SLFN11 expression as a predictor of PARP inhibitor sensitivity and MYC amplification or overexpression as a predictor for Chk1 and aurora kinase targeting. Many of these biomarkers are associated with pathways that contribute to replication stress (e.g., high MYC activity) or that promote replication arrest following DNA damage (e.g., high SLFN11)[4,5]. This supports the hypothesis that SCLC tumors under greater replication stress may be more susceptible to DDR inhibitors. Several PARP inhibitors (e.g., olaparib, rucaparib, niraparib) are now approved for the treatment of breast and ovarian cancer and inhibitors that hit other DDR targets are in various stages of clinical development. The availability of these agents – together with the preclinical data – has led to several clinical trials investigating DDR inhibitor targeting in SCLC. Results from a recently published randomized Phase 2 trial of temozolomide (TMZ) with either veliparib (PARP inhibitor) or placebo in 104 relapsed SCLC patients did not meet its primary endpoint of 4-month progression free survival (PFS)[6]. However, response rates were three times as high in the veliparib-treated patients (39% TMZ/veliparib vs. 19% TMZ/placebo, p=0.016). Furthermore, when patients were stratified by biomarker status, those patients with SLFN11-positive tumors (as measured by IHC) who received the PARP inhibitor had

significantly higher PFS and overall survival (OS) than biomarker-negative patients (interaction p-value 0.009). For example, SLFN11-positive patients treated with TMZ/veliparib had a median OS of 12.5 months as compared to 7.5 months in SLFN11-negative patients (p=0.014). In contrast, there was no difference in PFS or OS based on biomarker status in patients in the placebo (TMZ only) arm, supporting that the biomarker was in fact predictive of benefit from PARP inhibitor treatment. An ongoing study combining the PARP inhibitor olaparib with TMZ is further exploring this combination in relapsed SCLC patients (NCT02446704). In addition, two trials have now been conducted investigating veliparib in combination with frontline platinum-etoposide chemotherapy (NCT01642251 and NCT02289690). SLFN11 biomarker analysis from the first of these studies will be presented at this meeting. Other DDR inhibitors in clinical investigation include the Chk1 inhibitor prexasertib and the Wee1 inhibitor AZD1775 (alone or in combination with other DDR inhibitor or chemotherapy). DDR targeting may also potentiate the effect of immunotherapy. In other cancer types, recent reports describe enhanced activity of immune checkpoint inhibitors in cancers with inherent DDR deficiencies such as BRCA1 mutations. Clinical trials in multiple tumor types including lung cancer are underway investigating whether treatment with a DDR inhibitor could enhance response to immunotherapy. Emerging preclinical data suggests activity of DDR-immune targeting in SCLC. REFERENCES 1. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524:47-53. 2. Byers LA, Wang J, Nilsson MB, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. Cancer Discov 2012;2:798-811. 3. Sen T, Gay CM, Byers LA. Targeting DNA damage repair in small cell lung cancer and the biomarker landscape. Transl Lung Cancer Res 2018;7:50-68. 4. Sen T, Tong P, Stewart CA, et al. CHK1 Inhibition in Small-Cell Lung Cancer Produces Single-Agent Activity in Biomarker-Defined Disease Subsets and Combination Activity with Cisplatin or Olaparib. Cancer Res 2017;77:3870-84. 5. Steward, AC, Tong P, Cardnell RJ, et al. Dynamic variations in epithelial-to-mesenchymal transition (EMT), ATM, and SLFN11 govern response to PARP inhibitors and cisplatin in small cell lung cancer. Oncotarget 2017;8:28575-87. 6. Pietanza MC, Waqar SN, Krug LM, et al. Randomized, Double-Blind, Phase II Study of Temozolomide in Combination With Either Veliparib or Placebo in Patients With Relapsed-Sensitive or Refractory Small-Cell Lung Cancer. J Clin Oncol 2018:JCO2018777672.

Keywords: Small cell lung cancer (SCLC), DNA damage repair, Biomarkers

MS32 SCLC - FROM BENCHSIDE TO BEDSIDE - CLINICAL SCIENCE SESSION
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MS32.06 EPIGENETIC TARGETS

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Memorial Sloan Kettering Cancer Center, New York/NY/US

Lung cancer remains the most common cause of death in men and women, responsible for more deaths than colon, breast and prostate cancer combined. Lung adenocarcinoma (a type of NSCLC) and small cell lung cancer (SCLC) comprise two of the major subgroups within lung cancer and collectively contribute to a high degree of cancer mortality year after year. Despite recent success in developing and implementing targeted therapeutics for several prominent driver oncogenes in NSCLC, SCLC remains a critical unmet medical need in the cancer field, in part due to a relative paucity of actionable mutations and well-defined biomarker-directed therapies. New therapeutic strategies are desperately needed to improve clinical outcomes for patients with SCLC. Despite lacking known driver oncogenes, such solid tumors have been shown to have frequent inactivating mutations in epigenetic remodeling enzymes – the “reader” and “writers” of the epigenome – which collectively play a role in the regulation of transcription, cellular plasticity and the ability of cancer to adapt or resist therapeutic interventions. Known to be central to the role in regulation of gene expression are the SWI/SNF family of chromatin remodeling enzymes (also know as “BAF”), the Polycomb Repressive Complexes (PRC1/2), the p300-CBP transcriptional coactivator family, BRD4, LSD1-NuRD, MLL and others. These transcriptional rheostats have a central role in dynamic process of opening and closing chromatin to the access of transcription and elongation factors. It is increasingly appreciated that SCLC is particularly sensitive to perturbations in transcription. Small molecules now exist to target the catalytic function of many of these epigenetic targets and are proceeding to clinical testing for patients with molecularly defined cancers, offering a therapeutic opportunity in an otherwise barren space.

Keywords: EZH2, Epigenetic, LSD1

JCSE01 PERSPECTIVES FOR LUNG CANCER EARLY DETECTION
SUNDAY, SEPTEMBER 23, 2018 - 07:30-11:15

JCSE01.04 RISK MODELING FOR THE EARLY DETECTION OF TIN MINER LUNG CANCER IN CHINA

Y. Qiao

Department of Cancer Epidemiology, Cancer Institute/hospital, Chinese Academy of Medical Sciences, Beijing/CN

Result of National Lung Cancer Screening Program has demonstrated a 20% reduced lung cancer mortality with low-dose computed tomography among current or former smokers with a smoking history of 30 or more pack-years[1]. Selecting high risk population for LDCT screening is a key issue for lung cancer screening. Many studies have suggested that lung cancer risk model which incorporating these factors can be more accurate to identify high risk individuals suitable for LDCT screening than the NLST criteria[2]. Thus, more precise evaluation of association between these factors are warranted to developing lung cancer risk models. In this study, we developed and internal validated a lung cancer risk model with data of a occupational screening cohort in Yunnan, China with the aim to exploring potential improvement of yield of lung cancer screening with Chest X-ray and Sputum cytology due to the improved risk stratification. This study was a prospective occupational cohort study among tin miners from Yunnan Tin Corporation (YTC) initiated in 1992[3]. Participants were tin miners aged 40 or over and had at least 10 years of underground work or smelting history. Participants also had received annual lung screening from 1992 to 1999, and were annually followed up through December 31, 2001. Previous studies suggested that age, education level, smoking, occupational radon and arsenic exposure, prior chronic bronchitis were risk factors of lung cancer risk in this cohort[4-6]. During the study period, a total of 443 lung cancer deaths were confirmed among 9295 participants. To reduce the potential information bias, 69 lung cancer death with 1 year since enrollment were not included into the analysis. To stratified those with higher lung cancer risk, we increased the age criteria from 40 to 50 years old(model 0), then further developed three risk prediction models with multivariate logistic regression respectively, and the predicted probability of lung cancer death for each participants were also calculated based on logistic regression model respectively(table1). The goodness of fit, discrimination and calibration ability of the model performance were evaluated with -2log likelihood, area under the receiver operator characteristic curve (AUC) (C-index) and Hosmer-Lemeshow test. We found that the model incorporated age, gender, smoking, educational prior chronic bronchitis, occupational radon and arsenic had the best discrimination performance with area under ROC as of 0.821(95%CI:0.805-0.836) (figure1a). The calibration performance of this model was also good(Hosmer–Lemeshow type χ^2=5.413,p=0.773)(figure1b). The areas under ROC curve of model 2 and model 3 were significantly better than those of model1 and model 0(all p<0.001), however, no difference was found between model 2 and model 3. Besides, Bootstrapping techniques were used for internal validation of the model 3 to Correct for this overfit or optimism, and discrimination C-statistic from C-statics was the same to the original data. We stratified the participants into 4 quintiles for the predicted risk of death from lung cancer. The cumulative lung cancer death rate from quintile 1 with lowest risk to quintile 4 having the highest risk increased from 11.51, 47.66, 625.41 to 1732.37 per 10^5 person-years, while only 2.5% of all lung cancer deaths were in quintile 1 and 2. Similarly, in 210 screen-detected lung cancer deaths, the proportion in quintile 1 and 2 was only 2.4%. In conclusion, we have developed and internal validated a lung cancer risk model based on personal and occupation covariates in this occupational population, and this model showed good accuracy for the identification of lung cancer and might assist in identifying individuals at high risk of developing lung cancer in lung cancer screening in this occupational cohort. [1] Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011. 365(5): 395-409. [2] Tammemägi MC. Application of risk prediction models to lung cancer screening: a review. J Thorac Imaging. 2015. 30(2): 88-100. [3] Qiao YL, Taylor PR, Yao SX, et al. Risk factors and early detection of lung cancer in a cohort of Chinese tin miners. Ann Epidemiol. 1997. 7(8): 533-41. [4] Lubin JH, Qiao YL, Taylor PR, et al. Quantitative evaluation of the radon and lung cancer association in a case control study of Chinese tin miners. Cancer Res. 1990. 50(1): 174-80. [5] Fan YG, Jiang Y, Chang RS, et al. Prior lung disease and lung cancer risk in an occupational-based cohort in Yunnan, China. Lung Cancer. 2011. 72(2): 258-63. [6] Yao SX, Lubin JH, Qiao YL, et al. Exposure to radon progeny, tobacco use and lung cancer in a case-control study in southern China. Radiat Res. 1994. 138(3): 326-36.

Keywords: lung cancer, risk model, Tin Miners

JCSE01 PERSPECTIVES FOR LUNG CANCER EARLY DETECTION
SUNDAY, SEPTEMBER 23, 2018 - 07:30-11:15

JCSE01.05 BIOMARKERS AND LIQUID BIOPSY FOR EARLY DETECTION OF LUNG CANCER

K.C.A. Chan

The Chinese University of Hong Kong, Hong Kong/HK

The analysis of circulating DNA released by tumor cells, frequently known as liquid biopsy, provides a convenient and noninvasive way for the assessment of cancers. The most common application of liquid biopsy is to guide the choice of treatment in lung cancers. The detection of EGFR mutations in the plasma of patients with advanced lung cancers is useful for predicting the response to EGFR TKI treatment. Because of its noninvasive nature and quick turn-around time, liquid biopsy has been proposed to be a first line investigation for the assessment of EGFR mutational status. Another potential application of liquid biopsy is for the screening of early cancers. However, there is a lack of information regarding the biological feasibility of this approach as it is unclear if a small tumor would release sufficiently large amount of DNA into the circulation to allow early detection of the cancer. In this regard, we used nasopharyngeal cancer (NPC) as a model to address this biological question. As NPC is closely related to Epstein-Barr virus infection, we developed plasma EBV DNA as a marker for NPC. From 2013 to 2016, we screened over 20,000 asymptomatic men for NPC using a sensitive plasma EBV DNA assay. Subjects with positive test results were further investigated with nasal endoscopy and MRI. Through this arrangement, we identified 34 cases of NPC and almost half of them had stage I disease. Compared with historical cohorts, patients identified by screening had much improved progression-free survivial with a hazard ratio of 0.1. This study clearly demonstrates that a small early cancer can release sufficiently large amount of DNA into the circulation to allow sensitive detection by liquid biopsy. To apply these results to non-viral-associated cancers, we developed a generic cancer test based on copy number aberrations and altered methylation in plasma DNA. This test successfully detect various types of cancers, including lung cancer.

Keywords: cancer screening, EGFR testing, liquid biopsy

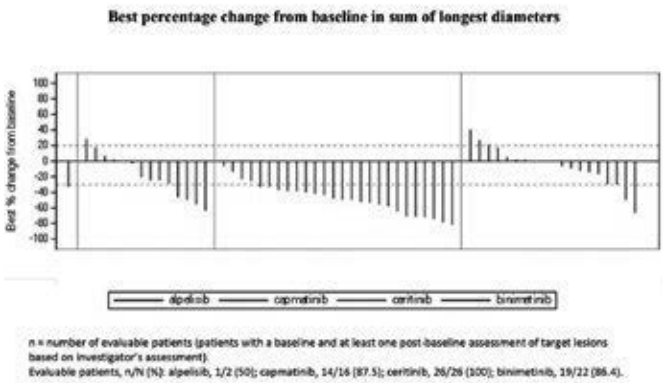
JCSE01 PERSPECTIVES FOR LUNG CANCER EARLY DETECTION
SUNDAY, SEPTEMBER 23, 2018 - 07:30-11:15

JCSE01.09 CLUSTER TRIAL: PH2 BIOMARKER-INTEGRATED STUDY OF SINGLE AGENT ALPELISIB, CAPMATINIB, CERITINIB AND BINIMETINIB IN ADVNSCLC

Y. Wu[1], Q. Zhou[1], X. Zhang[1], H. Tu[1], B. Gan[1], B. Wang[1], C. Xu[1], H. Chen[1], M. Zheng[1], Z. Wang[1], X. Bai[1], Y. Sun[1], A. Myers[2], X. Lv[2], Y. Chakraborti[3], S. Zhao[2], J.-. Yang[1], J. Callister[4]

[1]Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou/CN, [2]Novartis Institutes for Biomedical Research (China), Shanghai/CN, [3]Novartis Healthcare Pvt. Ltd, Hyderabad/IN, [4]Articulate Science, Manchester/GB

Several genetically altered signaling pathways have been profiled in NSCLC, enabling advanced management of NSCLC using targeted therapies. This study investigated the therapeutic spectrum of NSCLC with uncommon molecular alterations by allocating patients to treatment arms based on molecular aberrations; targeted therapies alpelisib (PI3Kαi), capmatinib (METi), ceritinib (ALKi), and binimetinib (MEKi) were evaluated.The study was based on the umbrella design. Key objectives: investigate feasibility of using one trial for different agents based on biomarker-integrated analysis, assess anti-tumor activity, characterize safety, tolerability and PK profiles of individual agents. Key eligibility criteria: age $\geq$18 years; ECOG PS $\leq$2; failed prior treatment/unsuitable for chemotherapy. Documentation of locally determined molecular alterations before treatment allocation was required (alpelisib, 350 mg QD: PIK3CA mutation/amplification; capmatinib, 400 mg BID (tablet): MET IHC overexpression/amplification; ceritinib, 750 mg QD: ALK or ROS1 rearrangement; binimetinib, 45 mg BID: KRAS, NRAS or BRAF mutation).Sixty-six patients with advNSCLC were enrolled (median age 58 years; 65.2% male: alpelisib, n=2; capmatinib, n=16; ceritinib, n=26; binimetinib, n=22). As of Feb 28, 2018, 10 patients in ceritinib and 2 in binimetinib arms were ongoing. Twenty-four patients had confirmed partial responses (36.4%): alpelisib, 0%; capmatinib, 18.8%; ceritinib, 73.1%; binimetinib, 9.1% (Figure). Longest mPFS (14.4 months) was in ceritinib arm. Among the most common treatment-related AEs: alpelisib: malaise, hyperglycemia, dysgeusia; capmatinib: nausea, anemia, peripheral edema, decreased appetite; ceritinib: diarrhea, vomiting, ALT/AST elevation; binimetinib: mouth ulceration, AST, blood CPK increased, rash. Most AEs were grade 1/2.



Objective responses/tumor shrinkage were observed in the study; highest ORR and mPFS were observed with ceritinib, although patient numbers differed between arms. All treatments were well tolerated; no new safety signals were observed. This study demonstrated the feasibility of an umbrella trial and importance of precision medicine in the management of advNSCLC with uncommon molecular alterations.

JCSE01 PERSPECTIVES FOR LUNG CANCER EARLY DETECTION
SUNDAY, SEPTEMBER 23, 2018 - 07:30-11:15

JCSE01.10 A PH3 STUDY OF NIRAPARIB AS MAINTENANCE THERAPY IN 1L PLATINUM RESPONSIVE EXTENSIVE DISEASE SMALL CELL LUNG CANCER PATIENTS

S. Lu[1], L. Jiang[2], X. Ai[3], J. Li[4], X. Dong[5], D. Zhang[6], Q. Liu[6]

[1]Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai Lung Cancer Center, Shanghai/CN, [2]Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai/CN, [3]Shanghai Chest Hospital, Shanghai/CN, [4]Department of Medical Oncology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences, Beijing/CN, [5]Department of Medical Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan/CN, [6]Zai Lab (Shanghai) Co., Ltd., Shanghai/CN

Small cell lung cancer (SCLC) accounts for 15% of lung cancer, characterized by early dissemination and rapid development of chemo-resistant disease after platinum response (60-80%). Less than 2% of extensive disease SCLC (ED-SCLC) patients survive 5 years. The bi-allelic loss or inactivation of TP53 and RB1 is common in SCLC, the poly(ADP-ribose) polymerase-1 (PARP-1), a critical DNA damage repair enzyme, is highly expressed in SCLC, and SCLC is sensitive to platinum based chemotherapy, suggesting that the defect in DNA damage repair pathways plays an important role in SCLC. ZL2306/ Niraparib is a highly selective PARP-1/2 inhibitor which was exclusively licensed for development in China by Zai Laboratory from TESARO. In SCLC PDX model, niraparib demonstrated anti-tumor activities as monotherapy. In addition, niraparib demonstrated promising tumor growth inhibition in maintenance post platinum treatment in platinum sensitive SCLC PDX models. Clinically, in phase III NOVA study, niraparib demonstrated clear clinical benefit as maintenance treatment by significantly extending progression free survival in all platinum-sensitive recurrent ovarian cancer patients regardless gBRCA or HRD status which led to the approval by FDA and EMA in ovarian cancer. It is suggested that niraparib maintenance therapy could provide potential clinical benefit in platinum responsive SCLC. ZL-2306-005 is a randomized double-blind multi-center phase 3 study to evaluate the efficacy and safety of niraparib versus placebo as maintenance therapy in ED-SCLC patients who have had responses to platinum based chemotherapy.Approximately 590 Chinese patients with histologically or cytologically confirmed ED-SCLC who have achieved either complete response or partial response to their platinum based chemotherapy to their newly diagnosed disease will be randomized (2:1) to 2 groups, receiving either ZL-2306 or placebo in ZL-2306-005 study. Patients need to complete 4 cycles of etoposide + cisplatin/ carboplatin. All patients will be stratified by gender, LDH level and history of prophylactic cranial irradiation. ZL-2306 will be started with 300mg PO QD for patients with a baseline body weight ≥77 kg and a baseline platelet count ≥150,000/μL, or 200 mg PO QD for patients with a baseline body weight <77 kg or a baseline platelet count <150,000/μL based on RADAR analysis in NOVA study. Patients will remain on treatment until disease progression or intolerable toxicity. The co-primary endpoints are PFS assessed by independent central radiologic review and OS; the secondary endpoints are PFS assessed by investigator, CFI, QoL, safety and tolerability.

JCSE01 PERSPECTIVES FOR LUNG CANCER EARLY DETECTION
SUNDAY, SEPTEMBER 23, 2018 - 07:30-11:15

JCSE01.11 DYNAMIC CTDNA MONITORING REVEALED NOVEL RESISTANCE MECHANISMS AND RESPONSE PREDICTORS OF OSIMERTINIB TREATMENT IN EAST ASIAN NSCLC PATIENTS

J. Chang[1], Z. Hu[1], D. Ji[1], S. Chuai[2], W. Shen[1], J. Cao[1], J. Wang[1], X. Wu[1]

[1]Fudan University Shanghai Cancer Center, Shanghai/CN, [2]Burning Rock Biotech, Guangzhou/CN

Advanced NSCLC patients, harboring *EGFR* T790M, exhibit marked diversity in tumor behavior and response to AZD9291, yet a discriminable molecular profile remains elusive. In addition, although *EGFR*C797S was involved in 30% of AZD9291 resistance cases in Western patients, mechanisms for the rest patients remain unclear, especially for the East Asian population. We utilized circulating tumor DNA (ctDNA) profiling to conduct dynamic monitoring in patients undergoing AZD9291, thus characterizing mutational heterogeneity and genomic evolution. Longitudinal plasma samples were collected before, during and post of the AZD9291 treatment in Chinese NSCLC patients with acquired T790M mutation. A ctDNA panel, spanning 160KB of human genome, was used to perform capture-based targeted sequencing that comprises critical exons and introns of 168 genes. The EGFR mutation abundance and dynamic changes of allele fraction (AF) were analyzed with progression-free survival (PFS) after AZD9291 treatment.A total of 61 samples were collected longitudinally from 14 patients, of which 9 have experienced progressive disease (PD). Six patients exhibited a rebound of ctDNA prior to radiographic PD, suggesting the potential of ctDNA in early detection of PD. Several acquired mutations were detected with the AZD9291 resistance, including newly identified EGFR G796S, L792H/F/R/V, V802F, V843I mutations, expect for the previously reported RB1 and EGFR C797S, L718Q mutations. Patients with a higher ratio of T790M and *EGFR*activating mutation at baseline had a significantly longer PFS (9.6m vs 4.5m, p=0.008). A lower ratio of *EGFR*activating mutation AF compared to baseline at first follow-up was significantly correlated with a longer PFS (8.5m vs 5.0m, p=0.027). Furthermore, patients harboring other known driver mutations in addition to T790M at baseline had an inferior PFS (4.9m vs 7.8m, P=0.039).Several novel resistance mechanisms were identified by ctDNA monitoring in the East Asian patients treated with AZD9291. Relative AF of T790M, changes of AF after treatment and the presence of concurrent driver mutations at baseline could predict clinical benefit of AZD9291 treatment.

JCSE01 PERSPECTIVES FOR LUNG CANCER EARLY DETECTION
SUNDAY, SEPTEMBER 23, 2018 - 07:30-11:15

JCSE01.14 EFFECTS OF NEOADJUVANT CHEMOTHERAPY ON THE EXPRESSION OF PROGRAMMED DEATH LIGAND-1 AND TUMOR INFILTRATING LYMPHOCYTES IN LUNG CANCER TISSUES

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Immune checkpoints programmed death 1(PD1)and its ligand PD-L1,PD-L2 pathways can mediate negative synergistic stimulation signals.Immunotherapy combined with chemotherapy can increase the objective response rate of cancer patients,but the mechanism of combination therapy is not clear.This study aims to analyze the changes of PD-L1,PD-L2 in lung cancer tissues and the changes of TILs (CD4+,CD8+,CD28+,and CD56+ lymphocytes) surrounding the tumor before and after neoadjuvant chemotherapy(platinum-based),in order to provide a theoretical basis for relevant clinical studies.Tumor samples were obtained from 26 patients who confirmed primary lung cancer before and after NAC from 2009 to 2016 in the First Hospital of Jilin University. The expression of PD-L1, PD-L2 in lung cancer specimens were assessed by IHC. 5%,10%,20%,30%,50% expression thresholds were used to define PD-L1, PD-L2 positive status, respectively. Of 16 patients (since the biopsy tissue specimens were limited, only 16 cases of biopsy and postoperative tissue specimens were collected), the expression of TILs around the tumor before and after NAC were assessed by IHC. We analyze the changes of PD-L1 and PD-L2 in lung cancer tissues before and after NAC, the correlation between the changes of PD-L1 in lung cancer tissues and tumor shrink rate, the interval from the end of NAC to operation, pathological type, gender and smoking status. Of 16 patients, the changes of TILs around the tumor before and after NAC were also evaluated. P<0.05 was considered statistically significant.1. When using 5%, 10%, and 20% as expression threshold to define PD-L1 positive status, PD-L1 was up-regulated after NAC (P=0.008,P=0.016,P=0.016). However, there were no obviously statistical significance about the expression of PD-L1 when using 30%, 50% expression threshold. The expression of PD-L2 were not show any statistical significance before and after NAC. 2. Of 16 patients, the expression of CD4+, CD8+ and CD28+ lymphocytes increased after NAC (P=0.014,P=0.038,P=0.021), whereas

the change of CD56+ lymphocytes was not statistical significant. 3. There were no significant difference between the changes of PD-L1 and tumor shrink rate, interval from the end of NAC to operation, pathological type, gender and smoking status .1. NAC up-regulates the expression of PD-L1 in lung cancer tissues when the expression thresholds are 5%, 10%, and 20%. 2. NAC up-regulates the expression of CD4+, CD8+, and CD28+ lymphocytes. 3. No correlation exists between the variation of PD-L1 and tumor shrink rate, interval from the end of NAC to operation, pathological type, gender and smoking status.

JCSE01 PERSPECTIVES FOR LUNG CANCER EARLY DETECTION
SUNDAY, SEPTEMBER 23, 2018 - 07:30-11:15

JCSE01.15 MOLECULAR CHARACTERISTICS OF ALK PRIMARY POINT MUTATIONS NON-SMALL-CELL LUNG CANCER IN CHINESE PATIENTS

J. Lai[1], W. Wang[2], C. Xu[3], Q. Zhang[3], W. Zhuang[3], Y. Huang[3], Y. Zhu[4], Y. Chen[3], G. Chen[3], M. Fang[2], T. Lv[5], Y. Song[6]

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Anaplastic lymphoma kinase (*ALK*) gene rearrangements have been identified in lung cancer at 3-7% frequency, thus representing an important subset of genetic lesions that drive oncogenesis in this disease. While the genetic locus of *ALK* primary point mutations NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *ALK* primary point mutations.A total of 339 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *ALK* primary point mutation and other genes were detected by next generation sequencing. *ALK* gene primary point mutation rate was 8.55% (29/339) in non-small cell lung cancer, including V163L (3 patients), F921Gfs*16 (2 patients), K1416N (2 patients), A585T (2 patients), P1442Q (1 patient), A348T (1 patient), K1525E (1 patient), S737L (1 patient), P115L (1 patient), Q515E (1 patient), E314D (1 patient), R395H (1 patient), S1219F (1 patient), S341G (1 patient), P1543S (1 patient), G129V (1 patient), Q167H (1 patient), L550F (1 patient), T1012M (1 patient), D302Y (1 patient), H755Q (1 patient), H331Q (1 patient), G1474E (1 patient) and E119D (1 patient), and median overall survival (OS) for these patients was 20.0 months. Among them, 27 patients with co-occurring mutations had a median OS of 20.0 months, and median OS of the 2 patients without complex mutations was 8.5 months. Statistically significant difference was found between the two groups (P=0.02). Briefly, patients with (n=8) or without (n=21) co-occurring *EGFR* mutations had a median OS of 24.0 months and 20.0 months respectively (P=0.73); patients with (n=21) or without (n=8) co-occurring *TP53* mutations had a median OS of 20.0 months and 17.0 months respectively (P=0.83).*EGFR* and *TP53* gene accompanied may have less correlation with *ALK* primary point mutation in NSCLC patients. Results of ongoing studies will provide a platform for further research to offer individualized therapy with the purpose of improving outcomes.

JCSE01 PERSPECTIVES FOR LUNG CANCER EARLY DETECTION
SUNDAY, SEPTEMBER 23, 2018 - 07:30-11:15

JCSE01.16 POSITIVE CORRELATION BETWEEN WHOLE GENOMIC COPY NUMBER VARIANT SCORING AND THE GRADING SYSTEM IN LUNG NON-MUCINOUS INVASIVE ADENOCARCINOMA

Z. Wang[1], S. Li[2], L. Zhang[1], L. He[1], D. Cui[1], C. Liu[1], Y. Gong[3], B. Liu[3], X. Li[3], W. Wu[3], D. Cram[3], D. Liu[1]

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Grading systems of Lung adenocarcinoma have been proposed by Sica and Kadota in stage I tumors,but the predominant architectural subtypes grading system is applicable for resection samples mostly. The correlation between the histological subtypes and grading with whole genomic copy number variation(WGCNV) is unknown, and was investigated in lung non-mucinous invasive adenocarcinoma (LNMIA) at this study. The predominant histological subtype from 58 resection specimens of LNMIA and 20 para-cancerous lung tissues were collected by laser microdissection from HE staining FrameSlides PEN-Membrane slides.7 of 58 specimens,two predominant subtypes in one cancerous nodule were collected simultaneously. Whole genome amplification followed by high-throughput sequencing was used to deteted WGCNV with the para-cancerous lung tissues as normal reference set and WGCNV was scored by a particular formula.

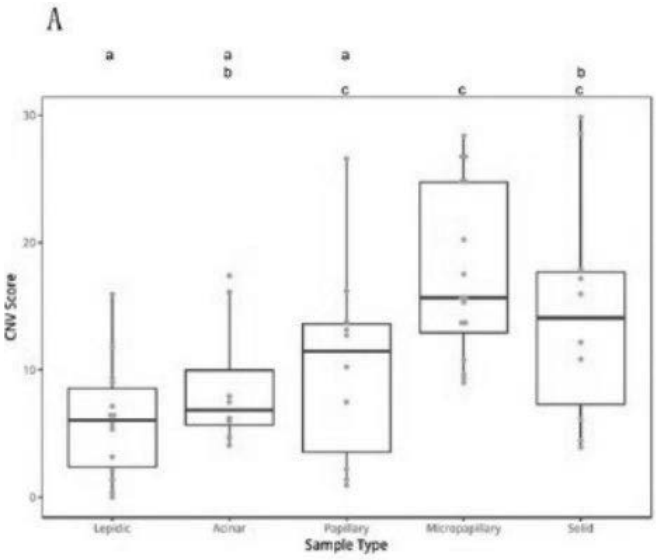
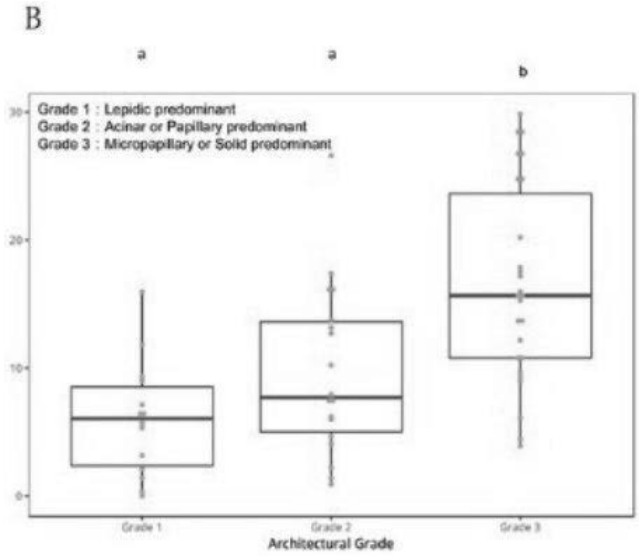


Table 1 WGCNV scores of different histological subtypes and the three tiered grades

Histological Subtypes (Number)	WGCNV score-low (0-7.15) (%, Number/Sum)	WGCNV score-medium (7.16-15.31) (%, Number/Sum)	WGCNV score-high (15.32-29.89) (%, Number/Sum)	Median WGCNV scores	Chi-Squared test# *p* value < 0.05
Lepidic type(14)	71.4%(10/14)	21.4%(3/14)	7.2%(1/14)	6.06(0-15.94)	a
Acinar type(8)	50.0%(4/8)	25.0%(2/8)	25.0%(2/8)	6.83(4.07-17.39)	ab
Papillary type(10)	30.0%(3/10)	50.0%(5/10)	20.0%(2/10)	11.46(0.93-26.59)	abc
Micropapillary type(16)	0%(0/16)	43.8%(7/16)	56.2%(9/16)	15.66(4.6-28.38)	d
Solid type(10)	30.0%(3/10)	20.0%(2/10)	50.0%(5/10)	14.07(3.91-29.85)	bcd
Architectural Grading System (Subtypes, Number)					
Grade 1 (Lepidic,14)	71.4%(10/14)	21.4%(3/14)	7.2%(1/14)	6.06(0-15.94)	a
Grade 2 (Acinar or Papillary,18)	38.9%(7/18)	38.9%(7/18)	22.2%(4/18)	7.7(0.93-26.59)	a
Grade 3 (Micropapillary or Solid, 26)	11.5%(3/26)	34.6%(9/26)	53.9%(14/26)	15.66(3.91-29.85)	b
# Same letters mean no significant differences by chi-squared test					



The letters above the figure show the results of Chi-squared test, and same letters mean no significant difference. WGCNV median scores of 5 histological subtypes of LNMIA with three tiered architectural grades are shown in Table1. The WGCNV scores have a positive correlation with either histological subtypes and architectural grading system (Figure1 A and B). The differences of WGCNV scores are detected betweem two predominant subtypes in one cancerous nodule.GWCNV scores display a positive correlation with three tiered architectural grading system and may has a potential value to predict prognosis in LNMIA.

JCSE01 PERSPECTIVES FOR LUNG CANCER EARLY DETECTION
SUNDAY, SEPTEMBER 23, 2018 - 07:30-11:15

JCSE01.17 WEEKLY NAB-PACLITAXEL PLUS CARBOPLATIN AS NEOADJUVANT THERAPY FOR IIIA-N2 LUNG SQUAMOUS CELL CARCINOMA: A PROSPECTIVE PHASE II STUDY

Y. Zhang, J.Q. Zhu, D. Yue, X. Zhao, Q. Zhang, H. Chen, C. Wang
Tianjin Medical University Cancer Institute and Hospital, Tian Jin/CN

To evaluate the safety and antitumor activity of weekly nab-paclitaxel combined with carboplatin in patients with advanced stage IIIA-N2 NSCLC patients with squamous histologyFrom April 2015 to August 2017, 36 treatment-naive, pathologically diagnosed IIIA-N2 lung squamous cell carcinoma patients were enrolled and given two cycles of weekly nab-paclitaxel (100mg/m^2, day1,8,15 of a 21-day cycle) plus Carboplatin (AUC = 5 at day 1, q3w) as neoadjuvant therapy. Then resectability was assessed and surgery was performed for resectable lesions. Post-operative adjuvant chemotherapy regimens is the combination of Nab-paclitaxel (100mg/m^2, qw x 6) and carboplatin (AUC 5, Q3W x 2) for patients with PD, adjuvant chemotherapy regimen will be changed. The primary objective is the safety and efficacy, and the secondary objectives are quality of life and the role of prognostic biomarker SPARC.Of 36 patients, 3 stopped treatment due to patient decision. 33 were finally evaluated and 1 is still on treatment. Significant tumor volume shrinkage was seen in some patients after the neoadjuvant therapy. 66.7% patients achieved partial response (PR), 21.2% patients achieved stable disease (SD). Disease control (PR +SD) rate was 87.9%. Finally, 23 patients underwent surgical resection, the respectability rate was 69.7%. 12.1% occurred disease progress and failed to achieve resection, including 3 with local progress and 1 with pulmonary metastatic nodule; Among 22 PR pts, 4 failed to achieve resection, in which 1 was due to heart function, the other 3 due to personal unwillingness. 2 of 7 with stable disease failed to achieve resection; the pathological improvement in T stage and N stage before and after treatment was 81.8% (18/22) and 50% (11/22) respectively. The major adverse event was neutropenia (grade I and II) and no serious AE was found.Nab-paclitaxel in combination with Carboplatin showed promising ORR rate and resection rate in of IIIA-N2 lung squamous cell carcinoma. The regimen could be a new chemo option as the neoadjuvant treatment. PFS and OS data will be reported after follow up completing.

JCSE01 PERSPECTIVES FOR LUNG CANCER EARLY DETECTION
SUNDAY, SEPTEMBER 23, 2018 - 07:30-11:15

JCSE01.18 A MULTICENTER SURVEY OF ONE YEAR SURVIVAL AMONG CHINESE PATIENTS WITH ADVANCED NONSQUAMOUS NON-SMALL CELL LUNG CANCER (CTONG1506)

P. Yu[1], Q. Zhou[2], Y. Song[3], X. Zhang[4], G. Chen[5], Y. Zhang[6], J. Chen[7], Z. Yu[8], Y. Hu[9], X. Song[10], D. Zhong[11], G. Feng[12], L. Yang[13], L. Zhan[13], L.D. Yao[13], Y. Chen[13], Y. Gao[14], Y. Wu[15]

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Previous results of CTONG1506 study showed that gene aberration test rate was increasing in Chinese NSCLC patients and first-line treatment was standardized accordingly. This survey further described one year survival of patients with different gene aberration status and under different first-line treatments.CTONG1506 was a two-year series cross-sectional study. Patients with advanced nonsquamous NSCLC who were admitted from August 2015 to March 2016 and who received first-line anti-cancer treatment at one of 12 tertiary hospitals across China were included. Data extracted from medical charts were entered into medical record abstraction forms, which were collated for analysis. Survival information was collected one year after patients were admitted to hospital. One year survival rate and its 95% confidence interval were analysed by Kaplan-Meier method.A total of 707 patients were analysed, with mean age of 57 years and 56.7% were male. Among the 487 patients who had survival data, 192 were *EGFR*- mutation positive (86 mutated in exon 19 [one year survival rate 0.90, 95% CI: 0.81-0.94] and 88 mutated in exon 21 [one year survival rate 0.84, 95% CI: 0.75-0.90]), 27 patients were *ALK* positive and 164 patients were *EGFR* and *ALK* wild type. Most *EGFR*mutation positive patients (128/192) received tyrosine kinase inhibitors (TKIs) as first-line treatment and most *EGFR* wild type patients (155/175) received first-line chemotherapy (Chemo). Pemetrexed was the most common non-platinum chemotherapy-backbone agent (120/155) in platinum doublet regimens. One year survival rates are shown in the table.

	First line treatment	N	One year survival rate	95% CI of survival rate
Total		487	0.76	0.72, 0.80
	Chemo	331	0.72	0.67, 0.77
	TKIs	148	0.86	0.80, 0.91
EGFR positive		192	0.86	0.80, 0.90
	Chemo	61	0.80	0.68, 0.88
	TKIs	128	0.90	0.83, 0.94
EGFR wild type*		175	0.70	0.63, 0.76
	Chemo	155	0.71	0.63, 0.77
	TKIs	NA	NA	NA
ALK positive		27	0.81	0.61, 0.92
EGFR and *ALK* wild type		164	0.70	0.62, 0.76

*No survival data for *EGFR* wild type patients with TKIs as first line treatment presented due to small number of patients.

This national-wide real world study of tertiary hospitals in China revealed that a majority of (>75%) advanced nonsquamous NSCLC patients survived more than one year and was comparable to well-controlled clinical trial results, indicating survival benefits by gene aberration status guided standard of care. This result may be further validated by our on-going two-year survey.

JCSE01.19 ALTER-0303 STUDY: TUMOR MUTATION INDEX (TMI) FOR CLINICAL RESPONSE TO ANLOTINIB IN ADVANCED NSCLC PATIENTS AT 3RD LINE

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Anlotinib is an effective multi-targeted receptor tyrosin kinase inhibitor (TKI) for refractory advanced Non-Small Cell Lung Cancer (NSCLC) therapy at 3rd line. ALTER-0303 clinical trial has been revealed that Anlotinib significantly prolongs progression free survival (PFS; Anlotinib: 5.37 months vs Placebo: 1.40 months) and overall survival (OS; Anlotinib: 9.63 months vs Placebo: 6.30 months) with the objective response rate (ORR) of 9.18% and the disease control rate (DCR) of 80.95%. Here, we sought to understand the gene mutation determinants for clinical response to Anlotinib via next generation sequencing (NGS) upon cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA) at baseline.Totally 437 advanced NSCLC patients enrolled in ALTER-0303 study, and 294 patients received Anlotinib therapy. Of the 294 patients, 80 patients were analyzed in the present study. Capture-based targeted ultradeep sequencing was performed to obtain germline and somatic mutations in cfDNA and ctDNA. Response analyses upon discovery cohort (n = 62) and validation cohort (n = 80) were performed by use of germline and somatic (G+S) mutation burden, somatic mutation burden, nonsynonymous mutation burden, and unfavorable mutation score (UMS), respectively. Based on the above independent biomarkers and their subtype factors, tumor mutation index (TMI) was developed, and then used for response analysis.Our data indicated that the patients harbouring less mutations are better response to Anlotinib therapy (G+S muatation burden, cutoff = 4000, Median PFS: 210 days vs 127 days, p = 0.0056; somatic mutation burden, cutoff = 800, Median PFS: 210 days vs 130 days; p = 0.0052; nonsynonymous mutation burden, cutoff = 50, Median PFS: 209 days vs 130 days; p = 0.0155; UMS, cutoff = 1, Median PFS: 210 days vs 131 days; p = 0.0016). TMI is an effective biomarker for Anlotinib responsive stratification (Median PFS: 210 days vs 126 days; p= 0.0008; AUC = 0.76, 95% CI: 0.62 to 0.89) upon discovery cohort and validation cohort (Median PFS: 210 days vs 127 days; p = 0.0006). Lastly, integrative analysis of TMI and IDH1 mutation suggested a more promising result for Anlotinib responsive stratification upon validation cohort (Median PFS: 244 days vs 87 days; p < 0.0001; AUC = 0.90, 95% CI: 0.82 to 0.97). This study provide a biomarker of TMI to stratify Anlotinib underlying responders, that may improve clinical outcome for Anlotinib therapy on refractory advanced NSCLC patients at 3rd line. Clinical trial information: NCT02388919.

JCSE01.20 OUTCOME IN SMALL CELL LUNG CANCER PATIENTS WITH CEREBRAL RECURRENCE AFTER PRIOR PROPHYLACTIC CRANIAL IRRADIATION

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Prophylactic cranial irradiation (PCI) is a standard therapy for both limited small cell lung cancer (SCLC) and extensive SCLC patients with good responses to first-line treatment. The aim of this study was to examine outcomes in SCLC patients in a single institution who underwent cerebral recurrence after prior PCI.We retrospectively examined the medical records of 219 consecutive SCLC patients who had initially received PCI(25 Gray in 10 fractions) between June 2007 to June 2017. Data were analyzed with regard to age, sex, smoking status, treatment, disease stage, data of PCI, time to cerebral recurrence, site of cerebral recurrence, re-irradiation after cerebral recurrence and time to death. Survival was estimated by the Kaplan-Meier method. Multivariate analyses were performed by the log-rank and Cox's proportional hazard model test.Of the 219 patients undergoing PCI, 180(82.2%) were LD-SCLC and 39(17.8%) were ED-SCLC. The median age was 59 years and the median follow-up time was 23.7 months. The median overall survival (OS) of all patients from the time of diagnosis was 39.0 months (95%CI, 29.6–48.4), in LD-SCLC it was 47.0 months (95%CI, 35.4–58.6), and in ED-SCLC it was 19.0 months (95%CI, 17.0–21.0). The difference was statistically significant with P=0.000. Forty-six patients (21.0%) were diagnosed with cerebral recurrence. 30(65.2%) of these presented with oligometastatic disease and 16(34.8%) had non-oligometastatic disease. Cox multivariate analysis identified disease stage (P=0.043) was the only significantly favorable prognostic factor for cerebral recurrence. The median survival time from PCI was 21.0 months (95%CI, 12.5–29.5), in oligometastatic disease it was 35.0 months (95%CI, 19.0–51.0), and in non-oligometastatic disease it was 16.0 months (95%CI, 12.1–19.9). The difference was statistically significant with P=0.007. Meanwhile, the median time from PCI to cerebral recurrence was 11.0 months (95%CI, 9.5–12.5), in oligometastatic disease it was 11.0 months (95%CI, 6.7–15.3), and in non-oligometastatic disease it was 10.0 months (95%CI, 8.4–11.6). There was no statistical significance between the two. Among forty-six patients with cerebral recurrence, 34 patients underwent re-irradiation using either Re-WBRT (11patients, 23.9%) or SRS /SRT (23patients, 50.0%), another 12 patients (26.1%) did not accept radiotherapy to brain. The median survival time from cerebral recurrence was 10 months (95%CI, 4.1-16.0) for re-irradiation and 4 months (95%CI, 2.3-5.8) for no radiotherapy group, respectively. The difference was statistically significant with P=0.000.PCI remains standard therapy for SCLC patients with good responses to first-line treatment. Cerebral recurrence is inevitable, however, cerebral re-irradiation after recurrence is proven to be beneficial for survival.

JCSE01.21 DIFFERENT RESPONSES TO OSIMERTINIB IN PRIMARY AND ACQUIRED EGFR T790M-MUTANT NSCLC PATIENTS

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Primary EGFR T790M could be occasionally identified by routine molecular testing in tyrosine kinase inhibitor TKI-naive non-small cell lung cancer (NSCLC) patients. This study was aimed to compare clinical characteristics of primary and acquired T790M mutations and their responses to Osimertinib in NSCLC patients. We collected clinical characteristics of patients diagnosed with epidermal growth factor receptor (EGFR) mutation from 2012 to 2017 in Shanghai Chest Hospital. For patients with primary and acquired T790M mutations, the responses to Osimertinib were analyzed.Primary T790M was identified in 1.03% (61/5900) of TKI-naive patients. Acquired T790M was detected in 45.50% (96/211) of TKI-treated patients. T790M always coexisted with sensitizing EGFR mutations. Primary T790M was always coexisted with 21L858R (45/61) whereas acquired T790M was coexisted with 19del (61/96). Among them, 18 patients with primary T790M mutation acquired Osimertinib and 75 patients with acquired T790M mutation received Osimertinib. The median progression-free survival (mPFS) of Osimertinib in primary T790M group was greatly longer than that in acquired T790M group (18.0 months:95% CI:15.0-21.0 VS 10.0months:95% CI:8.3-11.7, P=0.016). The DCR of both groups were 89.3% and 100%. In primary T790M group, the mPFS of concomitant occurrence of 20 T790M and 21 L858R or 19del were 15.7m and 24.0 m, respectively. In acquired T790M group, the mPFS of concomitant occurrence of 20 T790M and 21 L858R or 19del were 11.0m and 10.0m, respectively.Primary and acquired T790M-mutation patients showed different molecular characteristics. Both of them may respond to Osimertinib. However, primary T790M patients showed greater survival benefits from Osimertinib than acquired T790M patients.

JCSE01.22 DIFFERENTIAL MOLECULAR MECHANISMS ASSOCIATED WITH DRAMATIC AND GRADUAL PROGRESSION IN NSCLC PATIENTS WITH INTRATHORACIC DISSEMINATION

Y. Chen[1], B. Hua[2], W. Li[3], C. Zhang[1], W. Tang[1], A. Wang[2], X. Wu[2], J. Chen[1], J. Su[1], Y.W. Shao[2], Y. Wu[1], W. Zhong[1]
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Lung cancer is a highly heterogeneous disease with diverse clinical outcomes. The pleural cavity is a frequent metastasis site of proximal lung cancer. Better understanding of its underlining molecular mechanisms associated with dramatic and gradual progression of pleural metastasis in patients with non-small cell lung cancer (NSCLC) is essential for prognosis, intervention and new therapy development. We performed whole-exome sequencing (WES) of matched primary lung adenocarcinoma and pleural metastatic tumors from 26 lung cancer patients with dramatic progression (DP, n=13) or gradual progression (GP, n=13). Somatic alterations at both genome-wide level and gene level were detected. Kaplan-Meier survival analysis and multivariate Cox regression models were applied to analyze the association between

different somatic alterations and clinical parameters.We first analyzed the differences in somatic alterations between AP and RP group in the primary tumors, and identified higher somatic copy number alteration (SCNA) level in DP group compared to GP group, which is significantly (p=0.016) associated with poorer progression-free survival (PFS). More specifically, patients with chromosome 18q loss in the primary tumor showed a trend (p=0.107) towards poorer PFS. *PTEN* (p=0.002) and *GNAS* (p=0.002) mutations are enriched in the primary tumors of DP group, and are associated with poorer PFS. Furthermore, pleural metastatic tumors harbor a relatively higher level of mutation burden (p=0.105) and significantly increased SCNA (p=0.035) compared to the primary tumors. NSCLC patients in the attenuated progression group have more stable genomes. High level of genomic instability, *GNAS* and *PTEN*mutations, as well as chromosome 18q loss are associated with rapid progression.

JCSE01 PERSPECTIVES FOR LUNG CANCER EARLY DETECTION
SUNDAY, SEPTEMBER 23, 2018 - 07:30-11:15

JCSE01.22A TISLELIZUMAB COMBINED WITH CHEMOTHERAPY AS FIRST-LINE TREATMENT IN CHINESE PATIENTS WITH ADVANCED LUNG CANCER

J. Zhao[1], Z. Wang[2], Z. Ma[3], J. Cui[4], Y. Shu[5], Z. Liu[6], Y. Cheng[7], S. Leaw[8], J. Li[8], F. Xia[8], J. Wang[2]

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Immune checkpoint inhibitors have shown efficacy in patients with NSCLC as monotherapy and in combination with chemotherapy. Tislelizumab is a humanized IgG4 monoclonal antibody to PD1 specifically engineered to minimize FcγR binding on macrophages, possibly minimizing negative interactions with other immune cells. In a phase 1 study, tislelizumab was generally well tolerated and showed antitumor activity; 200mg IV Q3W was established as the recommended dose.

This multi-arm phase 2 study, consisting of safety run-in and dose-extension phases, assessed tislelizumab in combination with platinum-based chemotherapy (by tumor histology) as a potential first-line treatment for Chinese patients with lung cancer. All patients received tislelizumab at 200mg Q3W in combination with 4–6 cycles of platinum-doublet until disease progression. Nonsquamous (nsq) NSCLC patients received pemetrexed + platinum Q3W for 4 cycles followed by pemetrexed maintenance, while squamous (sq) NSCLC patients received paclitaxel + platinum (A) or gemcitabine + platinum (B) Q3W, and small-cell lung cancer (SCLC) patients received etoposide + platinum Q3W. Tumor response (RECIST v1.1) and safety/tolerability were evaluated.

As of 21 Feb 2018, 48 patients (median age, 62 years [range: 36–75], 71% male, 71% current/former smokers) received tislelizumab treatment (median, 3 cycles [range: 1–7]); 44 patients remain on the study. Across the four cohorts, confirmed and unconfirmed partial responses were observed in 13 and 9 patients, respectively (Table). The most frequent AEs were chemotherapy-related hematologic toxicities. The most commonly reported grade ≥3 treatment-related AEs were neutropenia (20.8%) and anemia (12.5%); the most common grade 3 immune-related AEs were pyrexia (6.3%) and rash (6.3%). One sqNSCLC patient experienced a fatal myocarditis/myositis following one cycle of paclitaxel/cisplatin; all other treatment-related AEs were managed/resolved by study-drug interruption (n=15) or discontinuation (n=4) and appropriate treatment.

Best Overall Response (Patients With ≥1 Post-Baseline Tumor Assessment)

	nsq-NSCLC (n=9)	sq-NSCLC [A] (n=12)	sq-NS-CLC [B] (n=5)	SCLC (n=8)	Total (N=34)
PR	**4 (44.4)**	**9 (75)**	**4 (80)**	**5 (62.5)**	**22 (64.7)**
	1 (11.1)	4 (33.3)	4 (80)	4 (50)	13 (38.2)
	3 (33.3)	5 (41.7)	0 (0)	1 (12.5)	9 (26.5)
SD	**3 (33.3)**	**2 (16.7)**	**1 (20)**	**2 (25)**	**8 (23.5)**
PD	**1 (11.1)**	**0 (0)**	**0 (0)**	**1 (12.5)**	**2 (5.9)**
NE	**1 (11.1)**	**1 (8.3)**	**0 (0)**	**0 (0)**	**2 (5.9)**

Data presented as n (%). Abbreviations: nsq-NSCLC, non-squamous non-small cell lung cancer; NE, not evaluable; PD, progressive disease; PR, partial response; SCLC, small cell lung cancer; SD, stable disease; sq-NSCLC, squamous non-small cell lung cancer.

Tislelizumab, in combination with platinum doublets, demonstrated preliminary antitumor activity and was generally well tolerated in patients with advanced lung cancer.

S01 IASLC CT SCREENING SYMPOSIUM: FOREFRONT ADVANCES IN LUNG CANCER SCREENING (TICKETED SESSION)
SUNDAY, SEPTEMBER 23, 2018 - 07:00-12:00

S01.04 LUNG CANCER SCREENING: 1999 TO DATE – WHAT HAVE WE LEARNT?

D. Yankelevitz

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In 1999, ELCAP published their initial results from baseline screening. It found that in a cohort of 1000 participants approximately 85% of the cancers could be diagnosed as clinical Stage I, and that compared with chest radiography found many more of the cancers. In a subsequent study the expanded I-ELCAP found that the long term survival as a measure of cure rate approached 80%. The publicity associated with this initial study was quite large and led to the initiation of several other trials including the NLST. The NLST published their results in 2011 and based this, screening was endorsed by insurers in the US and now other countries are similarly following suit. However, despite the positive result of the NLST, and reimbursement from insurers, screening has had extremely limited uptake in the US, with only approximately 2% of those eligible (among a restricted population) are being screened. Thus, we face a situation where the most common cancer killer has been studied in the most expensive screening trial ever performed which had a positive result, insurers are reimbursing for it, and few people are having it done. With lung cancer screening being touted as a major breakthrough in the war on cancer the question naturally arises as to why it is not being performed more frequently. There have been many reasons to explain the poor uptake, ranging from merely a slow start but expected steady increase, lack of awareness by the clinician or potential screenee, obstacles such as the shard decision making requirement, too many potential harms, and lack of significant benefits. This lack of perceived significant benefit is perhaps the most important aspect, since without a substantial benefit, even if the harms were minimized, why would anyone get screened and why would a clinician recommend it. It seems that this is clearly influencing the decision not to be screened as many experts and even guideline organizations consider the benefits to not be sufficient enough so as to recommend the screening. Even CMS considered the balance of the risks and benefits so tenuous that they took the unique step of requiring a shared decision making process to be included as necessary for reimbursement so that a person could balance the risks and benefits. It is this aspect of benefit that needs to be considered more carefully when explaining it to a potential screenee. Current decision aids, which are required as part of a shared decision making process, in the US and Canada rely almost exclusively on the NLST result and attempt to convert its findings into more visual aids. However, in translating those NLST results, it needs to be understood that they were highly dependent on the design parameters of the study itself, namely 3 rounds of screening and 6.5 years of follow-up. When these parameters change so do the benefits. In the US, current recommendations for screening include annual screening over the period of eligibility for the participant (although for Canada it is restricted to 3 years). Under the circumstance of continued annual screening, the reduction in mortality begins to approach the estimated cure rate for the cancer. It is this feature of cure rate that is really what is most important to any person interested in being screened, and it is substantially higher than the mortality reduction seen in a randomized trial where by necessity the mortality reduction is diluted by the time interval after screening has stopped and cancers are still being followed, and also by not including those cancers that are relatively slow growing and cured as a result of early treatment but not counted towards the mortality reduction because the trial has concluded before their counterpart in the control arm has died. Based on these considerations, it is possible to have a cancer that is 100% curable when screen detected, yet the trial may only show a 20% (or even lower) mortality reduction. Thus, there is inherently no incompatibility between the 80% cure rate seen in the I-ELCAP compared with the 20% mortality reduction seen in the NLST. The simple conversion of the 20% mortality reduction found in NLST into a cure rate as is so commonly done when explaining the benefit to a person interested in screening is highly misleading. The cure rate, which is the clinically relevant feature, is higher. This coupled with the way in which harms are currently expressed, based again almost solely on those NLST results has the effect of amplifying harms at the same time the benefits are being underestimated and surely affect the perception of overall value of CT screening both for physicians as well as people who might be interested.

Keywords: mortality reduction, Screening, curability

S01 IASLC CT SCREENING SYMPOSIUM: FOREFRONT ADVANCES IN LUNG CANCER SCREENING (TICKETED SESSION)
SUNDAY, SEPTEMBER 23, 2018 - 07:00-12:00

S01.07 THE U19 PLANS FOR INTEGRATION OF BIOMARKERS INTO FUTURE LUNG CANCER SCREENING

R. Hung[1], P. Brennan[2], C. Amos[3]

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We are performing a series of three integrated research projects with the unifying goal of reducing mortality from LC by applying targeted approaches to its prevention or early detection. These projects study (1) genetic susceptibility to nicotine dependence and lung cancer, (2) biomarkers for early detection, and (3) application of the results for LC screening. This proposal leverages an extensive collaborative framework and wealth of data from the International Lung Cancer Consortium (ILCCO), the Transdisciplinary Research in Cancer of the Lung (TRICL) Consortium and the Lung Cancer Cohort Consortium (LC3). Epidemiological data from 60 LC studies have been harmonized within ILCCO including 71,000 cases and more than 1 million cohort individuals. **Aims and Results** Project 1: Genomic Predictors of Smoking and Lung Cancer Risk. This project extends and augments genomic analyses that have been completed on 16,000 LC cases and 50,000 controls and extensively characterizes the contribution that genetic variation makes to LC susceptibility. The four aims are. **Aim 1: To precisely characterize the contribution of common genetic variation to LC etiology**. We will analyze a GWAS of LC of 47,506 genotyped LC cases and 63,687 controls. **Aim 2: To investigate uncommon genetic variants using imputation approaches. Aim 3: To identify genetic effects on smoking behavior.** A**im 4: To characterize joint effects of environmental and genetic interactions on LC risk.** For this aim we will take advantage of novel statistical approaches (Mendelian Randomization, Mediation analysis, gene by environment interactions and pathway based analyses) developed by our team to provide a comprehensive approach to evaluating the impact of environmental factors according to genetic background. Recent findings from project 1 include identification of 10 new loci influencing lung cancer risk, the identification of 3 novel gene-smoking interactions contributing to lung cancer risk, identification and validation of two rare variants that convey an over four fold higher risk for lung cancer among carriers, and Mendelian randomization studies that show excess BMI and shorter telomere lengths increase lung cancer risk in a histology-dependent fashion. Project 2: Biomarkers of Lung Cancer Risk. Multiple preliminary studies have implicated a wide range of circulating biomarkers in risk prediction for lung cancer. In Project 2, we hypothesize that a comprehensive and extensively validated risk prediction model that incorporates such risk biomarkers has the potential to substantially improve the selection of subjects at a high risk of developing LC and that these individuals are most likely to benefit from CT screening. This project involves three aims. **Aim 1**: To organize the LC3, including identifying the study population of 2,300 former and current smoking LC cases that were diagnosed within 5 years of donating their blood sample along with one smoking-matched control per case; and organize sample shipments and database preparation. **Aim 2:** To replicate a comprehensive panel of *promising risk biomarkers* and identify those that may be useful for risk prediction. This will involve assaying pre-diagnostic plasma samples for immune biomarkers, protein biomarkers such as pro-surfactant protein B, micro RNAs, methylation markers, and 34 additional promising biomarkers implicated in lung cancer. We will base this initial analysis on 800 case-control pairs from three LC3 cohorts, and define a panel of *replicated risk biomarkers* that provide non-redundant information on disease risk. **Aim 3:** To extensively evaluate all *replicated risk biomarkers* from Aim 2, identifying a minimum set of *validated risk biomarkers,* and ultimately evaluate the extent to which they improve risk prediction models. This will involve performing additional assays for 1,500 additional case-control pairs selected from 16 separate LC3 cohorts. The final outcome of this work will be risk prediction models incorporating a distinct set of biomarkers that provide meaningful information on disease risk, and these biomarkers will finally be evaluated in CT screening studies in collaboration with Project 3. This project recently completed analysis of a set of 4 biomarkers that improve the classification accuracy in prediction of lung cancer risk by 14% compared with a model that only included demographic and smoking information. Project 3: Translating Molecular and Clinical Data to Population Lung Cancer Risk Assessment will evaluate radiographic models using data from the National Lung Screening Trial (**NLST**), lung cancer CT screening programs in British Columbia Cancer Agency (**BCCA**), Early Detection of Lung Cancer – a Pan-Canadian Study (**PanCan**), and the International Early Lung Cancer Action Program- Toronto (**IELCAP-Toronto**) along with the UK Lung Screen Trial (**UKLS**), and the Dutch Belgian randomized Lung Cancer Screening trial (**NELSON**) trial. Data from Projects 1-2 will be used to improve the risk prediction model and the nodule probability models. There are 2 specific aims. **Aim 1 will establish an integrated risk prediction model**

to identify individuals at high risk of lung cancer, initially analyzing epidemiological and smoking related phenotypes and then integrating targeted biomarker, genomic profile, and lung function data applied to LC CT screening populations. We will study 950 CT-detected LC patients with biosamples from 46,057 screening individuals. **Specific Aim 2 will establish a comprehensive LC probability models for individuals with LDCT-detected non-calcified pulmonary nodules.** In this aim we will (a) first establish the 2D diameter-based probability model in N. American CT programs based on 36,481 participants, and then validate it based on 9,576 participants in the European LDCT programs; (b) establish the volume 3D and radiomics-based probability model in European CT programs based on 9,576 participants in European CT programs, and then validate it in the North American CT screening populations; and (c) assess the added predictive value and clinical usefulness of targeted genomic and molecular profiles in both the 2D diameter- and 3D and radiomics volume-based LC probability models based on risk stratification table analysis and decision curve analysis. Finally we will (d) compare the model performance with the existing classification system such as Lung-RADS. This project has developed and evaluated a polygenic risk score using data from project 1 which highly significantly improves risk prediction for lung cancer risk, but has a limited impact on prediction accuracy.

Keywords: Screening, Biomarkers, Genetics

OA01 IMPROVING OUTCOMES IN LOCOREGIONAL NSCLC I
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

OA01.01 10-YEAR UPDATED ANALYSIS OF NRG ONCOLOGY/RTOG 0214: A PHASE III COMPARISON OF PCI VS. OBSERVATION IN PATIENTS WITH LA-NSCLC

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Background: To determine if prophylactic cranial irradiation (PCI) improves survival in locally advanced non–small-cell lung cancer (LA-NSCLC), we conducted a prospective randomized phase III trial. Previously we reported that compared to observation, PCI significantly increased disease-free survival and reduced brain metastases. With extended follow-up, we sought to determine whether PCI conferred an overall survival benefit. **Method:** Patients with stage III NSCLC without disease progression after treatment with surgery and/or radiation therapy (RT) with or without chemotherapy were eligible. Participants were stratified by stage (IIIA v IIIB), histology (nonsquamous v squamous), and therapy (surgery v none) and were randomly assigned to PCI or observation. PCI was delivered to 30 Gy in 15 fractions. The primary end point of the study was overall survival (OS). Secondary end points were disease-free survival (DFS), neurocognitive function (NCF), and quality of life. Kaplan-Meier and log-rank analyses were used for OS and DFS. The incidence of brain metastasis (BM) was evaluated with the logistic regression model. **Result:** Among 356 patients entered to this study, 340 are eligible for analysis. The median follow-up time was 2.1 years for all patients, and 9.2 years for living patients. The survival estimates and hazard ratio indicate that there appears to be no improvement in survival with the use of PCI (p=0.12, HR=1.23, 95% CI: 0.95-1.59). Of note, with the current data there is only 45% power to detect the hypothesized difference HR=1.25 at 1-sided significance level of 0.025. The DFS estimates are better in the PCI arm (p=0.03, HR=1.32, 95% CI: 1.03-1.69). Patients in the observation arm were 2.33 times more likely to develop BM than those in the PCI arm (p= 0.004). On multivariate analysis PCI was significantly associated with decreased BM and improved DFS, but not OS. However, among the 225 non-surgical patients, use of PCI was associated with higher OS (p=0.026, HR=1.42, 95% CI: 1.04-1.94) and DFS (p=0.014), and lower BM (p=0.003). NCF was previously published (Sun, JCO 2011 and Gondi, IJROBP 2013), however, with longer follow-up, there is insufficient data for further analysis. **Conclusion:** In this 10-year updated analysis, use of PCI continued to significantly improve DFS and reduce brain metastases. However, the early accrual closure failed to provide adequate power to detect the hypothesized difference in OS and the survival rates were not significantly different between PCI and observation. Subgroup analyses based on stratification factors suggest that PCI may improve survival among non-surgical patients.

Keywords: Prophylactic Cranial Irradiation (PCI), Locally advanced Non-Small Cell Lung Cancer (LA-NSCLC), NRG Oncology/RTOG

OA01 IMPROVING OUTCOMES IN LOCOREGIONAL NSCLC I
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

OA01.02 THE ESTIMATE OF SHRINKING FIELD AND SIB RADIOTHERAPY GUIDED BY 18F-FDG PET/CT IN LOCALLY ADVANCED NSCLC PATIENTS: A PHASE 2 RANDOMIZED CLINICAL

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Background: Tumor control remains suboptimal in locally advanced lung cancer. Radiation dose acceleration has a positive effect to local tumor control, but is limited by radiation-induced lung injury (RILI). The aim of this study was to evaluate the safety and efficacy of adaptive radiation therapy guided by functional imaging 18F-FDG PET/CT in patients with locally advanced non-small lung cancer. Method: A total number of 72 patients with locally advanced NSCLC were enrolled between November 2012 and June 2017. After signing the inform consent form, 36 patients were randomized into the shrinking field and simultaneous integrated boost radiotherapy group, others were in the conventional radiotherapy group. The Objective Response rate (ORR), progression-free survival (PFS) and overall survival (OS) were compared, as well as the safety of shrinking field and simultaneous integrated boost radiotherapy (radiological dosimetry parameters and the incidence of grade 2 or higher radiotherapy-related toxicity). T-test was utilized to compare the differences between the quantitative data of two groups, while chi-square test or Fisher exact test were utilized to compare the differences between the count data of two groups. Kaplan-Meier curve was utilized to show PFS and OS, and the log-rank test analysis was utilized to compare the survival difference between two groups. P value less than 0.05 was considered statistical difference. Result: All the patients in both two groups had completed their treatment according to the study protocol. The shrinking field and simultaneous integrated boost radiotherapy group was significantly greater than the conventional radiotherapy group in ORR (77.8% vs. 52.8%, P=0.026). The median OS and PFS in shrinking field and simultaneous integrated boost radiotherapy group was 22.0 months (95%CI:18.1~25.9) and 12.4 months (95%CI:10.4~14.3), which is significantly longer than 18.1 months (95%CI:12.4~23.8) and 8.2 months (95%CI:5.2~11.2) in the conventional radiotherapy group (P=0.045 and P=0.013). There was no significant difference between the two groups in radiological metrological parameters and organ at risk (OAR). The incidence of grade 2 or higher RILI, radiation-induced esophagitis, radiation-related myocardial damage and myelosuppression between two groups has no statistically significant difference. Conclusion: Shrinking field and simultaneous integrated boost radiotherapy guided by function imaging 18F-FDG PET/CT is a safe and operable technique in practice. It can improve ORR, OS and PFS without increasing the risk of radiotherapy-related toxicity in patients with locally advanced NSCLC.

Keywords: non-small cell lung cancer, PET/CT, adaptive radiotherapy

OA01 IMPROVING OUTCOMES IN LOCOREGIONAL NSCLC I
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OA01.03 INTERACTION BETWEEN DOSE AND CALCIFICATIONS IS A PREDICTOR FOR OVERALL SURVIVAL IN LUNG CANCER PATIENTS RECEIVING RADIOTHERAPY

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Background: Recently, incidental dose to the heart was found to be predictive for overall survival in lung cancer patients receiving radiotherapy [McWilliam et al EJC 2017, Johnson et al Radiother Oncol 2018]. These patients often present with multiple comorbidities that should be incorporated in survival analysis. However, such data is often missing. We investigated whether calcifications, identified on the radiotherapy planning CT, can be used as a surrogate for cardiac health. In particular, we investigated the interaction between calcifications, dose and survival. **Method:** Data from 814 unselected non-small cell lung cancer patients was used, all treated with 55Gy in 20 fractions. Methodology was developed to automatically segment calcifications within the heart, the aortic arch and their surroundings. The 3D planning CT scans, and the associated lung and spinal cord delineations were processed using well-established image processing algorithms, e.g., convex hull, thresholding, morphological operations, connected pixel analysis and flood filling to detect calcifications. Moreover, shape analysis was included to enhance regions that presented tubular or plate-like appearance. The detection algorithm was validated in a small subset of 10 patients, and this group was used to determine the success and error rate of the automatic segmentation. Finally, a Cox-proportional hazards multivariate analysis was performed for overall survival of all patients accounting for tumour size, total calcification volume, mean dose across all identified calcifications, and interaction between calcification volume and dose. **Result:** The success rate of the algorithm for identifying calcifications was 81.8%, its error rate was 8.8%. The multivariate survival analysis identified tumour size (continuous, p<<0.0001) and the interaction of calcification volume and their mean dose (continuous, p=0.029) as significant. Calcification volume (p=0.57) or mean calcification radiation dose alone (p=0.269) were not found to be significant. **Conclusion:** Multivariate analysis shows a significant interaction between volume of the identified calcifications and their mean radiotherapy dose predicting survival. Further improvements to identify calcifications in the descending thoracic aorta and validation of our methodology are required. Further work linking our results with the established Agatston or Coronary Artery Calcium score is in progress. *EVO-FB share first authorship

Keywords: Comorbilities, survival analysis, Calcifications

OA01.05 PHASE II STUDY OF NEO-ADJUVANT CHEMO/ IMMUNOTHERAPY FOR RESECTABLE STAGES IIIA NON-SMALL CELL LUNG CANCER- NADIM STUDY-SLCG

M. Provencio[1], E. Nadal[2], A. Insa[3], R. García Campelo[4], G. Huidobro[5], M. Domine[6], M. Majem[7], D. Rodríguez-Abreu[8], V. Calvo[1], A. Martinez-Marti[9], J. De Castro[10], M. Cobo Dols[11], G. Lopez-Vivanco[12], E. Del Barco[13], R. Bernabé[14], N. Vinolas[15], I. Barneto[16], B. Massuti[17]

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Background: The combination of chemotherapy and immunotherapy (CT-IO) has a high response rate and longer survival in unselected patients (pts) with metastatic non-small cell lung cancer (NSCLC). There are no data about this combination in the neoadjuvant setting. **Method:** A Phase II, single-arm, open-label multicenter study of local-advanced resectable stage IIIA N2-NSCLC adult patients with CT plus IO (nivolumab (NV)) followed by adjuvant treatment for 1 year. Neoadjuvant treatment: Three cycles of NV 360mg IV Q3W + paclitaxel 200mg/m2 + carboplatin AUC 6 IV Q3W. After completing neoadjuvant therapy, tumor assessment is performed in patients prior to surgery. Surgery is performed in the 3rd or 4th week after day 21 of the third cycle of neoadjuvant treatment. Adjuvant treatment: NV 240mg IV Q2W for 4 months and NV 480mg IV Q4W for 8 months (total one year) after surgical resection. The study aims to recruit 46 pts. The primary endpoint is Progression-Free Survival (PFS) at 24 months. Efficacy is explored using objective pathologic response criteria. We present preliminary data on patients that completed 3 cycles and underwent surgical resection. **Result:** At the time of submission, 46 pts had been included and 20 underwent surgery. CT-IO was well-tolerated and surgery was not delayed in any patient. None of the pts was withdrawn from the study preoperatively due to progression or toxicity. Twenty surgeries had been performed and all tumors were deemed resectable. The overall clinical response rate was 5% complete (CR) and 65% PR. The pathological response evaluated after surgery: 13 cases (65.0%) achieved CR (CPR) (95% CI 40.8-84.6%), and 3 (15.0%) had a major pathologic response (MPR), defined as <10% viable tumor cells in the resection specimen. Considering both CPR and MPR, the overall response rate was 80.0% (95% CI 56.3-94.3%) and 60% of complete responses were unsuspected **Conclusion:** This is the first multicentric study testing CT-IO in the neoadjuvant setting with promising antitumor activity in locally advanced, potentially resectable NSCLC yields an unprecedented complete pathologic response rate. The data will be updated at the time of the congress. EudraCT Number: 2016-003732-20

Keywords: chemo/inmmunotherapy, neoadjuvant, NSCLC

OA01.06 DETERRED: PHASE II TRIAL COMBINING ATEZOLIZUMAB CONCURRENTLY WITH CHEMORADIATION THERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

S. Lin[1], X. Lin[1], D. Clay[2], L. Yao[1], I. Mok[1], D. Gomez[1], J. Kurie[2], G. Simon[2], G. Blumenschein[2], J. Young[3], S. Phan[3], A. Sandler[3], V. Papadimitrakopoulou[2], J. Heymach[2], A. Tsao[2]

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Background: While consolidation immunotherapy after chemoradiation (CRT) is the current standard of care for locally advanced NSCLC (LA-NSCLC), the effectiveness of immunotherapies may be enhanced when combined concurrently with CRT. We report on the safety and preliminary efficacy of combining PD-L1 blockade using atezolizumab (atezo) and concurrent CRT followed by consolidation full dose carboplatin/paclitaxel (CP) with atezo and maintenance atezo up to 1 year for LA-NSCLC. **Method:** This is a single institution phase II study in LA-NSCLC assessing the safety and feasibility of adding atezo to CRT in two parts: I) sequentially (N=10) with CP after completing CRT, or II) concurrently (N=30) with CRT followed by consolidation atezo with CP. Atezo was given at 1200 mg IV Q3 weeks for up to one year from the first dose. Radiation dose at 60-66 Gy in 30-33 fractions was combined with weekly low dose CP, followed by 2 cycles of full dose CP. Severe adverse events (AEs) ≥ grade 3 are defined within 15 weeks of start of therapy or any immune-related AEs during atezo treatment. Evaluable patients (pts) have received at least one dose of atezo. **Result:** From February 2016 to April 2018, we accrued 40 evaluable pts. For part 1, any grade 3+ AEs was seen in 6 pts (60%), with most common being pneumonia (2 of 10, 20%). Three grade 3+ AEs (30%) were attributed to atezo, including dyspnea, arthralgia and a grade 5 TE fistula. Grade 2 radiation pneumonitis (RP) was seen in 3 pts. Four progressed with disease during atezo maintenance and have died, ranging from 0.93 to 1.86 years. Four pts completed atezo and are in follow up without recurrence. For part 2, 17 of 30 pts had any grade 3+ AEs (57%), with pneumonia being the most common (6 of 30, 20%). Three (10%) were attributed to atezo (dyspnea, fatigue and heart failure). RP was seen in 3 pts, with 2 grade 2 and 1 grade 3, which led to atezo discontinuation. So far, 4 pts have progressed and 4 have died, 2 due to disease and 2 due to treatment (neutropenic sepsis and gastric hemorrhage). All others have completed CRT and are on maintenance atezo, ranging from 5 to 19 doses. Updated efficacy results will be presented. **Conclusion:** Concurrent atezo with CRT followed by consolidation and maintenance atezo appears safe without increased toxicities compared to CRT alone followed by consolidation and maintenance atezo.

Keywords: non-small cell lung cancer, immunotherapy, locally advanced

OA01.07 UPDATED RESULTS OF A PHASE II TRIAL OF CONCURRENT CHEMORADIATION WITH CONSOLIDATION PEMBROLIZUMAB IN PATIENTS WITH UNRESECTABLE STAGE III NSCLC

G. Durm[1], S. Althouse[2], A. Sadiq[3], S. Jalal[1], S. Jabbour[4], R. Zon[5], G. Kloecker[6], W. Fisher[7], K. Reckamp[8], E. Kio[9], R. Langdon[10], B. Adesunloye[11], R. Gentzler[12], N. Hanna[1]

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Background: Concurrent chemoradiation (CRT) has been the standard Rx for pts with unresectable stage III NSCLC. A recent phase III trial (PACIFIC) of consolidation durvalumab [PDL-1 inhibitor] demonstrated improved median PFS vs. placebo (16.8 vs. 5.6 mo, HR 0.52, p<0.001). 12-mo (55.9% vs. 35.3%) and 18-mo (44.2% vs. 27%) PFS were also improved. Toxicity was manageable with a grade 3-4 pneumonitis rate of 3.4%, and 4 patients experienced grade 5 pneumonitis. We report updated results of a phase 2 trial of consolidation pembrolizumab [PD-1 inhibitor] following concurrent CRT in patients with unresectable stage III NSCLC. **Method:** After completion of CRT with carboplatin/paclitaxel, cisplatin/etoposide, or cisplatin/pemetrexed + 59-66.6 Gy XRT, those pts w/o PD after 4-8 weeks off CRT received pembro 200 mg IV q3wk for up to 1 yr. The primary endpoint was time to metastatic disease or death [TMDD]. Key secondary endpoints included PFS, OS, and toxicity. **Result:** 93 pts enrolled [92 eligible for efficacy analysis]. Median f/u was 18.6 mo and median age 66 (45-84). 64.1% male and 35.9% female. Stages were 59.8% IIIA and 40.2% IIIB. 55.4% non-SqCC and 43.5% SqCC with 1 mixed histology. 94.6% were current/former smokers. Chemo regimens included carbo/pac (71.7%), cis/etop (26.1%), cis/pemetrexed (2.2%). Median number of cycles of pembro was 13.5 [1-19]. 16% received < 4 cycles; 84% received ≥ 4 cycles; 37% completed 1 yr pembro. Median TMDD was 22.4 months (95% CI 17.9-NR). Median OS was NR (95% CI 22.4-NR), and the estimates of 1-yr and 2-yr OS were 81% and 61.9% respectively. Median PFS was 17 months (95% CI 11.9-NR). 12, 18, and 24-month PFS were 60.2%, 49.9%, and 44.6% respectively. 16 (17.2%) pts developed G≥2 pneumonitis, 5 (5.4%) had G3-4 pneumonitis. There was 1 pneumonitis-related death. In those developing G≥2 pneumonitis, the median time was 8.4 wks [1.1-48.3]. No other G 3/4 toxicities exceeded 5% except dyspnea (5.4%). **Conclusion:** Consolidation pembrolizumab following CRT substantially improves TMDD and PFS compared with historical controls. Prelim OS data is promising and suggests a substantial gain in outcomes of patients with stage III NSCLC is possible with consolidation pembrolizumab. These data will be updated further prior to the World Conference on Lung Cancer Meeting.

Keywords: pembrolizumab, NSCLC, stage III

OA02.01 EFFICACY AND SAFETY OF ENTRECTINIB IN LOCALLY ADVANCED OR METASTATIC ROS1 FUSION-POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Entrectinib is a central nervous system (CNS)-active, potent, and selective inhibitor of ROS1 and TRKA/B/C, with an IC50 of 0.2 nM and ≤1.7 nM, respectively, and is approximately 30 times more potent against ROS1 than crizotinib, the only agent currently approved for the treatment of patients with *ROS1* fusion-positive non-small cell lung cancer (NSCLC). We previously reported interim data that demonstrated an objective response rate (ORR) by blinded independent central review (BICR) of 69% in 32 patients with *ROS1* fusion-positive, ROS1 inhibitor-naive NSCLC, including 11 patients with CNS disease at baseline (Ahn MJ WCLC 2017). Entrectinib was well tolerated; the majority of treatment-related adverse events (TRAEs) were Grade ≤2 in severity and were reversible. **Method:** Patients with locally advanced or metastatic *ROS1* fusion-positive NSCLC were enrolled across phase 1 and 2 studies of entrectinib (ALKA, STARTRK-1, STARTRK-2; EudraCT 2012-000148-88; NCT02097810; NCT02568267). Patients were screened for *ROS1* gene fusions, predominately using next-generation sequencing. Entrectinib was administered orally at 600 mg once daily in 4-week cycles. Safety was assessed by monitoring adverse events, laboratory tests, and clinic visits. Tumor assessments were performed at the end of cycle 1 and every 8 weeks thereafter. All scans were read locally and by BICR using Response Evaluation Criteria In Solid Tumors v1.1. **Result:** Data will be available in time for final submission. We expect to present ORR, duration of response, progression-free survival, and safety data. In addition, intracranial response data for patients with CNS disease at baseline will be presented. **Conclusion:** Section not applicable

Keywords: NSCLC, entrectinib, ROS1 gene fusion

OA02 NOVEL THERAPIES IN ROS1, HER2 AND EGFR
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OA02.02 SAFETY AND PRELIMINARY CLINICAL ACTIVITY OF ROPOTRECTINIB (TPX-0005), A ROS1/TRK/ALK INHIBITOR, IN ADVANCED ROS1 FUSION-POSITIVE NSCLC

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Background: Ropotrectinib is a potent ROS1/TRK/ALK inhibitor with a >90-fold greater ROS1 potency than crizotinib. Preclinical studies demonstrate robust activity against all known *ROS1* resistance mutations, including solvent-front mutation G2032R. **Method:** In this Phase 1 study (NCT03093116), TKI-naïve and TKI-refractory (≥1 TKI) pts with advanced *ALK*/*ROS1*/*TRK*+ solid tumors received ropotrectinib. Asymptomatic brain metastases were allowed. Primary objectives were to determine MTD and RP2D, with safety, pharmacokinetics, and preliminary antitumor efficacy as the secondary objectives. This is a safety analysis of all pts and subgroup efficacy analysis of the *ROS1*+ NSCLC pts on the study. **Result:** As of 16-April-2018, 72 pts have been treated at 6 dose levels from 40mg QD to 200mg BID. Most AEs were grade 1-2. Common (>10%) treatment-related AEs included dizziness (49%), dysgeusia (46%), paresthesias (29%), constipation (19%), fatigue (18%), nausea (11%), and anemia (11%). 4 DLTs were observed at ≥240mg/day: 1 grade 3 (Gr3) dyspnea/hypoxia, 2 Gr3 & 1 Gr2 dizziness. 31 of 72 pts had *ROS1*+ NSCLC by local testing (FISH, n=20; NGS, n=11) with 1 pt determined as *ROS1*-negative by central NGS. Antitumor activity in *ROS1*+ NSCLC has been observed at ROS1 dose levels 40mg QD-160mg BID per investigator assessment, with the best ORR 70% for TKI-naïve and 11% for TKI-refractory pts (17% for 1 prior TKI crizotinib, n=12) (Table). Two crizotinib-resistant pts with G2032R achieved durable cPR and cSD, respectively. Ongoing blinded independent review identified 7 evaluable pts with target CNS lesions at baseline; the intracranial best ORR was 43% (3 cPR, 1 PR*). Updated efficacy data and ctDNA biomarker analyses will be presented.

Dose Level	TKI Naïve (n = 10)		TKI Refractory (n = 20)	
	n	Best Overall Response	n	Best Overall Response
40 mg QD (n = 6)	2	2 cPR (ORR 100%)	4	2 cSD, 1 SD, 1 PD
80 mg QD (n = 5)	2	2 cPR (ORR 100%)	3	1 cSD, 2 SD
160 mg QD (n = 10)	4	2 cPR, 2 cSD (ORR 50%)	6	2 cPR, 2 cSD, 1 SD, 1 PD (ORR 33%)
240 mg QD (n = 2)	1	1 cPR (ORR 100%)	1	1 SD
160 mg BID (n = 7)	1	1 PR*	6	1 PR*, 1 SD*, 1 cSD, 2 SD, 1 NE
Total (n = 30)	10	7 cPR, 1 PR*, 2 cSD	20	2 cPR, 1 PR*, 6 cSD, 1 SD*, 7 SD, 2 PD, 1 NE
Best ORR	70%		11%	
Median follow-up	8 months with 90% still on treatment		4 months with 50% still on treatment	

cPR: confirmed partial response; SD: stable disease for 2 cycles; cSD: SD for at least 4 cycles; PR* or SD*: waiting for subsequent time point scan; PD: progressive disease; NE: inevaluable; ORR: objective response rate

Conclusion: Ropotrectinib is well tolerated and demonstrates promising activity in pts with advanced *ROS1*+ NSCLC, including TKI-naïve and TKI-refractory pts. RP2D has not yet been achieved. These Phase 1 data warrant further clinical testing of ropotrectinib in *ROS1*+ NSCLC.

Keywords: TPX-0005, G2032R, ros1

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OA02.03 CLINICAL ACTIVITY OF LORLATINIB IN PATIENTS WITH ROS1+ ADVANCED NON-SMALL CELL LUNG CANCER: PHASE 2 STUDY COHORT EXP-6

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Background: Among patients with ROS1-positive non-small cell lung cancer (NSCLC), most achieve initial benefit from crizotinib treatment but often develop resistance, and further treatment options are limited.

Lorlatinib is a potent, brain-penetrant third-generation ALK/ROS1 TKI with broad mutational coverage. It has shown compelling clinical activity in patients with ALK-positive and ROS1-positive advanced NSCLC, most of whom had CNS metastases and had received prior crizotinib. **Method:** This ongoing Phase 2 study (NCT01970865) enrolled patients with ROS1-positive advanced NSCLC ± asymptomatic CNS metastases without restriction on the type or number of prior lines of therapy (cohort EXP-6). Patients received lorlatinib 100 mg QD. Primary endpoints were overall and intracranial response by independent central review. Secondary endpoints included duration of response and progression-free survival. Safety was assessed in all treated patients (cohorts EXP-1–6); molecular profiling is ongoing. **Result:** As of the data cut-off (02 Feb 2018), 47 patients with ROS1+ NSCLC were treated; 25 had baseline CNS metastases; 34 had received prior crizotinib and 13 were crizotinib-naïve. Treatment with lorlatinib led to rapid and durable responses in both crizotinib-naïve and crizotinib-pre-exposed patients (Table).

ICR-assessed endpoint	Crizotinib-naïve	Crizotinib-pre-exposed	Total EXP-6
Overall, N	13	34	47
ORR, % (95% CI)	61.5 (31.6, 86.1)	26.5 (12.9, 44.4)	36.2 (22.7, 51.5)
Confirmed response, n	8	9	17
Response lasting at least 12 months, n	5	5	10
Median time to tumor response, months (range)	1.4 (1.3–8.3)	2.5 (1.4–4.2)	1.4 (1.3–8.3)
Intracranial (IC), N	6	19	25
IC ORR, % (95% CI)	66.7 (22.3, 95.7)	52.6 (28.9, 75.6)	56.0 (34.9, 75.6)
Confirmed IC response, n	4	10	14
IC response lasting at least 12 months, n	1	4	5
Median PFS, months (95% CI)[a]	21.0 (4.2, 26.7)	8.5 (4.4, 18.0)	9.9 (5.5, 21.0)
ICR, independent central review; PFS, progression-free survival. [a]Per Kaplan-Meier method.			

The most common treatment-related adverse events (TRAEs) in EXP-6, were hypercholesterolemia (83%) and hypertriglyceridemia (60%). In EXP-6, 36% and 23% of patients had TRAEs leading to dose interruptions and dose reductions, respectively. No permanent treatment discontinuations due to TRAEs or treatment-related deaths occurred. **Conclusion:** Lorlatinib showed clinically meaningful benefit in patients with ROS1-positive NSCLC, including those who had received prior crizotinib or were crizotinib-naive, as demonstrated by rapid and durable responses. These findings further suggest that the activity of lorlatinib differs depending on prior exposure to crizotinib. The safety profile of lorlatinib in ROS1 patients was comparable to that previously reported in the overall ALK/ROS1 population.

Keywords: lorlatinib, NSCLC, ros1

OA02.05 CK-101 (RX518), A THIRD GENERATION MUTANT-SELECTIVE INHIBITOR OF EGFR IN NSCLC: RESULTS OF AN ONGOING PHASE I/II TRIAL

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Background: CK-101 (also known as RX518) is a novel, oral, third-generation, irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that selectively inhibits both EGFR-TKI-sensitizing and resistance mutations, with minimal activity on wild-type EGFR. CK-101 is being studied in an ongoing first-in-human, multicenter, Phase I/II trial in advanced non-small cell lung cancer (NSCLC) patients (pts) with *EGFR* mutations and other advanced malignancies in the US, Australia, New Zealand and Thailand (NCT02926768). Following dose escalation in which 18 pts received CK-101 in dose groups ranging from 100 mg to 1200 mg/day, a first dose-expansion cohort was enrolled at 400 mg bid. **Method:** Eligible pts in dose escalation had a confirmed diagnosis of NSCLC or any advanced solid tumor where targeting *EGFR* was reasonable. Eligible pts in dose-expansion had a confirmed diagnosis of either (1) *EGFR* mutation-positive advanced or metastatic NSCLC without prior exposure to EGFR-TKI therapy, or (2) T790M-positive advanced or metastatic NSCLC with disease progression on previous EGFR-TKI therapy, with no limit on number of prior lines of systemic therapy. **Result:** As of 25 June 2018, 37 pts were treated in dose escalation and expansion and evaluable for safety; median age 59 years, 51% male, 51% Asian, 84% ECOG PS 1. No DLTs or treatment-related SAEs were reported. Most common treatment-emergent adverse events: nausea (16%), diarrhea (14%), lacrimation increased (14%) and vomiting (11%), all grade 1/2 except one grade 3 diarrhea; no grade 4. In dose-expansion, 19 pts were treated with CK-101 at a dose of 400 mg bid and evaluable for response; 8/19 (42%) pts were treatment-naïve, 6/19 (32%) pts had brain metastases; 16/19 (84%) pts remained on treatment. Disease control rate was 100% (19/19), with 16/19 pts (84%) experiencing target lesion reduction versus baseline and 8 pts achieving a partial response (7 confirmed, 1 pending confirmation). In treatment-naïve pts, 6/8 (75%) pts achieved a partial response. In pts with brain metastases, 3/6 (50%) pts achieved a partial response. Higher drug exposures were associated with higher response rate with a confirmed ORR of 55% (6/11) in pts achieving Cmax >400 ng/mL. Median duration of response and progression-free survival were not reached as of the data cutoff. **Conclusion:** CK-101 was well tolerated with a manageable safety profile. Durable anti-tumor activity was observed, particularly in treatment-naïve pts. Further study is ongoing to establish the optimal dose to maximize therapeutic effect in a planned Phase 3 study in treatment-naïve EGFR-mutant NSCLC pts.

Keywords: EGFR, NSCLC, T790M

OA02.06 A PHASE II TRIAL OF POZIOTINIB IN EGFR AND HER2 EXON 20 MUTANT NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Insertions/mutations in exon 20 of EGFR or HER2 occur in ~3% of all lung adenocarcinomas. These alterations are characterized by primary resistance to tyrosine kinase inhibitors (TKIs) with response rates of <12%. We previously showed that exon 20 insertions restrict the size of drug-binding pocket, limiting binding of most available TKIs. However, poziotinib can potentially circumvent these steric changes due to its smaller, flexible structure and is a potent inhibitor of EGFR and HER2 exon 20 mutants (Robichaux et al. Nat Med, 2018). Herein, we report the results of an investigator-initiated study of poziotinib in EGFR and HER2 exon 20 mutant NSCLC (NCT03066206). **Method:** Patients ≥18yrs with metastatic NSCLC bearing mutations/insertions in EGFR or HER2 exon 20 (except EGFR T790M) were eligible. Unlimited prior systemic and targeted therapies were permitted. Poziotinib 16mg PO daily was administered until progression, death, or withdrawal. The primary endpoint was objective response rate (ORR) based on RECIST v1.1. Response was evaluated every eight weeks. A Bayesian design was used with a plan to enroll patients in cohorts of 10 and to terminate the study if ORR was ≤20%. Secondary endpoints included DCR, PFS, OS and safety **Result:** As of May 3, 2018, the planned EGFR cohort of 50 patients was fully enrolled, and 40 patients were evaluated for response. 65.1% of patients had received at least two prior lines of therapy for metastatic disease. 60% of patients had ≥grade 3 adverse events; most common were skin-rash (27.5%) and diarrhea (12.5%). 45.0% of patients required dose reduction to 12mg, while 17.5% required dose reduction to 8mg. One patient stopped treatment due to grade 3 skin rash. ORR at eight weeks was 58% (95%-CI 40.9-73.0) and the DCR was 90% (95%-CI 76.3-97.2). Among 23 patients who achieved partial response, 15 responses were confirmed with subsequent scans, five responses were unconfirmed, and three patients are pending confirmation. Responses were observed in 8/13 (62%) patients that were previously treated with TKI. Median PFS was 5.6mo (95%-CI 5.06-NA). Furthermore, 13 patients were enrolled in HER2 cohort. Toxicities were similar to EGFR cohort except one case of grade 5 pneumonitis, assessed to be possibly drug related. Twelve patients were evaluated for response with ORR of 50% (95% CI 21.1-78.9) at eight weeks and DCR of 83%. **Conclusion:** In heavily pre-treated population with EGFR and HER2 exon 20 mutant NSCLC, poziotinib demonstrated encouraging antitumor activity in both TKI-naive and -refractory patients, and manageable toxicity profile.

Keywords: EGFR Exon 20 insertion, Novel therapy, Targeted theray

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OA02.07 UPDATED RESULTS OF PHASE 1 STUDY OF DS-8201A IN HER2-EXPRESSING OR –MUTATED ADVANCED NON-SMALL-CELL LUNG CANCER

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Background: DS-8201a is a HER2-targeting antibody-drug conjugate with a novel peptide-based cleavable linker, a topoisomerase I inhibitor payload, and a high drug-to-antibody ratio (7 to 8). In preclinical studies, DS-8201a showed broad antitumor activity, in a wide range of tumors. The ongoing phase 1 trial has a dose-escalation (part 1) and -expansion (part 2) and includes subjects with advanced breast cancer, gastric cancer, and other HER2-expressing/-mutated solid tumors. Here, we present updated results for subjects with HER2-expressing or -mutated non-small cell lung cancer (NSCLC). **Method:** Subjects with HER2-expressing (defined as IHC ≥1+ or amplified) or –mutated (detected by NGS or other platforms) NSCLC were eligible to enroll. HER2 expression and mutation were assessed using archival tissue. Adverse events (AEs), objective response rate (ORR), disease control rate (DCR: CR + PR + SD), and duration of response (DOR) were assessed. **Result:** [Results will be updated for presentation at meeting] As of Apr 18, 2018, 12 subjects with HER2-expressing and/or -mutated NSCLC received ≥1 dose of DS-8201a at 6.4 mg/kg. Median age was 58.5 y with median of 3 prior regimens. At data cutoff, 8 of 12 (66.7%) subjects remain on treatment. HER2 IHC status was available for 7 subjects. Median duration of treatment was 3.66 months (range 0.69, 14.19). Eight of 10 (80.0%) subjects with ≥1 post-baseline scan (ps) experienced tumor shrinkage (100.0% of them at 1st ps at 6 weeks). Overall, confirmed ORR and DCR in the evaluable subjects was 5 of 8 (62.5%) and 6 of 8 (75.0%), respectively. Among subjects with HER2 IHC 2+ or IHC 3+ expression, 2 of 5 (40.0%) had a PR. Overall, median DOR was 11.5 months (range 0.03+, 11.53). Three of 12 (25.0%) subjects experienced a grade ≥3 AE. Common AEs included decreased appetite 66.7% (0.0% grade ≥3), nausea 58.3% (0.0% grade ≥3), alopecia 41.7% (0.0% grade ≥3), and fatigue 41.7% (0.0% grade ≥3). One fatal case of interstitial lung disease was reported in this subgroup. **Conclusion:** DS-8201a demonstrated promising antitumor activity in heavily pretreated NSCLC subjects.

Keywords: HER2, NSCLC, Antibody-drug conjugate

OA03 ADVANCES IN LUNG CANCER PATHOLOGY
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OA03.01 THE IMMUNOPHENOTYPING AND GENOMIC CHARACTERISTICS OF PULMONARY SARCOMATOID CARCINOMA: PLEOMORPHIC, SPINDLE CELL AND GIANT CELL CARCINOMA

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Background: Pulmonary sarcomatoid carcinoma (PSC) is a poorly differentiated non-small cell lung cancer (NSCLC) and comprises a diagnostically and therapeutically challenging group of tumors. We explored the immunohistochemical characteristics and genetic profiles of PSC (except carcinosarcoma and pulmonary blastoma) **Method:** A total of 432 cases with surgically resected undifferentiated NSCLC (121 solid adenocarcinomas (ADC), 98 non-keratinizing squamous cell carcinomas (SQC), 118 large cell carcinomas (LCC) and 95 sarcomatoid carcinomas) were reviewed. Expression of epithelial-mesenchymal transition (EMT) markers (Cytokeratin (CK), Vimentin (Vim) and zinc-finger E-box binding homeobox 1 (ZEB1)) were studied by immunohistochemistry. 8 therapeutically-relevant genetic alterations(EGFR/BRAF/KRAS/HER2/MET exon 14 mutations and ALK/ROS1/RET fusion)of sarcomatoid carcinomas were detected by Capture-based targeted sequencing **Result:** The expression of CK was almost positive in ADC, SQC and LCC, which of sarcomatoid component (SC) of PSC was observed positively only in 80/95(84.2%). Although vim expression was higher (88/95, 92.6%) in SC, it was also positive in ADC (37/121, 30.6%), SQC (14/98, 14.3%), LCC (12/118, 10.2%), respectively. In the contrast, SC was detected with 100% ZEB1 expression in PSC (95/95). ZEB1 expression was focal positive only in 1 cases of SQC (1/98, 1.0%). In ADC and LCC, no ZEB1 expression was found. The expression of ZEB1 had higher specificity (99%) and sensitivity (100%) than Vim expression in SC of PSC. The most frequent mutation genes were KRAS (18/58, 31.0%), EGFR (6/58, 10.3%), MET exon 14 (7/58, 12.0%) and no BRAF/HER2/ALK/ROS1/RET alteration were detected. **Conclusion:** ZEB1 was a useful differential diagnostic marker for PSC. Targeted mutations testing may be useful for classifying and managing PSC patients.

Keywords: Pulmonary sarcomatoid carcinoma, differential diagnosis, molecular analysis

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OA03.02 NATIONWIDE COMPARATIVE STUDY OF PD-L1 IHC ASSAYS ON LUNG CANCER: INITIAL REPORT OF LC-SCRUM-IBIS PROJECT

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Background: Precision medicine requires accurate biomarkers for appropriate therapeutic decision. PD-L1 IHC is a predictive biomarker for immune checkpoint inhibitor (ICI), however, the complexity of PD-L1 IHC system could make interpretations confusion in practice. In this study, we compared four PD-L1 IHC systems using real-world clinical samples to reveal their properties and capability of harmonization as a part of nationwide immuno-oncology biomarker study of lung cancer (LC-SCRUM-IBIS). **Method:** Out of 1635 lung cancer patients enrolled in LC-SCRUM-Japan, four PD-L1 IHC assays (22C3, 28-8, SP263 and SP142) and whole-exome sequencing (WES) were analyzed in addition to NGS mutation screening by the Oncomine™ Comprehensive Assay (OCA). Planned accrual is 1000. IHC was evaluated by three certified lung pathologists independently. Three-tier scoring system (cutoff value of 1, 50%) applied for tumor cell (TC) in all assays, and TC+IC scoring algorism

in SP142, according to the manufactural instruction. We calculated Spearman's correlation coefficient and kappa value among TC proportion and the original protocol's criteria of each assays. Discordant rate among assays was examined. **Result:** 486 patients (438 nonsmall, 48 small cell carcinoma) completed IHC study analysis from February to December 2017. Compared to 22C3, TC-score of 28-8 (kappa value 0.896) were and SP263 (0.729) showed good, and SP142 resulted slight (0.159) correlations. SP142-tc+ic score showed fair correlation with 22C3/28-8/ SP263 TC-scores (kappa= 0.213/ 0.241/ 0.291, respectively). Our results showed substantial reproducibility of TC score among observers across different IHC assays (range of kappa: 0.675 – 0.837). Inter-observer concordance of the SP142-IC score was also acceptable (kappa 0.591-0.779). Of note, within 22C3 positive group (>1%), 4.5/15.6/67.7/55.0 % of 28-8/SP263/SP142-tc/SP142-(tc+ic) resulted in negative, respectively, indicating a risk of lower category switching for SP263 and SP142 compared to 22C3 and 28-8. A subset (8.3%) of 22C3-negative group resulted in SP142-positive and all such discrepancy was due to IC-positivity. There was no significant association between each PD-L1 expression and TMB by WES and OCA. Out of 77 patients treated with ICI, most responders (11/17, 65%) had PD-L1 high expression. **Conclusion:** Our results revealed an excellent/moderate/slight correlation between 22C3 and 28-8/SP263/SP142. SP142-positive-cases were fewer and more rigorous than the other three assays. A subset of lung cancer showed IC-only PD-L1-positivity. Inter-observer reproducibility was substantial for TC and moderate for IC. The scoring algorism affected concordance trend in a modest way. For harmonization, we should aware of each assays properties. PD-L1 IHC is not a perfect but a feasible biomarker for patients' selection of ICI therapy.

Keywords: PD-L1 IHC, PD-L1 comparative study, Biomarker reproducibility

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OA03.03 PHASE 2B OF BLUEPRINT PD-L1 IMMUNOHISTOCHEMISTRY ASSAY COMPARABILITY STUDY

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Background: PD-L1 immunohistochemistry (IHC) has been established as companion or complementary diagnostic assays, each developed as predictive biomarker for specific anti PD1/PD-L1 immunotherapies. The Blueprint (BP) phase 1 comparability study demonstrated that three PD-L1 assays (28-8, 22C3, SP263) showed comparable analytical performance for assessment of PD-L1 expression on tumor cells, while the SP-142 PD-L1 assay appeared to stain a lower percentage of tumor cells when compared to the other assays. The first part of BP phase 2 (BP2A) re-affirmed these findings in a larger cohort of 'real life' specimens scored by 25 experienced pulmonary pathologists, and also showed that the 73-10 assay developed for Avelumab showed greater sensitivity than all other assays to detect PD-L1 on tumour cells. BP2A also demonstrated generally excellent inter-observer agreement for tumor cell PD-L1 scoring using both glass slides and digital images, with slightly lesser agreement for the 8 cytology samples included in the study cohort. Inter-observer agreement for immune cell scoring on glass or digital slides was poor. Phase 2B of Blueprint aimed to compare PD-L1 scoring on triplet samples representing large tumor resection blocks, small biopsy samples and fine needle aspirate cell blocks prepared from the same tumor.

Method: Triplet samples of large resected tumor block, small biopsy sample and fine needle aspirate cell block (the latter two taken from the resected tumour specimen) were gathered from 30 resected primary lung cancers (15 adenocarcinomas, 15 squamous cell carcinomas). Sections from all ninety blocks were stained with the pharmDx 28-8 and 22C3, the FDA-approved SP142 and SP263, or clinical trial associated 73-10 PD-L1 assays, in a CLIA-approved immunohistochemistry laboratory. All H&E and PD-L1 IHC slides were scanned and digital images were used to score all cases by the same 25 pathologists involved in BP2A. As before, tumor cells PD-L1 staining were scored as continuous variable and into 7 cut-off-defined categories, as used in various immune checkpoint inhibitor trials. All assays were scored for immune cell PD-L1 staining based on the scoring system developed for the SP-142 assay.

Result: The inter-assay concordance of PD-L1 staining on tumor cells and tumor infiltrating immune cells will again be assessed using the mean scores from all pathologists. Score concordance will also be assessed between the different samples types (large block, small biopsy and cytology FNA) from the same tumors. Given that inter-observer concordance is expected to be high, and the performance of the various assays is well characterized, the results should provide some insight into the relative performance of small biopsy and cytology tumour aspirate samples in replicating the PD-L1 scores assessed on large tumour blocks when the latter are taken as 'gold standard'. **Conclusion:** Not applicable as this is a late-breaking abstract placeholder.

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OA03.05 CHARACTERIZATION OF THE IMMUNOLOGIC INTRA-TUMOR HETEROGENEITY IN EARLY STAGES OF NON-SMALL CELL LUNG CANCER BY MULTIPLEX IMMUNOFLUORESCENCE

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Background: Recurrence of non-small cell lung carcinoma (NSCLC) is associated with genetic and epigenetic intra-tumor heterogeneity (ITH). The interaction between malignant cells, stromal cells, and tumor-associated immune-cells (TAICs), such as T-cell lymphocytes (TCLs) and tumor-associated macrophages (TAMs), is important for progression of NSCLC and the characterization of the immunologic ITH might be relevant to predict recurrence in surgically treated patients at early stages of NSCLC. The aim of this study was to characterize the immunologic ITH of primary NSCLC tumors at early stages using image analysis and multiplex immunofluorescence (mIF) approaches. **Method:** Eight cases of stage IA and 8 cases of stage IB surgically resected NSCLC (11 adenocarcinomas, ADCs; and 5 squamous-cell carcinomas, SCCs) with a history of early recurrence were selected for this preliminary analysis. FFPE blocks were obtained and consecutive sections were stained with two panels of mIF for immune profiling, panel 1: pan-cytokeratin (AE1/AE3), PD-L1, PD-1, CD3, CD8, and CD68; panel 2: AE1/AE3, CD3, CD8, granzyme-B (GB), CD45RO, and FOXP3. Three not adjacent, intra-tumor regions (3mm^2 each) per case were randomly selected after gridding the whole tumor section. A total of 41 intra-tumor regions were scanned by Vectra multispectral-microscope and analyzed using InForm-software. TAICs were quantified in epithelial and stromal compartments from each intra-tumor region. G-Cross AUC (area under the curve) was computed for specific intervals of distances between TAICs and malignant cells. Median distance between TAICs and malignant cells within each region was calculated. **Result:** The median density of TCLs and TAMs were 1527 cells/mm2 and 635 cells/mm2, respectively, without significant differences between histologic subtypes. TCLs were predominantly concentered in stromal compartment (median, 2222 cells/mm2) compared with epithelial compartment (median, 332 cells/ mm2). Percentage and density of TCLs and TAMs varied 4 and 8 times, respectively, between cases and regions. Non-cytotoxic T-cells and inactive cytotoxic T-cells were the most prevalent phenotypes. Higher density of TAMs and antigen-experienced TCLs were observed in stage IB than stage IA. **Conclusion:** Characterization of immunologic ITH of NSCLC is able by mIF and image analysis with FFPE tumor tissue. There is

variability of TAICs densities between regions from the same tumor and different subpopulations were observed. TAMs and exhausted T-cells were more prominent in stage IB (tumor >3cm) suggesting these cells may play an important role in recurrence. Ongoing studies with a larger cohort and comparison with non-recurrent surgically treated patients are warranted. Supported by CPRITRP160668 and UTLungSPORE grants

Keywords: Tumor heterogeneity, non-small cell lung cancer, Multiplex Immunofluorescence

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OA03.06 EXTRACTION OF RADIOMIC VALUES FROM LUNG ADENOCARCINOMA WITH NEAR-PURE HISTOLOGICAL SUBTYPES

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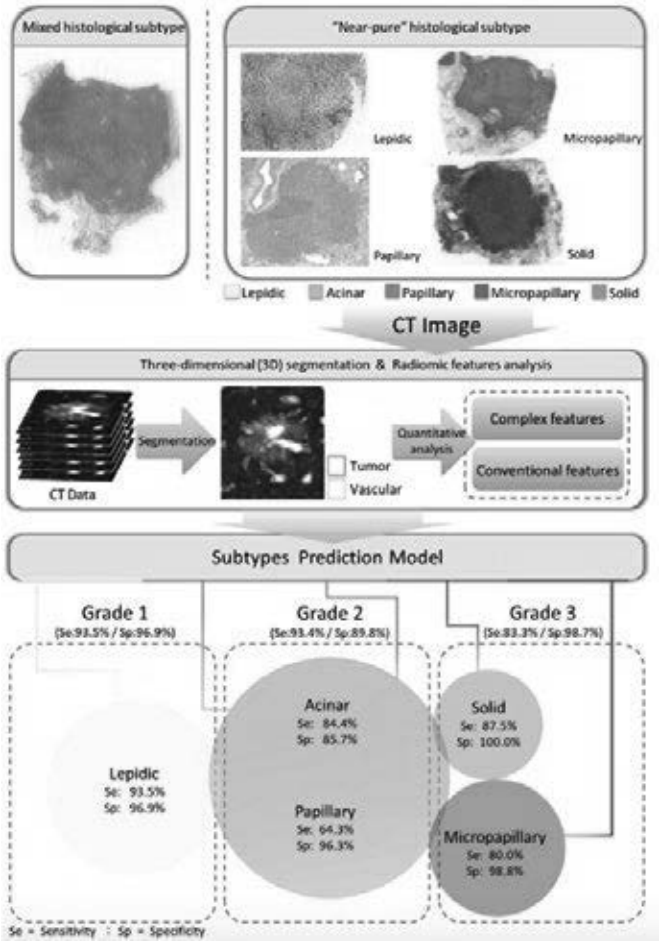
Background: Histological subtypes of lung adenocarcinomas classified by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) system have been investigated using radiomic approaches. However, the results have had limitations since of invasive lung adenocarcinomas may be heterogeneous, with two or more subtypes. To reduce the influence of heterogeneity during radiomic analysis, computed tomography (CT) images of lung adenocarcinomas with near-pure adenocarcinoma subtypes were analyzed to extract representative radiomic features of different subtypes. **Method:** We enrolled 95 patients who underwent complete resection for lung adenocarcinoma and a pathological diagnosis of a "near-pure" (≥70%) IASLC/ATS/ERS histological subtype. Conventional histogram/morphological features and complex radiomic features (grey-level-based statistical features and component variance-based features) of thin-cut CT data of tumor regions were analyzed. A prediction model based on leave-one-out cross-validation (LOOCV) and logistic regression (LR) was used to classify all five subtypes and three pathologic grades (lepidic, acinar/papillary, micropapillary/solid) of adenocarcinomas. The validation was performed using 36 near-pure adenocarcinomas in a later cohort. **Result:** A total of 31 lepidic, 14 papillary, 32 acinar, 10 micropapillary, and 8 solid adenocarcinomas were analyzed. With 21 conventional and complex radiomic features, for 5 subtypes and 3 pathological grades, the prediction models achieved accuracy rates of 84.2% (80/95) and 91.6% (87/95), respectively, while accuracy was 71.6% and 85.3%, respectively, if only conventional features were used. The accuracy rate for the validation set (n=36) was 83.3% (30/36) and 94.4% (34/36) in 5 subtypes and 3 pathological grades, respectively, using conventional and complex features, while it was 66.7% and 77.8% only using conventional features, respectively. **Conclusion:** Lung adenocarcinoma with high purity histological subtypes demonstrates strong stratification of radiomic values, which provide basic information for accurate pathological subtyping and image parcellation of tumor sub-regions.



Keywords: pathological stratification, lung adenocarcinoma, computed tomography

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OA03.07 THREE-DIMENSIONAL IMMUNOFLUORESCENCE ANALYSIS OF DYNAMIC VESSEL CO-OPTION OF SPREAD THROUGH AIR SPACES (STAS) IN LUNG CANCER

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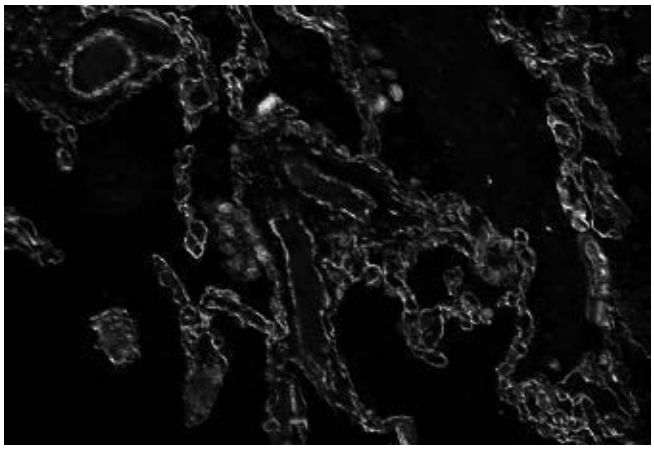
Background: STAS was identified, by the 2015 WHO classification, as a new method of invasion in lung adenocarcinoma, with poor prognosis. Blood vessel co-option is a mechanism by which spreading intraalveolar tumor cells connect to the surrounding vasculature to survive. The aim of this study was to visualize the dynamic mechanism of blood vessel co-option using a high resolution and high-quality 3D reconstruction, and multiplex immunofluorescence (IF). **Method:** A 3D reconstruction image of a case of invasive lung adenocarcinoma with extensive STAS was performed on the formalin fixed paraffin-embedded (FFPE) block. 150 serial sections were obtained by the automated sectioning system AS410 (DNS. Ltd, Japan), and stained with H&E (100 slides), and multiplex IF (30 slides) for CD31, type IV collagen, TTF-1 and E-Cadherin to assess the relation between STAS and the surrounding lung parenchyma and vasculature. The IF stained sections were scanned with 0.33um/pixel by Panoramic P250 Flash (3D Histech Ltd, Hungary) Whole Slide Imaging Scanner (WSI). The WSIs were reconstructed into 3D exported to Imaris 8.0 (Bitplane, MA, US) for signal assessment. **Result:** Serial 3D image analysis identifies the presence of STAS mainly in the form of micropapillary clusters. The multiplex IF staining highlighted the

co-option which was determined by the spread and then attachment of STAS (TTF-1 and E-Cadherin positive) to distant alveolar wall capillaries (CD31 positive) with preservation of the alveolar wall (figure). This relation between STAS and the surrounding lung parenchyma was visualized in all serial sections of the whole FFPE block thickness.



Conclusion: The survival of STAS, beyond the tumor edge, in lung adenocarcinoma is a viable mechanism for tumor recurrence. The combination of the high resolution and high-quality 3D reconstruction and multiplex immunofluorescence in our study, supports the concept that dynamic blood vessel co-option is a mechanism for STAS survival.

Keywords: Co-option, STAS, 3D immunofluorescence analysis

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OA04.01 WHAT IS THE COST OF A STRONG EVIDENCE FOR THE TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER?

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Background: Evidence-based medicine was developed to guide medical decisions based upon the strongest scientific evidence available in the literature. However, large randomized clinical trials are expensive. In addition, new antineoplastic drugs development is also extremely expensive. Therefore, we hypothesized that the strongest evidence available nowadays comes from studies developed by the pharmaceutical industry. **Method:** We carried out a search on network databases for studies published between 2014 and 2017. We included only experimental studies that assessed the treatment for advanced or metastatic non-small cell lung cancer. All included studies were divided into two groups: studies funded by pharmaceutical industry and studies funded by other sources. The primary end point was to compare the evidence strength of each group. Secondary end points were to compare other aspects, such as the number of patients included by each group of studies and the number of innovative drugs studied by each group of studies. **Result:** We found 1,502 studies and included 299 studies (154 sponsored by pharmaceutical industry and 145 funded by other sources). 52,988 patients were included in all studies (36,455 in studies sponsored by industry and 16,533 in studies with other funding sources; $p < 0.001$). The studies funded by pharmaceutical industry had the stronger evidence compared with studies with other sources of funding ($p = 0.005$). Moreover, studies sponsored by pharmaceutical industry studied more innovative therapies (72.4% versus 48.9%; $p < 0.001$) and had a higher proportion of open access manuscript (60.8% versus 43.9%; $p = 0.004$). Results are summarized in the table.

Parameter		Industry Sponsored		P value
		Yes 154 (100%)	No 145 (100%)	
Number of patients		36,455	16,533	<0.001
Mean N of patients		236.7	115.6	
Line	First	110 (71.4%)	94 (64.8%)	0.220
	Second or more	44 (28.6%)	51 (35.2%)	
Biomarker	Yes	55 (35.9%)	55 (37.9%)	0.723
	No	98 (64.1%)	90 (62.1%)	
Innovative Tx	Yes	110 (72.4%)	69 (48.9%)	<0.001
	No	42 (27.6%)	71 (51.1%)	
Phase	I	20 (13%)	25 (17.2%)	0.409
II 101 (65.6%) 97 (66.9%)				
	III	32 (20.8%)	21 (14.5%)	
	IV	1 (0.6%)	2 (1.4%)	
Evidence Level	1	0 (0%)	1 (0.7%)	0.005
	2	76 (49.4%)	52 (35.9%)	
	3	78 (50.6%)	87 (60%)	
	4	0 (0%)	5 (3.4%)	
Experi-mental	Yes	35 (47.3%)	26 (50%)	0.765
Superiority	No	39 (52.7%)	26 (50%)	
Open Access	Yes	93 (60.8%)	61 (43.9%)	0.004
Article	No	60 (39.2%)	78 (56.1%)	

Conclusion: Studies funded by pharmaceutical industry had stronger evidence, tested more innovative therapies, and were more accessible to the readers compared with studies developed with other sources of funding. These findings may alert oncology cooperative groups to the need of more studies with more evidence strength.

Keywords: clinical trials, Evidence-Based Medicine, lung cancer

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OA04.02 DEMOGRAPHIC, PSYCHOSOCIAL, AND BEHAVIORAL ASSOCIATIONS WITH CANCER SCREENING AMONG A HOMELESS POPULATION

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Background: Although cancer incidence and mortality is declining, cancer remains among the leading causes of death worldwide. Research shows that cancer morbidity and mortality can be reduced by early detection. Yet, both cancer risks and screening behavior remain understudied in the United States homeless population. Lung cancer is the deadliest of cancers. Given the recent lung cancer screening guideline, it is especially important to assess population-based awareness of the screening recommendation among the homeless population, a population known to have higher cancer risk behaviors and lower cancer screening rates. **Method:** Researchers conducted a cross-sectional survey of homeless individuals (n =201) who attended a 1-day community event. Eligible study participants were English-speaking adults, aged 21 and above. Willing participants completed a 1-page 33 item paper survey. The analysis describes the demographic, psychosocial, and behavioral

associations with cancer screenings and knowledge of the lung cancer screening recommendation. **Result:** Participants' mean age was 51.7 years (*SD* 13.6); the group was largely African American (77.3%) and male (67.9%). Despite higher cancer risk behaviors, knowledge of lung cancer screening and general participation rates for cancer screenings were below national benchmarks. Among women, the breast and cervical cancer screening rates were 46.5% and 85.1%. Among men, the prostate cancer screening rate was 34.2%. Among all participants, the colon cancer-screening rate was 44%. Cancer risk behaviors were higher than national rates and lung cancer screening knowledge was low (23.0%). Some cancer screening behaviors were associated with age, income, health status, obesity, tobacco use, and physical activity level. **Conclusion:** The associations of screening with modifiable risk factors such as smoking, physical activity and obesity suggests that relevant behavior change interventions are necessary among this high-risk population. Given the barriers to screening of poverty-stricken individuals, such as lack of transportation and access, nurses must not only educate patients on lung cancer screening, they must assist with identifying payment resources and care navigation. Moreover, nurses must be educated on the ambiguity and inconsistency among evidenced-based screening guidelines and be prepared to engage patients in shared decision-making that weighs the recommendations with the patient's individual cancer risks. To improve cancer survival among disparate populations, sustained community outreach is necessary to increase awareness of screening recommendations, identify high-risk individuals, and navigate them to resources. It is imperative that resources are provided to support relevant behavior change interventions, such as tobacco cessation in this high-risk population.

Keywords: lung cancer, homeless, screening

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OA04.03 THE ROLE OF COMPREHENSIVE GENOMIC PROFILING IN THE COMMUNITY SETTING

K. Rohan

This abstract is under embargo until September 24 at 10:30 Eastern Time.

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OA04.05 AN EARLY REHABILITATION INTERVENTION FOR ENHANCING OXYGENATION FROM LUNG CANCER SURGERY

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Background: The purpose of this study is to test the effects of an early rehabilitation intervention on oxygenation, postoperative complications, and recovery from lung cancer surgery. **Method:** The study uses an experimental design. Ninety patients scheduled for lung cancer surgeries was recruited from thoracic surgery units of a medical center in Taiwan. Patients were randomly assigned to the intervention or the control group. The intervention includes a 5-day postoperative in-hospital rehabilitation from post op day 1. The main components of the rehabilitation were aerobic and strength exercises as well as breathing training by using an incentive spirometry. Peripheral capillary oxygen saturation (SpO2) was measured in the morning of the preoperative day and of the 4 consecutive days from postoperative day one to four by using the Nellcor™ OxiMax N-65 Portable Pulse Oximeter. The SpO2/FiO2 (S/F) ratio was then calculated to assess patients' oxygenation. Data on postoperative pulmonary compilations and durations of chest tube drainage were collected from the patients' charts. **Result:** The patients' demographics and baseline measures were equivalent between groups. Results of GEE showed a significant group by time interaction effect on S/F ratio. As for the parameter estimates, from postoperative day 1 to day 4, the S/F ratio improvement in the intervention group was 74.49 (Wald X^2 = 46.42, p<0.001) more than in the control group. Result of Chi-square test showed that the number of postoperative lung complications in the intervention group (n =1) was significantly less (X^2 = 8.39, p = 0.004) than it in the control group (n =10). Result of t- test showed that the duration of chest tube drainage in the intervention group (2.00±1.00 days) was significantly shorter (t =-2.32, p = 0.022) than it in the control group (2.56±1.25 days). **Conclusion:** The study results support the effects of the early rehabilitation intervention on enhancing oxygenation, preventing complications, and promoting recovery from lung cancer surgery as indicated by shortened the duration of chest tube drainage. Surgery to remove the cancer is one of the primary treatment options for non-small cell lung cancer. However, lung cancer surgery may result in decreasing lung capacity and expansion; therefore, increase risks for postoperative pulmonary complications. Pulmonary rehabilitation designed to enhance lung expansion and ventilation may help to reduce postoperative lung complications and promote patients' recovery from lung cancer surgery.

Keywords: pulmonary rehabilitation, lung cancer surgery, oxygenation

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OA04.06 PERCEPTIONS OF NON-PARTICIPATION IN A REHABILITATION INTERVENTION AFTER SURGERY FOR NON-SMALL CELL LUNG CANCER

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Background: Patients with non-small lung cancer (NSCLC) are difficult to engage in clinical trials. Few studies have examined in-depth why these patients refuse to participate. In a Danish randomized clinical trial; 'Postoperative rehabilitation in operable lung cancer patients (PROLUCA)' only 32% of eligible participants consented to participate in the trial. The purpose of this qualitative study was therefore to explore perceptions, considerations and barriers of non-participation in PROLUCA. **Method:** This study was inspired by Reflective Life Research as developed by Dahlberg et al. as a descriptive and interpretive phenomenological research approach. Participants are patients who declined to participate in PROLUCA (non-participants). They were purposefully sampled and recruited from the group of patients who were found to be eligible for the exercise intervention but who declined to participate. Data were collected though telephone interviews. Openness, curiosity and sensitivity played an important role in carrying out the interviews. Analysis was performed according to Reflective Life Research. **Result:** Fifteen non-participants consented to participate in qualitative interviews. Nine men and six women with a mean age of 68 years (range 48-84) were included. Mean time since surgery was 21 month (range 12-28). Five patients were working and ten were retired, eleven patients lived with a partner. The analysis revealed three essential themes referred to the patients' experiences of being *'Between healthy life and good life', 'Under the influence of society'* and their experiences of *'Health and rehabilitation as a personal responsibility'.* Perceptions of non-participation in rehabilitation after surgery for lung cancer are moderated between freedom and necessity. Patients experience ambivalence between a wish to participate in rehabilitation and not having the energy to participate. Patients refused to participate due to daily life priorities and lack of motivation which furthermore is related to social and interpersonal relationships. The patients exercise history is also essential in declining participation. Additionally the patients are under influence of norms and health perceptions from the society. **Conclusion:** Patients' perception of "the good life" was fundamental for accepting or declining participation in a rehabilitation intervention study. Consideration and barriers of non-participation was influenced by norms from the society, motivation, priorities, exercise history, social and interpersonal relations. This study has contributed with a sensitive awareness of why patients following lung cancer surgery might refuse participating in rehabilitation. This knowledge can be taken into consideration in the planning of future clinical trials with lung cancer patients.

Keywords: Surgery, Rehabilitation, Non-participation

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OA04.07 EARLY INITIATED POSTOPERATIVE REHABILITATION REDUCES FATIGUE IN PATIENTS WITH OPERABLE LUNG CANCER: A RANDOMIZED TRIAL

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Background: Surgical tolerability and perioperative risk of complications are correlated with high age, smoking history, comorbidities, low cardiorespiratory fitness (VO_2peak) and low functional capacity, which paradoxically are characteristics describing the average patient with lung cancer. Little is known about the optimal amount and timing of exercise strain in concern of the operation wound and with regard improvement of physical function and quality of life (QOL). On this background, we decided to investigate the effect of early vs. late initiated postoperative rehabilitation in patients with operable lung cancer on exercise capacity, functional capacity, muscle strength, and QOL. **Method:** The study was designed as a two-armed randomized controlled trial with randomization to either early initiated postoperative rehabilitation (14 days after surgery (ERG)) or a control arm with late initiated postoperative rehabilitation (14 weeks after surgery (LRG)). The primary endpoint was a change in maximum oxygen consumption (VO2peak) from baseline to post intervention 26 weeks following lung resection. Fatigue was measured with EORTC QLQ C30 LC13. **Result:** From April 2013 to June 2016, 582 patients with operable NSCLC were screened for eligibility. With 119 patients randomized in the early rehabilitation group (ERG) (68 females, 51 males; median age 65), and 116 randomized to late rehabilitation group (LRG) (62 females, 54 males; median age 65) the recruitment rate was 52.6%. There was a non-significant decrease in VO_2peak in both ERG and LRG from baseline to 26 weeks and no significant difference between ERG and LRG (p=0.9269). There was a significant decrease from baseline to 14 weeks in both ERG (p=0.027) and LRG (p<0.001) and a significant difference between groups (p=0.0018). There was a non-significant increase from 14 weeks to 26 weeks in ERG (p=0.464) and a significant increase from 14 weeks to 26 weeks in LRG (p<0.001) and a significant difference between the two groups (p=0.0003). We found no significant differences in QOL but we found a significant difference between ERG and LRG from baseline to 14 weeks in fatigue level in favour of ERG. **Conclusion:** This is the first randomized controlled trial to investigate the effects of early vs. late initiated postoperative rehabilitation in patients with lung cancer. There is no difference in the commencement (early vs. late) of a postoperative exercise program for patients with lung cancer on exercise capacity. But to reduce fatigue patients should be recommended to initiate early exercise programs.

Keywords: post surgery rehabilitation, fatigue

OA05 CLINICAL TRIALS IN IO
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

OA05.01 EFFICACY/SAFETY OF ENTINOSTAT (ENT) AND PEMBROLIZUMAB (PEMBRO) IN NSCLC PATIENTS PREVIOUSLY TREATED WITH ANTI-PD-(L)1 THERAPY

M. Hellmann[1], P. Jänne[2], M. Opyrchal[3], N. Hafez[4], L. Raez[5], D. Gabrilovich[6], F. Wang[6], P. Ordentlich[7], S. Brouwer[7], S. Sankoh[7], E. Schmidt[8], M. Meyers[7], S. Ramalingam[9]

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Background: Treatment options are limited for lung cancer patients whose disease has progressed on anti-PD-(L)1 therapy. HDAC inhibitors may synergize with PD-(L)1 inhibition to overcome resistance. We report the interim results of a Phase 2 trial of entinostat (ENT), a class I selective histone deacetylase (HDAC) inhibitor, plus pembrolizumab (PEMBRO) in patients with NSCLC previously treated with anti-PD-(L)1 therapy. **Method:** ENCORE-601 is an open-label study evaluating the combination of ENT + PEMBRO in patients with recurrent or metastatic NSCLC and prior progression on anti-PD-1/PD-L1 therapy. Patients were eligible irrespective of histology or baseline PD-L1 expression. Patients were treated with ENT 5 mg PO weekly and PEMBRO 200 mg IV Q3W. The primary endpoint was ORR as assessed by irRECIST. Tumor biopsies and blood samples for immune correlates were taken prior to and during treatment in a subset of patients. A total of 70 patients will be enrolled. **Result:** Of 57 patients with anti-PD-(L)1 resistant/refractory NSCLC, the confirmed objective response rate with ENT + PEMBRO was 11% (6 of 57, 95% CI: 4-21%). Of 49 patients with post-baseline tumor measurements, 47% had at least some reduction in tumor. Anti-PD-(L)1 therapy was the most recent line of therapy in 38 of 57 patients, and the median time from last dose of prior anti-PD-(L)1 to study entry was 67 days. The median duration of response with ENT + PEMBRO was 5 months, with the longest over 14 months. Of the 6 responders, four were PD-L1 negative at study entry. Response was associated with a higher median baseline level of peripheral classical monocytes (CD14+CD16-HLA-DRhi) with 16.9% of total live PBMCs in responders (n=6) compared to 8.2% in non-responders (n=45). 5 patients (8.8%) experienced Grade 3/4 related irAEs (2 events each of pneumonitis and colitis, 1 event of hyperthyroidism). In addition, 19 patients (33.3%) experienced other Grade 3/4 related AEs with only fatigue, anemia, hypophosphatemia, and hyponatremia occurring in more than 1 patient. Additional correlative analyses to identify biomarkers of response, including whole exome sequencing and RNAseq, are in progress. **Conclusion:** ENT + PEMBRO demonstrated anti-tumor activity and acceptable safety in patients with NSCLC who have progressed on prior PD-(L)1 blockade. Ongoing analysis of immune correlates may identify strategies for effective patient selection.

Keywords: Entinostat, pembrolizumab, Monocytes

OA05 CLINICAL TRIALS IN IO
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

OA05.02 EPACADOSTAT PLUS PEMBROLIZUMAB IN PATIENTS WITH NON-SMALL CELL LUNG CANCER: PHASE 1/2 RESULTS FROM ECHO-202/KEYNOTE-037

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Background: Epacadostat (E) is a potent, highly selective inhibitor of the indoleamine 2, 3-dioxygenase 1 (IDO1) enzyme. ECHO-202/KEYNOTE-037 is an open-label, phase 1/2 study of E + pembrolizumab (P) in patients (pts) with advanced tumors (NCT02178722). We report updated efficacy and safety data for the phase 1 and 2 non-small cell lung cancer (NSCLC) cohort as of 8 Jan 2018 data cutoff. **Method:** Adult pts with prior platinum-based therapy (tx), no prior immune checkpoint inhibitors, and those intolerant to *EGFR*-targeted therapy were eligible. Pts could receive E (25, 50, 100, or 300 mg twice daily [BID]) + P (2 mg/kg or 200 mg every 3 weeks [Q3W]) during phase 1; maximum tolerated dose was not achieved. E (100 mg BID) + P (200 mg Q3W) tx doses were selected for phase 2 evaluation. Efficacy was assessed by RECIST v1.1 criteria. Programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) was evaluated using the 22C3 pharmDx assay. IDO1 status was measured by RNAScope. Safety was assessed in pts receiving ≥1 E + P dose. **Result:** A total of 70 pts (phase 1, n=12; phase 2, n=58) were evaluated. Median age was 63 years and 57% of pts were female. *EGFR* mutation status (+/-/not available) was 10%/71%/19%; *KRAS* status was 19%/26%/56%, respectively. Most pts had adenocarcinoma (70%), a history of smoking (76%), and 0–1 prior lines of tx (64%). PD-L1 TPS results were available in 55/70 pts; IDO1 status (+/-) in 41/70 pts. Overall, the objective response rate (ORR; complete response [CR] + partial response [PR]) and disease control rate (CR + PR + stable disease [SD]) were 29% (20/70; 17 PR) and 50% (35/70; 15 SD), respectively. ORR was 22% (2/9) in pts with TPS ≥50% and 0–1 prior tx; for pts with TPS <50% and 0–1 prior tx, ORR was 22% (5/23). ORR for pts with IDO1+ and IDO1- tumors were 24% (6/25) and 19% (3/16), respectively. At data cutoff, 10/20 responses were ongoing. Median progression-free survival (PFS) was 4.0 mo (90% confidence interval, 2.1–6.2 mo); PFS rates at 6, 12, and 18 mo were 43% (33%–53%), 31% (22%–40%), and 17% (10%–26%), respectively. Grade ≥3 treatment-related adverse events (TRAEs) were reported in 27% of pts; 3 pts discontinued due to TRAEs; and no TRAEs led to death. **Conclusion:** The E + P combination was generally well tolerated and associated with promising responses in pts with NSCLC.

Keywords: NSCLC, Epacadostat, pembrolizumab

OA05.03 SAFETY AND CLINICAL ACTIVITY OF ADOPTIVE CELL TRANSFER USING TUMOR INFILTRATING LYMPHOCYTES (TIL) COMBINED WITH NIVOLUMAB IN NSCLC

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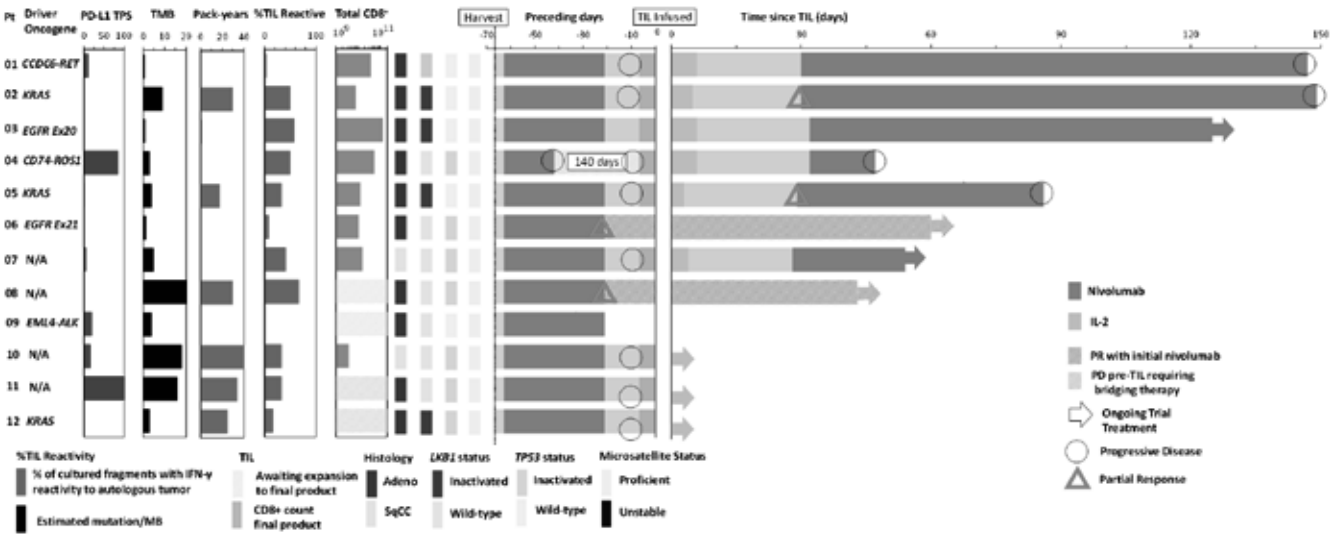
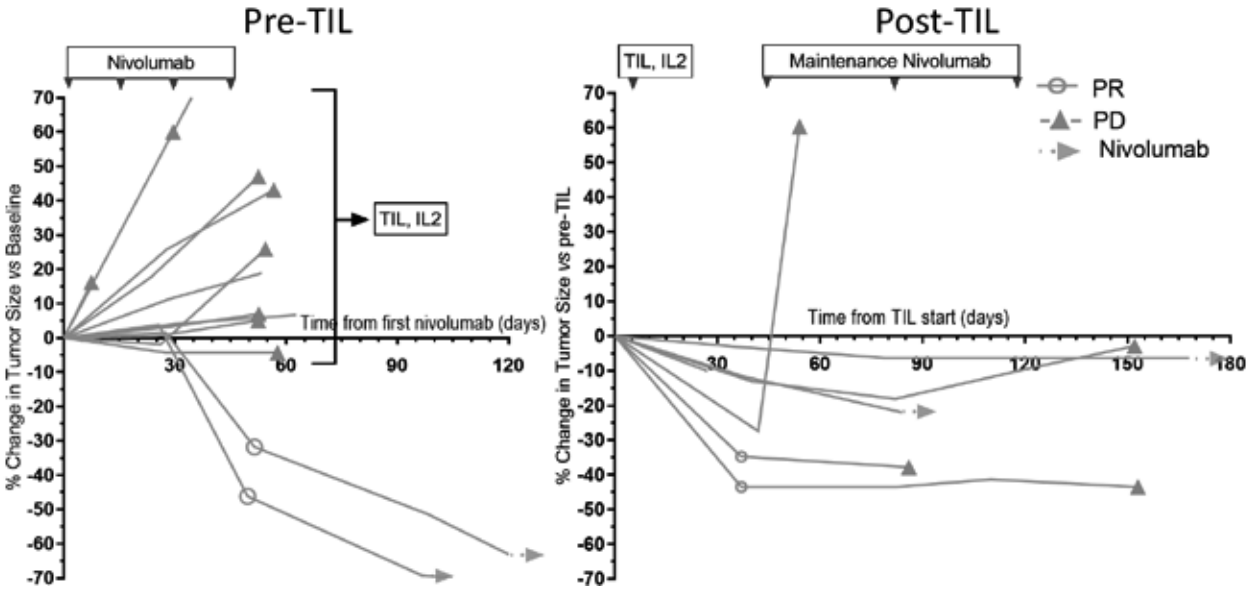
Background: Adoptive transfer of tumor infiltrating lymphocytes (TIL) can cause durable regression by recognition of neoantigens unique to the patient. NSCLC TIL has synergistic preclinical activity with nivolumab, and we hypothesized it may induce remissions in anti-PD1-refractory patients. We initiated a phase I trial with the primary objective to characterize the safety and preliminary activity of the combination. **Method:** Metastases from patients with Stage 4 NSCLC were resected, morselized, cultured, and tested for autologous reactivity. Reactive TIL fragments were pooled and cryopreserved. Patients received nivolumab over 8 weeks. Patients with progressive disease (PD) proceeded to lymphodepletion cyclophosphamide/fludarabine (Cy/Flu), TIL, and IL-2. Tumor whole exome sequencing, transcriptomics, and LC-MS/MS peptide sequencing was performed. TCR-Vß rearrangements were analyzed from tumor, TIL, and pre-/post-infusion peripheral lymphocytes. **Result:** Of 14 patients enrolled to date, 13 had successful *ex vivo* TIL expansion from resected metastases. TIL had high proliferative capacity, expanding to median 81 billion $CD3^+$ cells infused per patient (range 27–138 billion) and median 27% of fragments were autologously reactive (range 0-67%). Demographics: median age 54 (range 44-74), median TMB 4 mutations/MB (range 0.9–25), median PD-L1 proportion-score 0% (range 0–100%), and 4 had *LKB1* allelic inactivation. Predicted neoantigens correlated with variants on proteomic sequencing. Outcomes: 9 patients had confirmed PD on nivolumab, and proceeded to receive Cy/Flu/TIL/IL-2. No unexpected serious adverse reactions (SUSARs) were identified. Of these 9 patients, 7 had reduction in sum of target lesions at Day+28 CT scan (Figure 1). Peripheral lymphocytes expanded at Days 2-7 in the majority of patients. In patients tested to date, TIL clonotypes persisted through Day+100, and $CCR7^+CD95^+CD45RA^+$ stem cell-like memory (T_{SCM}) cells were increased at post-infusion timepoints.

Conclusion: Adoptive cell transfer with TIL and nivolumab for NSCLC had acceptable toxicity and preliminary activity in this ongoing trial.

Keywords: Tumor-specific neoantigen testing, Phase I NSCLC trials, Adoptive cell transfer of tumor infiltrating lymphocytes (TIL)





OA05.05 AVELUMAB VS DOCETAXEL FOR PREVIOUSLY TREATED ADVANCED NSCLC: PRIMARY ANALYSIS OF THE PHASE 3 JAVELIN LUNG 200 TRIAL

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Background: Avelumab is a human anti–PD-L1 IgG1 monoclonal antibody that is an approved treatment for metastatic Merkel cell carcinoma (various regions) and platinum-treated advanced urothelial carcinoma (US). We report findings from a global, open-label, phase 3 trial of avelumab vs docetaxel in patients with advanced NSCLC after platinum failure (NCT02395172). **Method:** Patients with stage IIIB/IV or recurrent NSCLC with disease progression after platinum doublet therapy were randomized 1:1 to avelumab 10 mg/kg Q2W or docetaxel 75 mg/m^2 Q3W, stratified by PD-L1 status (PD-L1+/PD-L1−) and histology (squamous/nonsquamous). The primary endpoint was overall survival (OS) in the PD-L1+ population (expression on ≥1% of tumor cells, assessed using the PD-L1 IHC 73-10 assay). **Result:** Between April 2015 and February 2017, 792 patients were randomized to receive avelumab or docetaxel, including 264 and 265 with PD-L1+ tumors, respectively; 0.8% vs 7.5% did not receive study treatment. Median follow-up in the avelumab and docetaxel arms was 18.9 and 17.8 months; 15.5% vs 1.5% remained on treatment at data cutoff (November 22, 2017). In the avelumab and docetaxel arms, 39.8% vs 47.5% received subsequent anticancer therapy after discontinuation, including checkpoint inhibitors in 5.7% vs 26.4%, respectively. In the PD-L1+ population, median OS in the avelumab and docetaxel arms was 11.4 vs 10.3 months (hazard ratio [HR], 0.90 [96% CI, 0.72-1.12]; *P*=0.1627, 1-sided). Pre-planned exploratory analyses based on higher PD-L1 cutoffs showed increased OS with avelumab vs docetaxel, including PD-L1-high (≥80% cutoff, 29% of patients; 17.1 vs 9.3 months; HR, 0.59 [95% CI, 0.42-0.83]; *P*=.0022, 2-sided) and PD-L1-medium/high (≥50% cutoff, 40% of patients; 13.6 vs 9.2 months; HR, 0.67 [95% CI, 0.51-0.89]; *P*=0.0052, 2-sided) subgroups. In the PD-L1+ population (≥1% cutoff), ORR was 18.9% vs 11.7% (odds ratio, 1.76 [95% CI, 1.08-2.86]; *P*=0.0105, 1-sided); median duration of response was not reached with avelumab (95% CI, 9.9-not estimable [NE]) vs 6.9 months with docetaxel (95% CI, 3.5-NE). Overall rates of treatment-related adverse events (AEs) were lower with avelumab than docetaxel, including all grades (63.9% vs 85.8%) and grade ≥3 (9.9% vs 49.3%). Immune-related AEs occurred in 16.5% of avelumab-treated patients (grade ≥3 in 2.8%). **Conclusion:** Avelumab showed increasing clinical activity in patients who had platinum-treated NSCLC with higher tumor PD-L1 expression; however, the trial did not meet its primary objective of improving OS vs docetaxel in PD-L1+ tumors (≥1% cutoff). OS findings may have been confounded by subsequent checkpoint inhibitor therapy in the docetaxel arm.

Keywords: Phase 3, avelumab, docetaxel

OA05.06 CHECKMATE 227: PATIENT-REPORTED OUTCOMES OF FIRST-LINE NIVOLUMAB + IPILIMUMAB IN HIGH TUMOR MUTATIONAL BURDEN ADVANCED NSCLC

J. Brahmer[1], M. Schenker[2], K.H. Lee[3], M. Provencio[4], M. Nishio[5], K. Lesniewski-Kmak[6], R. Sangha[7], S. Ahmed[8], J. Raimbourg[9], K. Feeney[10], R. Corre[11], F. Franke[12], E. Richardet[13], J. Penrod[14], Y. Yuan[14], F. Nathan[14], P. Bhagavatheeswaran[14], M. De Rosa[15], F. Taylor[15], R. Lawrance[16], M. Reck[17]

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Background: The randomized, open-label, multipart phase 3 study CheckMate 227 (NCT02477826) demonstrated a significant progression-free survival benefit (co-primary endpoint) with first-line nivolumab+ipilimumab versus histology-based, platinum-doublet chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) and high tumor mutational burden (TMB; ≥10 mutations/Mb). Patient-reported outcomes (PROs) for this population within CheckMate 227 are presented. **Method:** Eligible chemotherapy-naïve patients had stage IV or recurrent NSCLC, ECOG performance status 0–1, and no known sensitizing *EGFR/ALK* alterations. PROs were assessed as an exploratory endpoint; this analysis included patients with high TMB randomized to nivolumab+ipilimumab or chemotherapy; specific outcomes included proportion of patients with disease-related symptom deterioration by 12 weeks and time to deterioration in symptoms (by Lung Cancer Symptom Scale [LCSS] Average Symptom Burden Index [ASBI]), and assessment of quality of life and overall health status (by EuroQoL-5 Dimension [EQ-5D] utility index [UI] and visual analog scale [VAS]). PROs were evaluated each cycle (Q2W, nivolumab+ipilimumab; Q3W, chemotherapy) for the first 6 months, every 6 weeks thereafter during treatment, and at follow-up visits 1/2. EQ-5D was also assessed during survival follow-up. **Result:** PRO completion rates were ~90% at baseline and >80% for nearly all on-treatment assessments. Among patients with high TMB, fewer patients in the nivolumab+ipilimumab (n=139) versus chemotherapy (n=160) groups reported symptom deterioration by week 12, irrespective of whether they were still on therapy or had discontinued (22.3% versus 35.0%; absolute risk reduction: 12.7% [95% CI: 2.4–22.5]). Time to first deterioration (TTD) using common assessment time points (on/off treatment) was delayed with nivolumab+ipilimumab versus chemotherapy for the LCSS ASBI (hazard ratio [HR]: 0.40; 95% CI: 0.26–0.63) and 3-Item Global Index (3-IGI; HR: 0.56; 95% CI: 0.38–0.82). The estimated benefit in TTD generally favored nivolumab+ipilimumab for individual symptoms in the ASBI and each item in the 3-IGI (HRs: 0.48–0.74), except for hemoptysis (HR: 1.20), which exhibited very low burden; an advantage for nivolumab+ipilimumab was also seen in the EQ-5D VAS (HR: 0.62; 95% CI: 0.42–0.92) and UI (HR: 0.50; 95% CI: 0.34–0.73). Mean changes from baseline with nivolumab+ipilimumab showed early and clinically meaningful improvements in LCSS ASBI/3-IGI and EQ-5D VAS/UI; for patients treated with chemotherapy, symptoms and quality of life remained stable (LCSS ASBI/3-IGI, EQ-5D UI) or improved following completion of chemotherapy (EQ-5D VAS). **Conclusion:** Nivolumab+ipilimumab demonstrated early and sustained improvements in health-related quality of life versus chemotherapy in patients with advanced NSCLC and high TMB.

Keywords: NSCLC, first-line nivolumab, Patient-reported outcomes

OA05.07 IMPOWER132: PFS AND SAFETY RESULTS WITH 1L ATEZOLIZUMAB + CARBOPLATIN/CISPLATIN + PEMETREXED IN STAGE IV NON-SQUAMOUS NSCLC

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This abstract is under embargo until September 24 at 13:30 Eastern Time.

OA06.01 CASE-SERIES STUDY IN EVER- AND NEVER-SMOKING FEMALES AND MALES WITH NSCLC: EXPOSURES, TUMOR FACTORS, BIOLOGY AND SURVIVAL (SWOG S0424)

K. Albain[1], A. Darke[2], P. Mack[3], M. Redman[2], T. Cheng[4], J. Moon[2], W. Holland[3], A. Borczuk[5], C. Chay[6], P. Morris[7], E. Vallieres[8], R. Kratzke[9], J. Molina[10], J. Kolesar[11], Y. Chen[12], R. Macrae[13], S. Matsumoto[14], M. Reid[15], G. Zirpoli[16], W. Davis[15], R. Ondracek[15], W. Bshara[15], A. Omilian[15], D. Gandara[3], K. Kelly[3], R. Santella[17], C. Ambrosone[15]

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This abstract is under embargo until September 24 at 13:30 Eastern Time.

OA06 EARLY STAGE LUNG CANCER: OUTCOMES AND INTERVENTIONS
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

OA06.02 VIDEO-ASSISTED THORACOSCOPIC SURGERY VS. THORACOTOMY FOR NON-SMALL CELL LUNG CANCER: ONCOLOGIC OUTCOME OF A RANDOMIZED TRIAL

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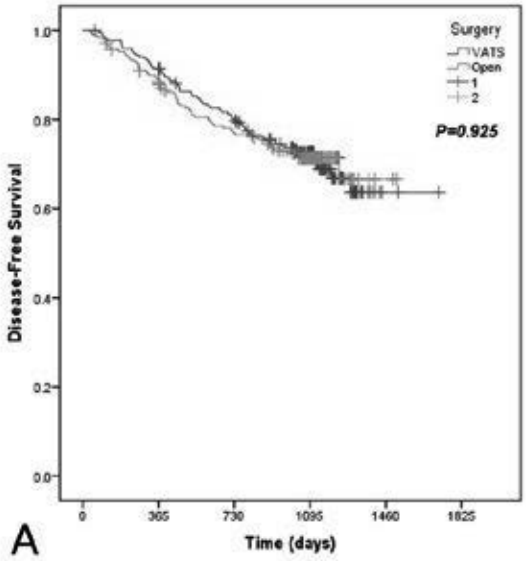
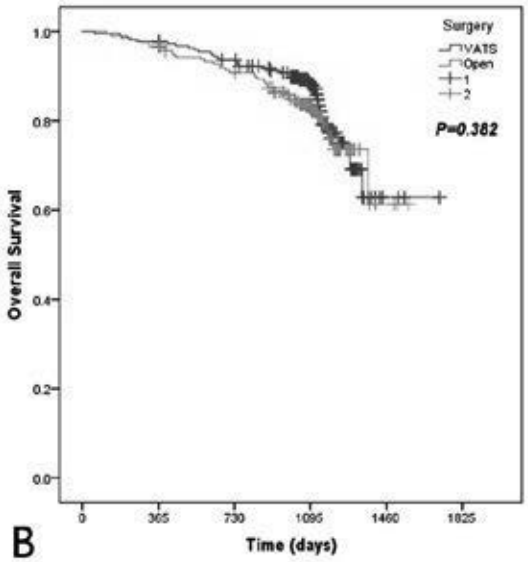
Background: Video-assisted thoracoscopic surgery (VATS) has been widely used in the treatment of early-stage non–small cell lung cancer (NSCLC). However, there has not been a robust randomized control trial (RCT) to conclude VATS has similar oncologic efficacy to open surgery. Therefore, a large multicenter RCT in China was designed and initialed in order to verify the role of VATS. **Method:** A non-inferiority phase 3 RCT was undertaken at five thoracic surgical centers in China. Patients aged 18-75 years who were diagnosed of clinically early-stage NSCLCs were randomized in a 1:1 ratio into VATS and thoracotomy groups. Radical lobectomy plus hilar and mediastinal lymph node dissection was the standard surgical intervention as per protocol. The long-term oncologic outcomes including 3-year locoregional recurrence rate, overall survival (OS) and disease-free survival (DFS) would be analyzed and reported here. This study is registered with the ClinicalTrials.gov, number NCT01102517. **Result:** A total of 508 patients were recruited in the trial between January 2008 and March 2014. And 433 patients were eligible for final analysis (222 cases in VATS group and 211 cases in thoracotomy group). At 3 years, the locoregional recurrence rates were 4.5% in VATS group and 5.7% in thoracotomy group respectively (P=0.664). Patients who received VATS procedures had a similar DFS rate to those who underwent open surgery (66% versus 69%, P=0.925; Fig 1A). Again, the 3-year OS rates were of no significant difference between VATS and thoracotomy groups (74% versus 73%, P=0.382; Fig 1B).





Conclusion: VATS in the treatment of clinically early-stage NSCLCs was associated with equivalent oncologic efficacy when compared to open surgery.

Keywords: Video-assisted thoracoscopic surgery, non-small cell lung cancer, thoracotomy

OA06 EARLY STAGE LUNG CANCER: OUTCOMES AND INTERVENTIONS
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

OA06.03 SUBLOBAR RESECTION IS EQUIVALENT TO LOBECTOMY FOR SCREEN DETECTED LUNG CANCER

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Background: Despite the lack of survival data from modern, ongoing randomized clinical trials (CALGB 140503, JCOG 0802), sublobar resection (SLR) is increasingly offered to patients with small, peripheral lung cancers. In particular, SLR may be an attractive surgical strategy for screen detected lung cancers, some of which may be less biologically aggressive than cancers detected by other means. Utilizing prospective data collected from patients undergoing surgery in the National Lung Screening Trial (NLST), we sought to determine whether the extent of resection affected survival for patients with screen detected lung cancer. **Method:** The NLST database was queried for patients who underwent surgical resection for confirmed lung cancer. Numerical variables were compared using Mann-Whitney U test. Categorical variables were

compared using Chi-squared test. Propensity score matching analysis (lobectomy versus sublobar resection) controlling for age, gender, race, tumor size, and stage was performed (nearest neighbor, 1:1, matching with no replacement, caliper 0.2). Overall survival (OS) and cancer specific survival (CSS) were compared using log rank test in Kaplan Meier curves. **Result:** Among 1,029 patients who underwent resection for lung cancer, we identified 821 patients (80%) who had lobectomy and 166 patients (16%) who had SLR, among whom the majority (n=114, 69%) had wedge resection. Patients who underwent SLR were older (64 vs. 61, p=0.66), more likely to be female (53% vs. 41%, p=0.004), had smaller tumors (2 cm vs. 4.5 cm, p<0.001), and were more likely to be stage I (80% vs. 75%, p=0.001). At five years, for stage I patients undergoing SLR (n=129) there was no difference in OS (77% vs. 77%, p=0.889) or CSS (83% vs. 83%, p=0.959) compared to patients undergoing lobectomy (n=613). In order to more accurately compare surgical outcomes, we propensity matched 134 patients from each group undergoing SLR and lobectomy. Among these matched groups, there were no differences in age, gender, histology, or stage. Postoperatively, patients undergoing SLR had less total complications (22% vs. 32%, p=0.05) than those undergoing lobectomy (HR 0.59, CI 0.38-0.94). In matched patients at five years, there was no difference in OS (67% vs. 70%, p=0.629) or CSS (74% vs. 74%, p=0.980) for patients undergoing SLR compared to those undergoing lobectomy. **Conclusion:** For patients with screen detected lung cancer, SLR confers equivalent survival to lobectomy. By decreasing perioperative complications and potentially preserving lung function, SLR may provide distinct advantages in a screen detected lung cancer patient cohort.

Keywords: surgery, sublobar resection, screening

OA06 EARLY STAGE LUNG CANCER: OUTCOMES AND INTERVENTIONS
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OA06.05 DO SBRT PLANNING AND DELIVERY FACTORS INFLUENCE LOCAL CONTROL FOR EARLY STAGE NON-SMALL CELL LUNG CANCER (E-NSCLC)?

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Background: Stereotactic Body Radiation (SBRT) utilizes a variety of techniques to deliver very high-dose radiation to moving targets in the lung. We investigated the impact of dose-delivery factors on local failure (LF) by surveying our 12 year experience with e-NSCLC from our prospective database. **Method:** Curative SBRT was administered to 1,085 patients (pts) between 2005 and 2016 and planned with either pencil beam (PB) or collapsed cone convolution (CCC) dose calculation algorithms (DCA), using open (dynamic arcs) or modulated beams (IMRT or VMAT), immobilized by abdominal compression or automatic breathing control (ABC), and treated with/without available CBCT (aligned to external fiducials and KV x-rays to bone if no CBCT, PTV margins were not altered based on availability of CBCT). We limited our analysis to standard fractionation regimens, [60 Gy/3, 48 Gy/4, 50 Gy/5, & 30-34 Gy/1) chosen per the treating physician in a risk-adapted approach relative to tumor size and location. The intreaction of technical variables with known patient and tumor factors on LF was analyzed using Fine and Gray univariate regression, with significant predictors selected for a forward step-wise multivariate regression model. **Result:** At mean follow-up time of 25.6 months the cumulative incidence of LF at 1, 2, & 5 years was 3.0, 8.3, and 9.8% respectively. Overall survival (1, 2, 5 years) was 83, 62, & 28%. Univariate correlates with LF were PB TPS (HR 2.87, p=0.0004), modulated beam (HR 2.3, p=0.005), lack of CBCT (HR 2.69, p=0.0004), SBRT dose relative to 60 Gy/3 (HR 5.2, p=0.0001 for 4-5 fx; HR 2.7, p=0.051 for 1 fx), tumor size (HR 1.2 per cm, p=0.0009), PET SUV (HR 1.04 per SUV, p=0.0039), and squamous histology (HR 1.8, p=0.0051). Immobilization with ABC (n=96) versus abdominal compression (n=989) did not correlate with LF (p=0.99). On multivariate analysis PET SUV, modulated beam, and use of CBCT were no longer significant correlates with LF, while TPS (HR 2.62, p=0.0019), SBRT dose (HR 4.1, p=0.0009 for 4-5 fx relative to 60 Gy/3) & HR 2.9, p=0.039 for 1 fx versus 60 Gy/3), tumor size (HR 1.2 per cm, p=0.042) and squamous histology (HR 1.7, p=0.027) remained statistically significant. **Conclusion:** While the use of PB versus CCC DCA was associated with higher rates of LF after SBRT, the use of abdominal compression vs ABC (univariate), open vs modulated beam, and CBCT vs bony alignment (multivariate) were not correlated with higher rates of LF after SBRT in e-NSCLC.

Keywords: local failure, SBRT, Radiotherapy planning

OA06 EARLY STAGE LUNG CANCER: OUTCOMES AND INTERVENTIONS
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OA06.06 MISSILE-NSCLC: A PHASE II TRIAL MEASURING THE INTEGRATION OF STEREOTACTIC RADIOTHERAPY PLUS SURGERY IN EARLY-STAGE NON-SMALL CELL LUNG CANCER

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Background: Stereotactic Ablative Radiotherapy (SABR) has emerged as a standard treatment option in patients with medically inoperable early-stage non-small cell lung cancer (NSCLC), yet the pathologic complete response (pCR) rate after SABR is unknown. Neoadjuvant SABR in operable patients has been proposed as a mechanism of improving local control and inducing anti-tumor immune activity. **Method:** This phase II study (NCT02136355) enrolled patients with biopsy-proven clinical T1-2N0M0 NSCLC who were candidates for surgical resection. Patients underwent neoadjuvant SABR using a risk-adapted fractionation of 54 Gy/3 fractions, 55 Gy/5 or 60 Gy/8. Surgical resection took place 10 weeks after SABR. Patients also underwent dynamic FDG-PET and dynamic contrast-enhanced CT prior to SABR and approximately 2 weeks prior to surgery. The primary endpoint was the pCR rate, and secondary endpoints included local, regional, and distant recurrence, quality of life using the FACT Trial Outcome Index (TOI), and toxicity. **Result:** Accrual began in Sept 2014 and completed in August 2017 with 40 patients enrolled. Median age was 69 years (range 44–83 years), and 58% were female. Thirty-one patients (78%) had T1 tumors and 9 (23%) had T2 tumors; histology was adenocarcinoma (n=26; 65%), squamous cell (n=13; 33%) and NSCLC not otherwise specified (n=1; 3%). Baseline FEV_1 was median 73% percent predicted (range 50%–117%). Nine patients (23%) received the 3-fraction regimen, 21 (53%) received 5 fractions and 10 (25%) received 8 fractions. Thirty-five patients underwent surgery and were evaluable for the primary endpoint. The pCR rate was 60% (95% CI 44%–76%). 30-day and 90-day post-surgical mortality rates were both 0%. Eighteen percent of patients had grade 3 or 4 toxicities, most commonly pulmonary in nature (Grade 4: atelectasis and respiratory failure [n=1]; Grade 3: pneumonia/pneumonitis [n=2]; bronchopleural fistula [n=1]). In the patients receiving surgery, 2-year outcomes were: overall survival 77%, local control 100%, regional control 53% and distant control 76%. There were no significant changes in FACT-TOI score within the first year of follow-up. **Conclusion:** The pCR rate after SABR for T1 and T2 NSCLC was 60%. Toxicity of the combined approach appears favorable, compared to historical series of surgery alone, and there was no perioperative mortality. Larger studies are needed to determine the clinical role of this combined treatment approach.

Keywords: Early-stage lung cancer, stereotactic radiation, Surgery

OA06 EARLY STAGE LUNG CANCER: OUTCOMES AND INTERVENTIONS
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

OA06.07 PREDICTORS AND CONSEQUENCES OF REFUSING SURGERY FOR CLINICAL STAGE I NSCLC: A NATIONAL CANCER DATABASE ANALYSIS

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Background: Given perceived morbidity of lung cancer surgery, patients may instead pursue other treatment options, particularly in the current era of shared decision-making. We sought to determine predictors of refusal of surgery for clinical stage I non-small cell lung cancer (NSCLC) patients and to determine associated outcomes. **Method:** The NCDB (2004-2014) was queried for clinical stage I NSCLC patients who underwent or were recommended to undergo surgery. A unique field in the NCDB allows identification of those patients who were recommended to have surgery, but refused. We only included cases in which surgery was refused "by the patient, patient's family member or guardian". We excluded patients with multiple primary tumors, unknown treatment modality/sequence, those who did not undergo recommended surgery for unknown reasons, and those initially not recommended to have surgery. Survival was compared using log rank test in Kaplan Meier curves. Logistic regression was performed to identify predictors of refusing surgery. **Result:** We identified 118,0217 patients undergoing surgery and 3,210 (2.6%) who were recommended, but refused surgery. By multivariate analysis older age (HR=1.09, CI=1.08-1.09), non-white race (HR=2.18, CI=1.97-2.42), low income (HR=1.28,CI=1.16-1.41),

lack of insurance (HR=2.62,CI=1.89-3.62), squamous histology (HR=1.40,CI=1.29-1.53), and larger tumor size (HR=1.57,CI=1.42-1.73) predicted refusal of surgery.Patients refusing surgery were treated with chemoradiation (n=249, 7.8%), radiation or chemotherapy alone (n=1,568, 48.8%), or no treatment (n=1393, 43.4%). Median survival was worse for patients who refused any treatment versus those who received other treatment modalities (19.8 vs 42.2 months, P<0.001). Among those patients refusing surgery who were treated with radiation, we identified 758 patients (23.6%) who received stereotactic body radiation therapy (SBRT). The proportion of patients who refused surgery and received SBRT increased over time, from 3.8% in 2004-2006, to 17% in 2007-2009, to 31.1% in 2010-2012, and to 37.9% in 2013-2014. Patients receiving SBRT had improved survival compared to other patients refusing surgery (47.9 vs. 25.2 months, p<0.001), although survival in the SBRT group was inferior to patients undergoing surgery as recommended (47.9 vs. 82.8 months, p<0.001). **Conclusion:** Although patients may be reluctant to undergo surgery for early stage NSCLC, refusal of surgery when recommended comes at the expense of decreased survival. Socioeconomic factors may be associated with refusal of surgery. The use of SBRT is an effective and increasingly used alternative in these patients, which improves survival compared to no treatment but which is still not equivalent to surgery in this unmatched, retrospective cohort.

Keywords: Refusal of surgery, SBRT, Lung cancer survival

OA07 OLIGOMETASTASIS: WHAT SHOULD BE THE STATE-OF-THE-ART?
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

OA07.01 PHASE II STUDY OF PEMBROLIZUMAB FOR OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) FOLLOWING COMPLETION OF LOCALLY ABLATIVE THERAPY (LAT)

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Background: Patients (pts) with oligometastatic NSCLC may benefit from LAT (e.g., surgery, stereotactic radiation (SRT)). It is unclear if systemic therapy can provide benefit after LAT. We completed a Phase II study evaluating the efficacy of pembrolizumab after LAT, hypothesizing that immunotherapy would be effective in the setting of a minimal disease burden. **Method:** Eligibility stipulated oligometastatic NSCLC (up to 4 sites) with completion of LAT to all known sites of disease. Within 4-12 weeks of completing LAT, pts began pembrolizumab 200 mg every 21 days for 6 mos, with a provision to continue for up to a year in the absence of progression (PD) or toxicity. Progression-free survival (PFS) and overall survival (OS) were measured from the start of LAT. A sample size of 42 pts would provide 80% power for a test at 5% 1-sided type I error to increase PFS to >=10 mos compared to a historical control PFS of 6.6 mo. **Result:** Since January 2015, 45 pts have been enrolled. Median age is 64 years; 53% male; 89% Caucasian; 89% current and former smokers. Most common metastatic sites are lung (16 pts), brain (18), liver (9), and bone (9). LAT included surgery (30 pts), SRT (30), and chemoradiotherapy (23). Adverse events have been mostly mild. There were two episodes of Grade 3 pneumonitis, two episodes of Grade 3 colitis, and one episode of Grade 3 adrenal insufficiency. Median follow-up from start of LAT is 20.1 mos. To date, 19 pts have had PD or died. Median PFS was 25 mos. PFS rates (+ SE) at 12, 18 and 24 mos are 72%+7%, 54%+9% and 50%+9%, with 10 free of PD/death beyond 24 mos. To date, 10 pts have died. Median OS has not yet been reached. OS rates (+ SE) at 12, 18 and 24 mos are 91%+4%, 82%+7% and 73%+8%, with 14 pts alive beyond 24 mos. Median PFS was 16.9 mos for pts with metachronous disease (n=33), not yet reached for pts with synchronous disease (n=12). Median OS has not yet been reached in either group. **Conclusion:** Pembrolizumab after LAT for oligometastatic NSCLC is feasible and well tolerated. PFS appears quite favorable, preliminarily Final analysis will be performed September 2018. Updated survival estimates and biomarker data will be presented.

Keywords: Oligometastatic, pembrolizumab, locally ablative therapy

OA07 OLIGOMETASTASIS: WHAT SHOULD BE THE STATE-OF-THE-ART?
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

OA07.02 ATOM: A PHASE II STUDY TO ASSESS EFFICACY OF PREEMPTIVE LOCAL ABLATIVE THERAPY TO RESIDUAL OLIGOMETASTASES AFTER EGFR TKI

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Background: NSCLC patients (Pts) harboring EGFR mutation invariably develop resistance to EGFR TKI at a median time of 9-13 months. Prior studies have showed that local ablative therapy (LAT) upon oligoprogression (OP) can extend the duration of TKI therapy effectively. We postulate that residual positron emission tomography (PET) avid lesions after initial treatment of EGFR TKI may harbor resistant clones and preemptive LAT may improve progression free survival (PFS). **Method:** This single-arm phase II study aims to determine the efficacy of preemptive LAT to residual metabolic active oligo-metastases after initial TKI. Pts with stage IIIB/ IV EGFR M+ NSCLC who possessed oligoresidual (OR) disease (≤ 4 PET-avid lesions with SUV ≥2.5) after a 3-mth TKI therapy were enrolled. Those with initial PR underwent screening PET-CT. PET avid ORs would be treated by LAT, either by stereotactic ablative radiotherapy (SABR) or surgery per clinicians' discretion. TKI was continued after LAT until it was considered ineffective. PET-CT was done on the 3rd and 12th month post-LAT (or at progression), apart from regular imaging. Further LAT was allowed if OP was detected. Primary endpoint was PFS rate at 1 year from enrollment. Overall survival (OS), treatment safety and comparison with screen failure cohorts were secondary endpoints. **Result:** 18 Pts were enrolled from 2014-17. Recruitment was stopped before the planned number (n = 34) due to slow accrual. Two were not analyzed due to consent withdrawal and significant protocol violation. Median follow up was 28.7 mth. Among the 16 analyzed Pts, the 1 year PFS rate (i.e. 15 mth post TKI) was 62.5%. OS data was not yet mature. All LAT were done by SABR, and none experienced ≥grade 3 SABR related toxicities. Compared with screen failure cohort (n = 43, metabolic CR or PR with residual disease not fulfilling LAT criteria), the 1 year and 2 year PFS favored treatment arm, though statistically not significant (62.5% vs 47.1%, 30.0% vs 7.9%; p = 0.15). **Conclusion:** The 1-yr PFS rate is encouraging. A trend of improved long term PFS is noted in Pts receiving preemptive LAT to residual PET-avid OM after initial TKI compared with Pts without LAT. Further studies are warranted. *Clinical Trial information: NCT01941654*

Keywords: Oligoresidual disease, Stereotactic ablative radiotherapy

OA07 OLIGOMETASTASIS: WHAT SHOULD BE THE STATE-OF-THE-ART?
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

OA07.03 ADDITION OF LOCAL THERAPY TO EGFR TKI SHOWED SURVIVAL BENEFIT IN EGFR-MUTANT NSCLC PTS WITH OLIGOMETASTATIC OR OLIGOPROGRESSIVE LIVER METASTASES

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Background: Our previous study demonstrated that EGFR-mutant NSCLC patients (Pts) with liver metastases (LM) showed poor response to EGFR-TKIs than those without LM, suggesting that additional treatment is warranted. Recently, several clinical studies indicated that local therapy (e.g. surgery and radiotherapy) could significantly improve progression-free survival (PFS) in NSCLC Pts with oligometastatic or oligoprogressive disease. This study aimed to investigate whether addition of local therapy to EGFR-TKIs could provide a better survival benefit than TKIs alone in EGFR-mutant NSCLC Pts with oligometastatic or oligoprogressive LM. **Method:** Pts with EGFR-mutant NSCLC and LM were enrolled. Oligometastatic LM was defined as ≤ 5 sites in liver without extrahepatic metastases at initial diagnosis. Oligoprogressive LM was defined as ≤ 5 sites in liver without extrahepatic metastases during TKIs therapy. For oligoprogressive cohort, PFS1 was calculated from time of initiation of TKI therapy to first RECIST 1.1 defined progress disease (PD) or death. PFS2 was calculated from time of initiation of TKI therapy to off-TKI PD. **Result:**

Totally, 135 cases with EGFR-mutant NSCLC and LM were eligible (64 with oligometastatic LM and 71 with oligoprogressive LM). In oligometastatic cohort, 20 Pts received EGFR-TKIs (E) and 23 Pts received EGFR-TKIs plus local therapy (E+LT) as first-line treatment. The addition of local therapy showed a significantly longer PFS (12.9 vs. 7.9 m, P = 0.041) and OS (36.8 vs. 21.3 m, P = 0.034) than EGFR-TKIs alone. In oligoprogressive cohort, 24 Pts received continuation of EGFR-TKIs plus local therapy (cE+LT) and 25 Pts received switch therapy (ST). Median PFS1 was similar. Median PFS2 (13.9 vs. 9.2 m, P = 0.007) and OS (28.3 vs. 17.1 m, P = 0.011) was significantly longer in cE+LT group than in ST group. Multivariate analysis revealed that addition of local therapy was independently associated with prolonged PFS (HR = 0.435, P = 0.028) and OS (HR = 0.434, P = 0.071) in Pts with oligometastatic LM. Distant metastatic sites were the major pattern of failure in EGFR-TKI plus local therapy group while locoregional recurrence including primary lesions and LM was the major reason in TKI alone group. **Conclusion:** The current study suggested that EGFR-TKIs plus local therapy demonstrated the prolonged survival benefit than EGFR-TKIs alone in EGFR-mutant NSCLC Pts with oligometastatic or oligoprogressive LM. These findings suggest that local therapy should be further explored in large-scale, strictly designed clinical trials as a standard treatment option in this clinical scenario.

Keywords: Liver Metastasis, EGFR mutation, non-small cell lung cancer

OA07.05 LOCAL ABLATIVE THERAPY IMPROVES SURVIVAL IN PATIENTS WITH SYNCHRONOUS OLIGOMETASTATIC NSCLC HARBORING EGFR MUTATION TREATED WITH EGFR-TKIS

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Background: Non-small-cell lung cancer (NSCLC) is the most common cause of cancer deaths worldwide. Patients with oligometastatic disease can represent an indolent phenotype that could benefit from local ablative therapy(LAT). Howerver, whether first-line continual EGFR-TKIplus LAT could have potential benefit in EGFR-mutant NSCLC patients with oligometastatic disease remains undetermined. **Method:** Patients with stage IV EGFR-mutant NSCLC and no more than five metastases at diagnosis in 2 months were enrolled. All patients were treated with first-line EGFR-TKIs. Consolidation LAT included radiotherapy or surgery. Overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan-Meier curves. **Result:** From October 2010 to May 2016, 145 patients were enrolled, including 51 (35.2%) who received consolidation LAT to all oligometastatic sites (All-LAT group), 55 (37.9%) who received consolidation LAT to either primary tumor or oligometastatic sites (Part-LAT group), and 39 (26.9%) who did not receive any consolidation LAT (Non-LAT group). The median PFS in All-LAT, Part-LAT, and None-LAT group were 20.6 months, 15.6 months, and 13.9 months, respectively (P<0.001). The median OS in All-LAT, Part-LAT, and None-LAT group were 40.9 months, 34.1 months, and 30.8 months, respectively (P<0.001). The difference was significant between All-LAT group and Part-LAT or Non-LAT group but was not significant between Part-LAT and Non-LAT group. The median OS was significantly improved with consolidation LAT for primary tumor (40.5 versus 31.5 months, P<0.001), brain metastases (38.2 versus 29.2 months, P=0.002), adrenal metastases (37.1 versus 29.2 months, P =0.032). Adverse events (Grade≥3) due to radiotherapy included pneumonitis (7.7%) and esophagitis (16.9%). **Conclusion:** The current study demonstrated that consolidation LAT to all sites was a feasible option among patients with EGFR-mutant oligometastatic NSCLC during first-line EGFR-TKI treatment, with significantly improved PFS and OS compared with consolidation LAT to partial sites or observation alone.

Keywords: EGFR-TKI, Local ablative therapy, synchronous oligometastatic NSCLC

OA07.06 EFFICACY OF LOCAL CONSOLIDATIVE THERAPY FOR OLIGOMETASTATIC LUNG ADENOCARCINOMA PATIENTS HARBORING EGFR MUTATIONS.

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Background: For oligometastatic lung adenocarcinoma patients with sensitive EGFR mutations, the role of local consolidative therapy (LCT) remains debatable. The purpose of this study was to investigate the efficacy of LCT in these patients. **Method:** Advanced stage patients with oligometastatic lung adenocarcinoma who harboring EGFR mutation were identified at the Shanghai Chest Hospital from 2010 to 2016. **Result:** A total of 253 patients (149 patients who received LCT plus EGFR-TKIs [combination group] and 104 patients who received EGFR-TKIs [TKI monotherapy group] were included. The median PFS time in the combination group was 14 months versus 9 months in the TKI monotherapy group (HR=0.57, 95% [CI] 0.44, 0.79, p<0.01, Figure 1 A). The median OS time in the combination group was 33 months versus 20 months in the TKI monotherapy group (HR=0.56, 95% [CI] 0.41, 0.75, p<0.01, Figure 1D). Survival benefit was independent of EGFR mutation type (PFS: 19del, p=0.02, Figure 1B; 21L858R, p<0.01, Figure 1C; OS: 19del, p=0.0189, Figure 1E; 21L858R, p<0.01, Figure 1F) and metastatic sites.

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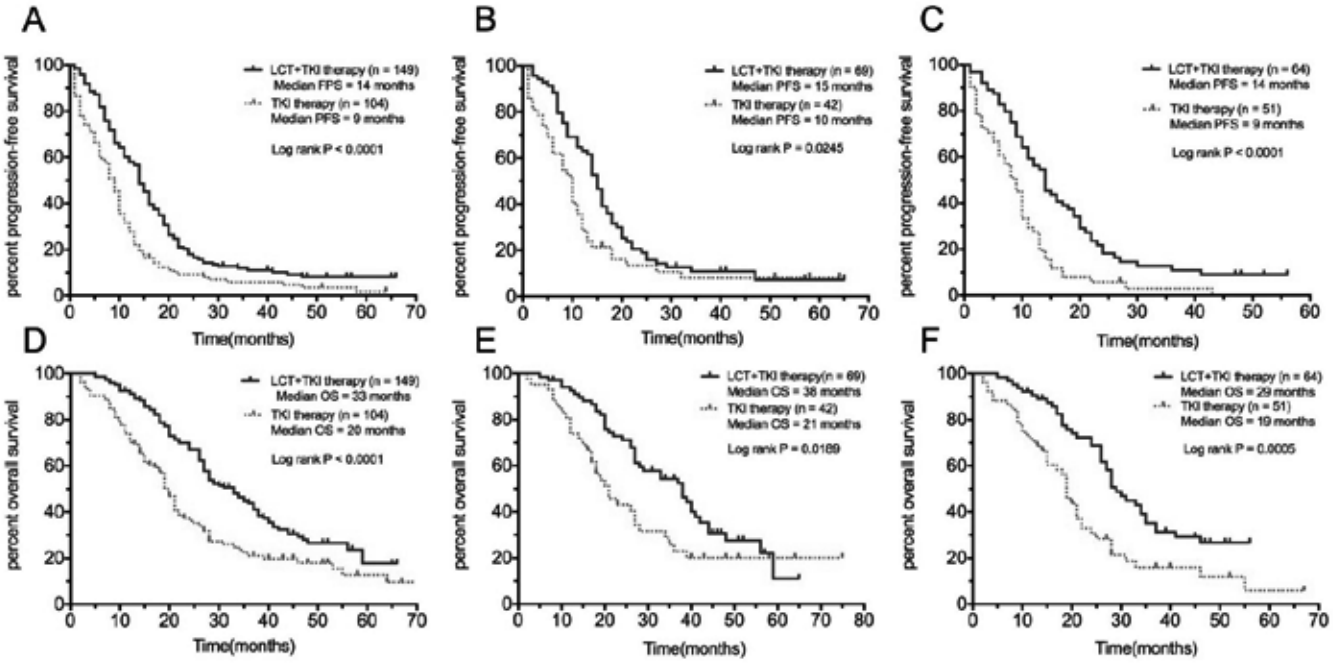

Conclusion: LCT combined with TKI therapy was feasible and significantly improved PFS and OS among oligometastatic lung adenocarcinoma patients with sensitive EGFR mutations, and thus, should be considered as an important medical treatment during clinical management.

Keywords: Oligometastasis, Adenocarcinoma, local consolidative therapy

OA07 OLIGOMETASTASIS: WHAT SHOULD BE THE STATE-OF-THE-ART?
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

OA07.07 PFS AND OS BEYOND 5 YEARS OF NSCLC PATIENTS WITH SYNCHRONOUS OLIGOMETASTASES TREATED IN A PROSPECTIVE PHASE II TRIAL (NCT 01282450)

D. De Ruysscher[1], R. Wanders[1], L. Hendriks[2], A. Van Baardwijk[1], B. Reymen[1], R. Houben[1], G. Bootsma[3], C. Pitz[4], A. Dingemans[5]

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Background: There is increasing interest in the treatment of synchronous oligometastases of NSCLC. Two randomized studies demonstrated an increased PFS by adding a radical local treatment to systemic therapy in responding patients, but long-term data are lacking. We previously reported a median PFS of 12 months and a median OS of 13.5 months in 39 radically treated patients with synchronous oligometastases in a prospective study (De Ruysscher J Thorac Oncol 2012). As the minimal follow-up is now exceeding 6 years, we here report the long-term PFS and OS. **Method:** Prospective single-arm phase II trial. The main inclusion criteria were pathologically proven NSCLC stage IV with less than five metastases at primary diagnosis, amendable for radical local treatment (surgery or radiotherapy). No previous response to systemic treatment was required. **Result:** Forty patients were enrolled, 39 of whom were evaluable (18 men, 21 women); mean age was 62.1 ± 9.2 years (range, 44-81). Twenty-nine (74%) had local stage III; 17 (44%) brain, seven (18%) bone, and four (10%) adrenal gland metastases. Thirty-five (87%) had a single metastatic lesion. Thirty-seven (95%) of the patients received chemotherapy as part of their primary treatment. Median overall survival (OS) was 13.5 months (95% CI 7.6-19.4); 1-, 2-, 3-, 4-, 5, 6-year OS was 56.4%, 23.3%, 12.8 %, 10.3 %, 7.7 %, 5.1 % (2 patients), respectively. Median progression-free survival (PFS) was 12.1 months (95% CI 9.6-14.3); 1-, 2-, 3-, 4-, 5, 6-year PFS was 51.3%, 13.6 %,12.8 %, 7.7 %, 7.7 %, 2,5 % (1 patient), respectively. Of the 3 patients with a PFS after 5 years, 1 had a squamous cell cancer T2N2 with a single pathologically proven bone metastasis in the sternum, 1 had a NSCLC-NOS T4N0 with a single adrenal metastasis, and 1 a T1N2 adenocarcinoma with a pathologically proven contralateral lung metastasis. The latter patient is still free of disease. Two patients developed a second primary cancer: 1 tongue carcinoma after 70 months and 1 an adenocarcinoma in the contralateral lung after 71 months. Both patients died of their second cancer. Three patients (7.7 %) had a local recurrence, all in the PTV of their primary tumor. Only one patient was treated with a TKI (gefitinib) at progression. **Conclusion:** After radical treatment of oligometastases, approximately 8 % of the patients achieve a PFS after 5 years. Entering patients in trials combining local therapy with novel systemic agents (e.g. chemo-immunotherapy) remains mandatory.

Keywords: non-small cell lung cancer, oligometastases, phase II trial

OA08 MESOTHELIOMA: IMMUNOTHERAPY AND MICRORNA FOR DIAGNOSIS AND TREATMENT
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

OA08.01 LONG-TERM EFFICACY AND SAFETY OF NIVOLUMAB IN SECOND- OR THIRD-LINE JAPANESE MALIGNANT PLEURAL MESOTHELIOMA PATIENTS (PHASE II: MERIT STUDY)

T. Nakano[1], M. Okada[2], T. Kijima[3], K. Aoe[4], T. Kato[5], N. Fujimoto[6], K. Nakagawa[7], Y. Takeda[8], T. Hida[9], K. Kanai[10], F. Imamura[11], S. Oizumi[12], T. Takahashi[13], M. Takenoyama[14], H. Tanaka[15], Y. Ohe[16]

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Background: Malignant Pleural Mesothelioma (MPM) is a rare and highly aggressive malignancy with poor prognosis and no treatment is approved for patients (pts) progressing after 1st line pemetrexed-platinum doublet. Here, we report latest analysis of MERIT study in previously treated Japanese MPM pts to update the previous report (WCLC 2017, Goto Y, et al). **Method:** This open-label study enrolled advanced or metastatic MPM pts previously treated with up to two regimens of chemotherapy

including pemetrexed-platinum doublet. Enrollment criteria also included histologically-confirmed, unresectable MPM without prior surgery, measurable lesion and ECOG performance status 0-1. There was no restriction of PD-L1 status. Pts received Nivolumab 240 mg flat dose Q2W until progression or unacceptable toxicity. Primary endpoint was objective response rate (ORR) (modified RECIST by independent review committee, expected response rate was 19.2%); secondary endpoints included disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS) and safety. **Result:** Thirty-four pts received Nivolumab in this study. Males: 85.2%, median age: 68.0 years (range 43-78), PS 1: 61.8%, epithelial/sarcomatoid/biphasic: 79.4%/8.8%/11.8%, 1 prior regimen: 70.6% and PD-L1 (≧1%)/PD-L1 (<1%)/not evaluable: 58.8%/35.3%/5.9%. At a median follow-up of 16.8 months (range: 1.8-20.2), ORR was 29.4 % (n=10, 95%CI: 16.8-46.2). DCR was 67.6% (n=23, 95%CI: 50.8-80.9). Median DOR was 11.1 months (95%CI: 3.5-16.2). Median PFS was 6.1 months (95%CI: 2.9-9.9) in all pts, 7.2 months (2.8-15.0) in PD-L1 (≧1%) and 2.9 months (1.4-9.3) in PD-L1 (<1%). Median OS was 17.3 months (95%CI: 11.5-NR) in all pts, 17.3 months (8.2-NR) in PD-L1 (≧1%), 11.6 months (5.8-NR) in PD-L1 (<1%), across tissue types, 15.7 months (95%CI: 8.0-NR) in epithelioid and not reached in sarcomatoid/biphasic pts. Six- and 12-month survival rates were 85.3% (95%CI: 68.2-93.6) and 58.8% (95%CI: 40.6-73.2). Twenty-six (76.5%) pts experienced treatment-related adverse event (TRAE), and 11 (32.4%) experienced grade 3/4 TRAEs. Most commonly reported TRAEs were skin disorder (n=6, 17.6%), elevated lipase (n=5, 14.7%), elevated amylase and diarrhea (n=4, 11.8%). Four pts required dose discontinuation because of interstitial pneumonia (n=2, grade2 and 3) and pneumonitis (n=2, grade3). **Conclusion:** Nivolumab shows durable long term efficacy and manageable safety profile in Japanese 2nd/3rd line MPM pts.

Keywords: Nivolumab, PD-1, malignant pleural mesothelioma

OA08 MESOTHELIOMA: IMMUNOTHERAPY AND MICRORNA FOR DIAGNOSIS AND TREATMENT
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OA08.02 DREAM - A PHASE 2 TRIAL OF DURVALUMAB WITH FIRST LINE CHEMOTHERAPY IN MESOTHELIOMA: FINAL RESULT

A. Nowak[1], P. Kok[2], W. Lesterhuis[3], B. Hughes[4], C. Brown[2], S. Kao[5], D. Karikios[6], T. John[7], N. Pavlakis[8], K. O'Byrne[9], S. Yip[2], W. Lam[10], K. Briscoe[11], C. Karapetis[12], M. Stockler[2]

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Background: We report here the final results of a single-arm, phase 2 trial designed to determine the activity, safety and tolerability of durvalumab, cisplatin and pemetrexed as first line therapy in MPM. ANZ Clinical trial registry number: ACTRN12616001170415 **Method:** Participants were considering first line chemotherapy for MPM, were unsuitable for radical surgery, had an un-irradiated target lesion, and had good performance status (ECOG PS 0-1). Objective tumour response (OTR) and progression free survival (PFS) were assessed primarily according to the modified Response Evaluation Criteria in Solid Tumors for MPM (mRECIST) and as secondary endpoints according to RECIST modified for immunotherapy (iRECIST). Study treatment was durvalumab 1125mg, cisplatin 75mg/m^2, and pemetrexed 500mg/m^2 all given intravenously on day 1, and repeated every 3 weeks for a maximum of 6 cycles, followed by durvalumab 1125 mg every 3 weeks until progression, unacceptable toxicity, or a maximum total of 12 months. The primary endpoint was PFS at 6 months (PFS6). The sample size of 54 provided 90% power to distinguish the observed proportion PFS6 from a null hypothesis of 45% versus an alternative of 65% with a 1-sided alpha of 5%. Tissue and blood samples were required and collected for translational correlative studies. **Result:** We recruited 54 participants from Dec 2016 to Sep 2017. Median age was 68 (range 42-82), 82% were male, 60 had ECOG PS 0, and 82% had epithelioid histology. Dose intensities were 97% for cisplatin and 94% for durvalumab. The proportion PFS6 was 57% (31/54, 90% CI 45-68%); median PFS was 6.9 months (95% CI 5.5-9.0). The OTR rate was 48% (95% CI 35-61%) according to mRECIST and 50% (95% CI 37-63) according to iRECIST. The median duration of response was 6.5 months. Grade 3-5 adverse events occurred in 36 participants, including neutropenia in 13%, nausea in 11%, anaemia in 7%, fatigue in 6% and any grade peripheral neuropathy in 35%. There were 4 deaths on study, none attributed to durvalumab. Immune-related adverse events occurred in 17 participants, and were of grade 3 or worse in 8, including increased lipase (1), pancreatitis (1), and renal impairment (1). **Conclusion:** The combination of durvalumab, cisplatin, and pemetrexed has demonstrated sufficient activity, safety, and tolerability as first line therapy in MPM to warrant further evaluation in a large-scale, randomised phase 3 trial.

Keywords: durvalumab, Mesothelioma, Immunotherapy

OA08 MESOTHELIOMA: IMMUNOTHERAPY AND MICRORNA FOR DIAGNOSIS AND TREATMENT
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OA08.03 PHASE II TRIAL OF PEMBROLIZUMAB (NCT02399371) IN PREVIOUSLY-TREATED MALIGNANT MESOTHELIOMA (MM): FINAL ANALYSIS

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[1]Department of Medicine, Section of Hematology/oncology, The University of Chicago, Chicago/US, [2]The University of Chicago, Chicago/US

Background: We conducted a phase II trial to assess the activity of pembrolizumab in a non-selected population of mesothelioma patients and determine a PD-L1 expression threshold. **Method:** Eligible patients had histologically-confirmed pleural or peritoneal MM, PS 0-1, prior pemetrexed/platin, disease progression on ≤2 prior regimens. Pembrolizumab 200 mg was administered Q21 days; CT scans were obtained Q9 weeks. The primary endpoints determined: 1) the objective response rate (ORR) in an unselected and a PD-L1 positive population; 2) the optimal threshold for PD-L1 expression using the 22C3 IHC tumor cell/tumor proportion score (TPS) assay. Proceeding to a second stage required ≥3 responses in 35 PD-L1 unselected patients in Part A. Part B would PD-L1 preselect only if a threshold was determined in Part A. At WCLC 2016, we reported 7 responses in Part A, and no PD-L1 threshold was identified (ROC 0.62). Thus, Part B enrolled 30 additional patients without biomarker enrichment. **Result:** 65 patients enrolled 5/15-2/18; 1 withdrew. PS 0: 53%; male: 77%; median age: 68 (range 26-85); 1 prior chemotherapy 61%; pleural 87.5%; epithelioid 76.6%, biphasic 15.6%, sarcomatoid 7.8%. Mean cycles: 9 (range 1-34). Partial response: 19%, stable disease: 47%, disease control rate: 66%. ORR by histology: epithelioid 16%, biphasic 10%, sarcomatoid 40%. ORR by disease site: pleural 20%, peritoneal 12.5%. Median progression-free survival: 4.5 months (95% CI: 2.3, 6.2). Median overall survival: 11.5 months (95% CI: 7.6, 14). Grade ³/₄ toxicity: adrenal insufficiency 3%, pneumonitis 3%, rash 3%, colitis 1.6%, confusion 1.6%, hepatitis 1.6%, hyperglycemia 1.6%. Grade 5: hepatitis 1.6%, unknown 1.6%. PD-L1 expression by TPS (N = 62): none (< 1%) 45%; low (1-49%) 32%; high (≥50%) 23%. ORR by TPS: none 7%, low 26%, high 31%. PD-L1 did not correlate with RR as a continuous metric (ROC area 0.65; 95% CI: 0.48, 0.82), though there was a trend towards a higher ORR in PD-L1 ≥1% (28%) compared with PD-L1 <1% (7%). Median PFS by TPS: none 3.1 months, low 6.2 months, high 6.1 months; 1-year PFS by TPS: none 7%; low 7%; high 31%. **Conclusion:** Single-agent pembrolizumab has robust activity in PD-L1 unselected, previously-treated mesothelioma. There were no unexpected toxicities. Responses were more frequent in pleural and sarcomatoid MM. Although an optimal PD-L1 threshold could not be identified, a trend towards a higher response rate and more durable PFS with increasing PD-L1 expression was observed. Funded in part by a Mesothelioma Foundation grant.

Keywords: pembrolizumab, Mesothelioma, PD-L1

OA08 MESOTHELIOMA: IMMUNOTHERAPY AND MICRORNA FOR DIAGNOSIS AND TREATMENT
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OA08.05 QUANTIFYING TUMOUR INFILTRATING LYMPHOCYTES (TILS) IN MALIGNANT PLEURAL MESOTHELIOMA (MPM) -DEFINING THE HOT, THE WARM AND THE COLD TUMOURS.

B. Thapa[1], M. Walkeiwicz[1], G. Rivalland[1], C. Murone[1], K. Asadi[2], S. Barnett[3], S. Knight[4], S. Hendry[5], P. Russell[6], T. John[1]

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Background: Immunological infiltrates into tumor tissues have been associated with improved prognosis in many cancers including breast, colorectal, cervical, melanoma and lung. While most studies evaluating TILs have been based on evaluation of individual types of T lymphocytes,

more recently, a morphological assessment of the TILs based on a simple hematoxylin & eosin (H&E) slide examination has been shown to be an independent positive prognostic factor in HER2 positive early stage breast cancer and lung cancer. We used similar methods to explore the immune microenvironment in a large mesothelioma cohort. **Method:** Using full face sections of MPM tumour samples, we assessed lymphocytes infiltrating tumour stroma.TILs score was calculated as a % of stromal area assessed to be covered by TILs by an experienced pathologist. Tissue microarrays (TMA) were constructed and stained with PD-L2, LAG3 and TIM3 antibodies. These data were combined with PD-L1 expression, CD4+ and CD8+ infiltration in the same cohort reported previously. We explored the clinical and pathological correlates of the level of TILs. **Result:** Amongst 329 patients evaluated, 308 samples were evaluable for TILs characterisation. The scores ranged from 0-90 (median 30). Stratified using tertiles, 142 patients had low TILs, 68 had medium and 98 had high TILs. High TILs were seen in patients who were PD-L1 (Chi square test p = 0.002) and PD-L2 positive (Chi square test p <0.0001) and of non-epithelioid histological subtype (Fischer's exact test p = 0.01). On univariate analysis, PD-L2 positivity (HR = 3.2; CI = 2.2-4.6; Log rank P < 0.0001), high TILs (HR = 2.03; CI = 1.5-2.6; Log rank P < 0.0001), and high TIM3+ lymphocytes (HR = 1.3; CI = 1.0-1.7; Log rank P < 0.04) were found to be related to poorer overall survival (OS). On multivariate analysis, higher TILS was found to remain significantly associated with poorer OS along with non-epithelioid histology and poor physiological status. **Conclusion:** High TILs correlated with non-epithelioid histology and greater expression of PD-L1 and PD-L2. In contrast to other tumor types, a high TIL infiltrate was negatively prognostic.

Keywords: malignant pleural mesothelioma, Tumour infiltrating lymphocytes

OA08 MESOTHELIOMA: IMMUNOTHERAPY AND MICRORNA FOR DIAGNOSIS AND TREATMENT
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OA08.06 TUMOUR SUPPRESSOR MICRORNAS MODULATE DRUG RESISTANCE BY TARGETING ANTI-APOPTOTIC PATHWAYS IN MALIGNANT PLEURAL MESOTHELIOMA (MPM)

M. Williams[1], Y.Y. Cheng[1], M. Phimmachanh[1], P. Winata[1], G. Reid[2]

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Background: Malignant Pleural mesothelioma (MPM) is an aggressive thoracic malignancy with limited treatment options. MPM has a poor prognosis, predominately due to its inherent drug resistance and its limited response to current therapies. Aberrant microRNA expression is a common event in neoplasms with many implicated in chemo-resistance, however their role in MPM drug resistance is largely unexplored. **Method:** To investigate the role of microRNAs in MPM drug resistance, we generated MPM cell lines with acquired drug resistance to cisplatin, gemcitabine and vinorelbine by periodic treatment with the IC50 of each chemotherapeutic agent. Expression levels of mature microRNAs were compared between parental MPM cell lines and cell lines with acquired drug resistance using RT-qPCR. BCL2 is an anti-apoptotic gene and a known target of miR-15a/16-1 and miR-34a. To determine if microRNAs potentiate drug sensitization via a Bcl-2 mediated anti-apoptotic pathway, drug sensitivity assays were carried out following reverse-transfection with microRNA mimics and Bcl-2 siRNAs combined with cisplatin, gemcitabine and vinorelbine treatment. Following microRNA mimic transfection in 6-well plates, levels of apoptosis and necrosis were determined by PI and annexin V staining while Bcl-2 mRNA and protein expression was determined by RT-qPCR and Western blotting respectively. **Result:** Expression of miR-15a/16-1 and miR-34a was downregulated in MPM cells with acquired resistance to cisplatin, gemcitabine and vinorelbine, compared to the parental counterpart. Transfection with mimics corresponding to miR-15a/16-1 were most effective in improving sensitivity to all chemotherapeutics tested in drug resistant cell lines. In parental cell lines, miR-15a/16-1 mimic induced sensitization was also observed but restoration of miR-34a and miR-34b was also capable of improving response to cisplatin and vinorelbine. Forced miR-15/16 and miR-34a expression also sensitized both parental and resistant cell lines to cisplatin, gemcitabine and vinorelbine via induction of apoptosis; their ability to increase levels of drug-induced apoptosis suggest they may sensitize cells to chemotherapeutics via an anti-apoptotic mechanism involving Bcl-2. miR-15a/16-1 and miR-34a transfection caused Bcl-2 mRNA and protein reduction, confirming their regulation of Bcl-2 in MPM. Furthermore, siRNA induced knockdown of Bcl-2 also induced a modest improvement in drug sensitivity. **Conclusion:** Restoration of microRNA expression sensitized both drug resistant and parental cell lines to chemotherapeutic agents and increased levels of drug-induced apoptosis. Taken together, this data suggests that miR-15a/16-1 and miR-34a are involved in the acquired and intrinsic drug resistance phenotype of MPM cells in part by modulation of apoptotic mechanisms via targeting Bcl-2.

Keywords: Mesothelioma, drug resistance, microRNA

OA08 MESOTHELIOMA: IMMUNOTHERAPY AND MICRORNA FOR DIAGNOSIS AND TREATMENT
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OA08.07 IN SILICO DISCOVERY OF UNANNOTATED MIRNAS IN MALIGNANT PLEURAL MESOTHELIOMA REVEALS NOVEL TISSUE-OF-ORIGIN MARKERS

B. Minatel[1], E. Marshall[1], C. Anderson[1], K. Ng[1], K. Enfield[1], A. Sage[1], Z. Xu[2], W. Lam[1], V. Martinez[1]

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Background: Malignant pleural mesothelioma (MPM) is an aggressive disease. One of the major clinical challenges associated with MPM is the lack of biomarkers capable of distinguishing primary MPM from cancers that have metastasized to the pleura. The current gold standard consists of a panel of positive and negative protein markers to confirm tissue-of-origin; however, many cases remain undistinguishable from other thoracic cancers. Recent studies have suggested that the human genome encodes more microRNAs (miRNAs) than currently annotated. These undescribed sequences have been shown to display enhanced tissue and lineage specificity. Therefore, we hypothesize that MPM tumors express a specific set of previously unannotated miRNA sequences with tissue-specific expression capable of distinguishing MPM from other thoracic diseases. **Method:** Novel miRNA candidates were detected from small RNA-sequencing data generated by The Cancer Genome Atlas (TCGA) (n=87 MPM) using the miRDeep2 algorithm, a well-established novel-miRNA prediction algorithm. The possible biological roles of these miRNA candidates were investigated by performing a genome-wide 3'UTR target prediction analysis. Additionally, their tissue-specificity was assessed using expression profiles of 1,093 lung tumors from four independent cohorts of adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC). Finally, we developed a miRNA-based classifier model using the weighted voting class prediction method to distinguish MPM from other thoracic cancers. **Result:** Our initial analysis revealed 424 miRNA candidates, which were subsequently filtered by RNA structure, abundance of sequencing reads, and genomic location, resulting in 154 previously unannotated miRNA sequences. Interestingly, the novel miRNAs were predicted to target protein-coding genes involved in MPM biology, including the *Ataxia Telangiectasia Mutated* (*ATM*) gene, a tumour-supressor gene frequently mutated in MPM. Likewise *BRCA1 Associated Protein 1* (*BAP1*), involved in the DNA damage response pathway, was also a predicted target. Principal component analyses revealed that novel-miRNA expression was able to distinguish MPM from LUAD and LUSC. Furthermore, our miRNA-based classifier model revealed 10 novel miRNAs capable of successfully identifying 86 out of the 87 MPM cases (98.80%) and 100% of LUAD cases (true positive rate = 98.85%, false positive rate = 1.150%). **Conclusion:** Here, we provide evidence for the presence of 154 previously unannotated miRNA species relevant to MPM. These miRNAs not only significantly expand the miRNA repertoire but also unveil specific roles in MPM biology. Most importantly, the strikingly high sensitivity and specificity of the novel miRNA-based classifier in distinguishing MPM from LUAD illustrates the potential of using these novel miRNAs to supplement current clinical markers to define MPM.

Keywords: novel microRNAs, Tissue-of-origin markers, Mesothelioma

OA09 PREVENTION AND CESSATION
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

OA09.01 5AS TO 3AS: EVOLUTION OF THE SYSTEMATIC APPROACH TO SMOKING CESSATION IN ONTARIO'S REGIONAL CANCER CENTRES

E. Cameron[1], M. Haque[1], N. Schwartz[1], S. Khan[1], R. Truscott[1], W. Evans[2]

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Background: Smoking is responsible for approximately 30% of all cancer deaths in Canada, and more than 85% of lung cancer cases. Cancer patients who continue to smoke experience decreased treatment efficacy and safety, increased toxicities, greater risk of cancer recurrence and second primaries, poorer quality of life, and decreased survival. Evidence suggests that quitting smoking after diagnosis can significantly reduce these adverse effects. In 2012, Cancer Care Ontario (CCO) introduced a Framework for Smoking Cessation to be implemented across the

province's 14 Regional Cancer Centres (RCCs). In 2017, the Framework was revised from a 5As (Ask, Advise, Assess, Assist, Arrange) to a 3As (Ask, Advise, Act) brief intervention model. **Method:** The transition to a 3As model was based on emerging evidence, feedback from CCO's Smoking Cessation Advisory Committee and Regional Smoking Cessation Champions, as well as learnings from a preliminary program evaluation. The revised Framework recommended an "opt-out" approach to referring smokers to cessation services. Following an environmental scan and site visit with each RCC to assess the current state, site-specific action plans were developed to promote alignment with the revised Framework. Action steps were given priority ratings in the areas of data capture, referrals, and resources. Two phone calls were held with each RCC to monitor progress on action plan implementation. Knowledge translation resources were created to support healthcare providers' uptake of the 3As model. **Result:** Smoking cessation interventions are often perceived by health care providers as time-consuming; the 3As model made the intervention briefer but no less effective. Over 3,000 knowledge translation resources were distributed to support healthcare providers working directly with cancer patients, including pocket cards and posters with suggested scripts. While the revised Framework officially launched in April 2018, early adopters of the 3As model and opt-out approach have seen improved performance on the Accepted a Referral indicator (proportion of smokers who accepted a referral to cessation services). In 2017, one RCC's rate tripled from 10.1% to 30.9% in 6 months, while another improved from 13.2% to 36.9% in the same period. **Conclusion:** To improve program effectiveness, CCO's smoking cessation initiative transitioned from a 5As to a 3As model and an opt-out referral process. Frontline staff have indicated a willingness to adopt the simplified approach, and early results show a promising increase in the number of smokers who are connected to smoking cessation services.

Keywords: Cancer patients, Framework, Smoking Cessation

OA09 PREVENTION AND CESSATION
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OA09.02 ACCEPTANCE OF SMOKING CESSATION SERVICES IN CANCER CARE ONTARIO'S LUNG CANCER SCREENING PILOT FOR PEOPLE AT HIGH RISK

W. Evans[1], G. Darling[2], B. Miller[3], E. Cameron[3], M. Yu[3], M. Tammemagi[4]

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This abstract is under embargo until September 24 at 15:15 Eastern Time.

OA09 PREVENTION AND CESSATION
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

OA09.03 DISCUSSIONS BETWEEN HEALTH PROFESSIONALS AND SMOKERS ABOUT E-CIGARETTES: RESULTS FROM THE ITC POLICY EVALUATION PROJECT

S. Gravely[1], J. Thrasher[2], K.M. Cummings[3], J. Ouimet[1], A. Mcneill[4], G. Meng[1], E.N. Lindblom[5], R. Loewen[1], R. O'Connor[6], M.E. Thompson[1], S.C. Hitchman[4], D. Hammond[1], B.W. Heckman[3], R. Borland[7], H. Yong[7], T. Elton-Marshall[8], M. Bansal Travers[6], C. Gartner[9], G. Fong[1]

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Background: The current scientific evidence on the effectiveness of e-cigarettes for smoking cessation is limited, but shows e-cigarettes may be at least as effective as nicotine replacement therapy (NRT), which is a standard treatment for cessation and broadly recommended by health professionals (HPs). E-cigarettes are now more popular for cessation than licensed NRT and prescription medications in countries such as England, the United States (US), and Canada; however, debate exists on whether HPs should advise smokers to use e-cigarettes, particularly for those who have medical comorbidities (e.g., chronic lung disease). The present study included smokers from four countries to examine: (1) the prevalence of: (i) HP advice to quit smoking, (ii) discussions about e-cigarettes, and (iii) recommendations to use e-cigarettes; and (2) smoker's characteristics associated with discussing e-cigarettes and receiving advice to use them. **Method:** Data come from the 2016 International Tobacco Control (ITC) Policy Evaluation Project Four-Country Tobacco and E-cigarette Survey, which includes nationally representative samples of adult (≥18 years) smokers from Canada (n=1,922), the US (n=1,501), England (n=2,105), and Australia (n=1,038). Participants eligible for analysis had visited a HP in the last year. **Result:** Among all smokers who visited a HP in the last year, 47.5% received advice to quit smoking, 6.8% reported discussing e-cigarettes, and 2.1% of smokers were recommended to use an e-cigarette (36.1% of those who had a discussion). Discussions and e-cigarette recommendation were more common among smokers who were: younger, highly educated, advised to quit smoking, more frequent e-cigarette users, positive about e-cigarettes, and believed that the public approved of vaping. While smokers with diabetes (p=0.026) or cancer (p=0.018) were more likely to discuss e-cigarettes with a HP, they were not more likely to be recommended to use them. Smokers with chronic lung disease were more likely to be recommended to use an e-cigarette than smokers without lung disease (p=0.026). **Conclusion:** These findings suggest that HPs are not taking advantage of discussions with smoking patients to encourage cessation, to provide information about different smoking cessation methods (e.g., suggest e-cigarettes as a cessation aid for smokers who are not willing or able to quit with other strategies), and to encourage smokers who are not inclined to quit to use e-cigarettes as a less-harmful alternative to smoking. More research is urgently needed to assess whether e-cigarettes are a viable alternative to cigarettes for people with lung disease to help them stop smoking and prevent further lung deterioration.

Keywords: e-cigarettes, health professionals, Smoking Cessation

OA09 PREVENTION AND CESSATION
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

OA09.05 POTENTIAL REDUCTION IN LUNG CANCER MORTALITY IN THE US FROM 2015-2065: A COMPARATIVE MODELING APPROACH

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Background: Tobacco control efforts implemented since the 1960s in the US have led to considerable reductions in smoking and smoking-related diseases including lung cancer. It is, however, unclear to what extent tobacco use and lung cancer mortality will be further reduced during the next half century due to control efforts that have already been implemented until 2015. To address this question, we developed simulation models that explicitly relate smoking temporal patterns to future lung cancer rates. **Method:** Four independent lung cancer natural history models were developed using US smoking (1964-2015) and lung cancer mortality (1969-2010) data. Each model projected lung cancer mortality by smoking status (ages 30-84) from 2015 to 2065 under a status quo scenario, in which current smoking patterns are assumed to continue into the future. Sensitivity analyses were conducted comparing optimistic and pessimistic assumptions relative to the status quo. **Result:** Models validated well to observed lung cancer mortality. Under the status quo scenario, age-adjusted lung cancer mortality is projected to drop 79% from 2015 to 2065. Concomitantly, the annual number of lung cancer deaths is projected to decrease from 135,000 to 50,000 (63% reduction). Despite these decreases, 4.4 millions deaths from lung cancer are projected to occur in the US from 2015-2065. **Conclusion:** Tobacco control efforts since the 1960's will continue to lead to reductions in lung cancer rates well into the next half century. Nonetheless, additional prevention efforts are required to sustain and expand these gains, and further reduce the lung cancer burden in the US.

OA09 PREVENTION AND CESSATION
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

OA09.06 MOLECULAR ALTERATIONS AND ESTIMATED INDOOR RADON IN NSCLC PATIENTS FROM THE FRENCH NATIONAL CANCER INSTITUTE REGISTRY: RADON FRANCE STUDY

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Background: Radon is a radioactive gas, considered the leading cause of lung cancer in non-smokers. We assessed the correlation between the radon exposure areas in France and the molecular alterations nationally registered in non-small cell lung cancer (NSCLC) patients. **Method:** We retrospectively collected all NSCLC tested for *EGFR*, *BRAF*, *HER2* and *KRAS* mutations (m) and *ALK* and *ROS1* rearrangements (r) on the 28 French Plateform led by INCa (French National Cancer Institute). The prevalence of molecular alterations by region was correlated to the indoor radon risk area based on the official French (*Institut de Radioprotection et de Sûreté Nucléaire,* INSN, France). Paris and its region Ile-de-France were not included in this analysis due to its high rate of patients that are native from other regions. **Result:** 116.424 NSCLC were included. Overall, KRAS was positive in 27,7% (27.314/98.522), EGFR in 11,27% (13.125/116.424), ALK in 3,2% (2.928/91.291), BRAF in 2,3% (2.419/105.919), ROS1 in 1,12% (373/33.222) and HER2 in 0,8% (816/97.749) of all cases. We stratified the French regions in 3 areas based on their exposure to radon: high (Auvergne-Rhône-Alpes, Bretagne, Normandie, Pays de la Loire), intermediate (Bourgogne-Franche-Comté, Nouvelle Aquitaine, Occitanie, Provence-Alpes-Cote-d'Azur) and low explosure (Centre Val-de-Loire, Grand Est, Hauts de France). The prevalence of driver alterations (*EGFR, BRAF, HER2* and *ROS1* were significantly higher in high exposure area. The prevalence of *KRAS* mutations was significantly higher in low exposure area.

	Low risk	Intermediate	High	P
EGFR mutation	1962 (10%)	4338 (11%)	4176 (11.4%)	<0.0001
ALK rear-range-ment	577 (3.3%)	1019 (3%)	896 (3%)	0.35
BRAF mutation	327 (1.8%)	830 (2.4%)	692 (2.4%)	0.0001
HER2 mutation	109 (0.6%)	266 (0.9%)	252 (0.8%)	0.01
ROS1 rear-range-ment	61 (0.9%)	133 (0.9%)	126 (1.3%)	0.005
KRAS mutation	4717 (29.8%)	9215 (28.2%)	7895 (27%)	<0.0001
Molecular drivers*	3037 (3.9%)	6587 (4.4%)	6142 (4.4%)	<0.0001

*** EGFR, BRAF & HER2 mutations, ALK & ROS1 rearrangements; KRAS mutation excluded.**

Conclusion: NSCLC molecular alterations that are linked to low tobacco consumption were higher in the French region with high radon exposure. Role of the radon in lung cancer carcinogenesis of specific molecular subtypes should be further explored.

Keywords: radon, NSCLC, molecular drivers

OA09 PREVENTION AND CESSATION
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

OA09.07 ASSOCIATION BETWEEN OUTDOOR AIR POLLUTION AND LUNG CANCER IN FEMALE NEVER SMOKERS

R. Myers[1], M. Brauer[2], S. Ladhar[1], S. Atkar-Khattra[1], J. Yee[3], C. Ho[4], A. Mcguire[3], K. Grant[3], A. Lee[3], B. Melosky[4], S. Sun[4], M. Tammemägi[5], S. Lam[1]

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ORAL ABSTRACT SESSIONS TUESDAY, SEPTEMBER 25, 2018

OA10 RIGHT PATIENT, RIGHT TARGET & RIGHT DRUG - NOVEL TREATMENTS AND RESEARCH PARTNERSHIPS
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

OA10.01 PATIENT PREFERENCES FOR TYROSINE KINASE INHIBITOR TREATMENTS FOR EGFR MUTATION POSITIVE METASTATIC NSCLC

J. Bridges[1], M. De La Cruz[2], M. Pavilack[3], E. Flood[2], E. Janssen[2], N. Chehab[3], A. Fernandes[3]

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Background: EGFR mutation positive (EGFRm) NSCLC responds to EGFR-tyrosine kinase inhibitors (TKIs). First-, second-, and third-generation EGFR-TKI treatment attributes vary in efficacy, side effects, and dosing regimen. We used two different methods to explore treatment preferences among patients with EGFRm metastatic NSCLC. **Method:** Patients with EGFRm metastatic NSCLC were recruited in the US to participate in an online survey containing two complimentary preference elicitation methods. First, preferences were assessed through direct elicitation exercises where participants chose between competing treatment profiles. The first exercise compared two profiles with a large difference in progression-free survival (PFS) (6 vs 18 months). The second exercise compared two profiles with a smaller difference (10 vs 18 months). Both exercises compared the same side effect risks (0–1% vs 2–16% risk). Second, a discrete choice experiment (DCE) was used to assess preferences for variation in treatments in terms of PFS, severity of side effects (mild/moderate/severe), and mode of administration. These attributes and levels were varied based on a D-efficient design. Participants completed 10 DCE choice tasks where they saw pairs of hypothetical treatments with different attribute levels and selected their preferred treatment. A choice model was estimated using conditional logit regression. **Result:** Between 10/2017 and 03/2018, 90 patients with EGFRm metastatic NSCLC were recruited and completed the survey: 42% female; 79% white; 76% taking first-line or second-line EGFR-TKIs at time of survey. Median time since diagnosis: 2.1 years (inter-quartile range: 1.1–2.7). In the direct elicitation exercise, participants opted for shorter PFS in exchange for more favorable side effects, but were less likely to do so for a large difference in PFS (52% of participants) vs a smaller difference (66%; p<0.001). Participants who chose shorter PFS when difference in PFS was large were more likely to be taking EGFR-TKIs (odds ratio: 21.4; 95% confidence interval: 2.24, 204.88). No relationship between choice and treatment characteristic was observed when difference in PFS was small. In the DCE, conditional logit regression indicated that to avoid severe levels of nausea/vomiting, diarrhea, rash, or fatigue, participants on average would accept reductions in PFS of 13, 11, 9, and 8 months, respectively. Participants would accept reduction in PFS of 7 months for oral treatment taken with/without food vs IV. **Conclusion:** In this online survey of patients with EGFRm metastatic NSCLC, some patients were willing to accept shorter PFS for a better safety profile and dosing convenience; however, PFS remained an important attribute in treatment choice.

Keywords: treatment preference, EGFR-TKI, NSCLC

OA10 RIGHT PATIENT, RIGHT TARGET & RIGHT DRUG - NOVEL TREATMENTS AND RESEARCH PARTNERSHIPS
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

OA10.02 ONCOGENE-DRIVEN PATIENT GROUPS: A NEW ERA FOR RESEARCH PARTNERSHIPS

J. Freeman-Daily[1], I. Elkins[2], L. Greco[3], M. Horn[4], B. Addario[5], D. Leduc[6], R. Doebele[7], C. Lovly[8]

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OA10.04 AFATINIB WITH OR WITHOUT CETUXIMAB FOR EGFR-MUTANT NON-SMALL CELL LUNG CANCER: SAFETY AND EFFICACY RESULTS FROM SWOG S1403

S. Goldberg[1], M. Redman[2], R. Lilenbaum[1], K. Politi[1], T. Stinchcombe[3], L. Horn[4], E. Chen[5], S. Mashru[6], S. Gettinger[1], M.A. Melnick[7], J. Miao[2], J. Moon[8], K. Kelly[9], D. Gandara[10]

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Background: Several EGFR tyrosine kinase inhibitors (TKIs) are used for the treatment of EGFR-mutant non-small cell lung cancer (NSCLC), however resistance inevitably develops. The combination of the irreversible ErbB family TKI afatinib and the EGFR monoclonal antibody cetuximab was previously shown to overcome resistance to first-line EGFR TKIs. To attempt to delay resistance, we conducted a randomized trial of afatinib plus cetuximab versus afatinib alone in treatment-naïve patients with advanced EGFR-mutant NSCLC (NCT02438722). **Method:** Patients with previously-untreated EGFR-mutant NSCLC were randomized to afatinib 40mg PO daily plus cetuximab 500mg/m2 IV every 2 weeks or afatinib 40mg PO daily. The study was designed to accrue a total of 212 patients, comparing progression-free survival (PFS) between the arms at the 1-sided 0.025 level when 134 PFS events had been observed. Secondary objectives included comparison of overall survival (OS), time to treatment discontinuation (TTD), and toxicity. An interim analysis evaluating early stopping for futility occurred when at least 64 PFS events were reported. **Result:** Between March 26, 2015 and April 23, 2018, 170 eligible patients were accrued: 86 to afatinib/cetuximab and 84 to afatinib. Median age was 66.4 years, 66% were female, 64% had an EGFR exon 19 deletion mutation and 36% had an L858R point mutation. With 109 events observed, there was no improvement in PFS with the combination compared to single-agent (HR 1.17, 95% CI 0.80-1.73, P = 0.42, median 10.6 months vs 13.1 months). OS was also not improved with the addition of cetuximab (HR 1.23, 95% CI 0.62-2.44, P = 0.55, median 26.9 months vs not reached). TTD was similar between the two groups (HR 0.95, 95% CI 0.64-1.39, P = 0.79, median 12.5 months vs 12.2 months). Grade ≥ 3 treatment-related adverse events (AEs) were more common among patients treated with afatinib/cetuximab, and more patients in the combination arm required at least 1 dose reduction of afatinib (57% vs 26%). However, treatment discontinuations due to AEs were similar between the two groups (11.6% vs 10.7%). **Conclusion:** There was no difference in PFS, OS or TTD with the addition of cetuximab to afatinib for treatment-naïve patients with EGFR-mutant NSCLC. The trial was closed to accrual at the interim analysis having met the criteria for futility. Correlative analysis of tumor tissue and blood from patients is ongoing.

Keywords: NSCLC, EGFR

OA10.05 AN OPEN-LABEL, MULTICENTER, PHASE II SINGLE ARM TRIAL OF OSIMERTINIB IN NSCLC PATIENTS WITH UNCOMMON EGFR MUTATION(KCSG-LU15-09)

J.H. Cho[1], J. Sun[2], S. Lee[1], J.S. Ahn[1], K. Park[2], K.U. Park[3], E.J. Kang[4], Y.H. Choi[5], K.H. Kim[6], H.J.A. An[7], H.W. Lee[8], M. Ahn[2]

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Background: Approximately 10% of EGFR mutants harbor uncommon mutations, which represent a heterogeneous group of rare molecular alterations within exons 18-21 and the sensitivity to EGFR TKIs is variable. Osimertinib is a potent irreversible inhibitor of both sensitizing EGFR mutation and T790M. In preclinical data, osimertinib was found to be active against most uncommon EGFR mutants, apart from the exon 20 insertion variant. Here we present the efficacy and safety of osimertinib in patients with uncommon EGFR mutation positive NSCLC. **Method:** Patients with histologically confirmed metastatic or recurrent NSCLC with activating EGFR mutation other than exon 19 deletion, L858R, T790M and insertion in exon 20 were eligible. Patients received 80mg of osimertinib orally, once daily until progression or unacceptable toxicity. Response was assessed every 8 weeks by investigator. The trial was registered with ClinicalTrials.gov, number NCT03424759. **Result:** Between Mar 2016 and Oct 2017, 35 patients were enrolled. Median age was 59, 63% male, 43% never smoker, 97% adenocarcinoma. 63% of patients were treated as first-line therapy. The mutations identified were G719A/C/D/S/X (19, 54.3%) followed by L861Q (9, 25.7%), S7681 (8, 22.9%), and others (3, 8.6%). The overall response rate was 50.0% (95% CI 32.8-67.2) and DCR was 88.9% (95% CI 78.1-99.7). Seven patients (77.8%) with L861Q mutation achieved partial response; 10/19 (52.6%) with G719A/C/D/S/X mutation; 3/8 (37.5%) with S768I mutation. At data cutoff (Apr, 2018), the median PFS was 8.2 months (95% CI 1.9- 14.4) and median duration of response was 9.8 months (95% CI 7.6-12.0). The most common adverse events were rash (n=11, 31.4%), anorexia (n=8, 22.9%), and diarrhea (n=7, 20.0%). Grade 3 or 4 AEs were reported in 8 of 35 patients (23%), but all of AEs were manageable. **Conclusion:** Osimertinib showed highly active in NSCLC patients harboring uncommon EGFR mutation with manageable safety profile, consistent with previous reports. Further analysis will be provided.

Keywords: non-small cell lung cancer, osimertinib, uncommon EGFR mutation

OA10.06 A FIRST-IN-HUMAN PHASE 1 TRIAL OF THE EGFR-CMET BISPECIFIC ANTIBODY JNJ-61186372 IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

K. Park[1], M. Ahn[2], S. Lee[3], H.R. Kim[4], M.H. Hong[4], D. Millington[5], M. Curtis[6], S. Triantos[6], S. Chaplan[5], N. Haddish-Berhane[6], R. Knoblauch[6], Z. Aguilar[5], S. Laquerre[6], M. Lorenzi[6], B.C. Cho[4]

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Background: JNJ-61186372 (JNJ-372) is a bispecific antibody targeting both EGFR and cMET. In preclinical studies, JNJ-372 demonstrated efficacy in EGFR and cMET driven tumor xenograft models (including EGFR T790M and MET-amplified/HGF secretion), consistent with inhibition of ligand binding, receptor degradation, and ADCC activity. The goal of Part 1 of this study (reported here) was to assess the safety, pharmacokinetics (PK), and preliminary efficacy of JNJ-372 and to identify the recommended phase 2 dose(s) to be explored in Part 2. **Method:** Patients with previously treated, advanced NSCLC were enrolled at two sites and treated with escalating doses of JNJ-372 administered IV weekly for the first 4-week cycle, then biweekly for each subsequent cycle. PK sampling was taken at multiple time points within cycle 1 and 2. Disease assessments were performed every 8 weeks. Tumors were characterized at baseline through next-generation sequencing of circulating tumor DNA (Guardant 360). **Result:** 25 patients were treated with JNJ-372 during dose escalation: 140mg (n=3), 350mg (n=3), 700mg (n=9), 1050mg (n=7), 1400mg (n=3). Median age was 63y, 48% were male, 100% were Asian, 84%/12%/4% had adenocarcinoma/squamous/other histology, and median prior therapies was 4. No dose-limiting toxicities were observed at any dose level tested. The most frequent treatment-emergent AEs were infusion-related reactions (76%), rash/acneiform dermatitis (40%), dyspnea (24%), paronychia (24%), pruritus (20%), fatigue (20%), and nausea (20%); incidence of peripheral edema (cMET-related toxicity) was 12%. Infusion-related reactions were grade ≤2 severity, observed primarily with the first dose. The worst severity of rash/acneiform dermatitis was grade 2 (16%). One treatment-related AE of grade ≥3 severity was reported (neutropenia grade 3, possibly related). JNJ-372 demonstrated linear PK at dose levels 350 mg and above with non-linear PK at lower concentrations, suggesting target-mediated drug disposition. Doses ≥700mg resulted in average steady-state concentrations at or above the preclinically established therapeutic target level. Preliminary evidence of efficacy (maximum change from baseline in sum of target lesion diameters) was observed in a patient with squamous cell carcinoma (-20%), a patient with wtEGFR adenocarcinoma (-20%), and 4 patients with EGFR-mutant adenocarcinoma (≥-30%). **Conclusion:** JNJ-372 is a novel EGFR-cMET bispecific antibody. The manageable safety profile and preliminary evidence of clinical activity support active accrual of patients with previously treated EGFR-mutant NSCLC. The first recommended dose of 1050mg is being evaluated in Part 2.

Keywords: cMET, NSCLC, EGFR

OA10.07 RESISTANCE MECHANISMS OF OSIMERTINIB IN CHINESE NON-SMALL CELL LUNG CANCER PATIENTS: ANALYSIS FROM AURA17 TRIAL

C. Zhou[1], M. Hu[2], X. Zhu[2], Y. Sun[2], X. Lu[3], J. Wang[4], M. Wang[5], Y. Cheng[6], Y. Chen[7], Y. Zhao[8], Y. Shi[9], Y. Lu[10], M. Shi[11], H. Zhang[12], X. Huang[13], Z. Wang[3], Z. Ding[2], H. Li[4], G. Chen[4], Y. Wu[14]

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Background: Osimertinib is approved for metastatic NSCLC patients with EGFR T790M mutation after progression from TKI therapy. Despite impressive tumor responses, drug resistance usually develops. The resistance mechanisms of osimertinib are emerging but studies with large cohorts of Chinese patients and association with clinical outcomes are lacking. Here we report a biomarker study of osimertinib using plasma samples from 107 Chinese patients who had progressed by 24 months after LSFD (Oct. 2017) of AURA17 (NCT02442349), the 2nd-line pivotal trial in China. **Method:** Serial plasma cell-free DNA (cfDNA) were collected from baseline until progressive disease (PD) by investigator assessment. Capture-based 75-gene NGS panel with unique molecular index (UMI) system was used to identify resistance mechanisms to osimertinib by comparing paired cfDNA at baseline and PD. Droplet digital PCR (ddPCR) was used to dynamically monitor EGFR mutation changes (L858R, Ex19Del, T790M and C797S) during treatment course. Association of cfDNA biomarkers based on valid test results with objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) from DCO3 (Mar. 20, 2018) was analyzed. **Result:** The 107 patients were with ORR of 68.2%, median PFS of 8.2 months, and median OS of 21.5 months. Eight-two had detectable EGFR sensitizing mutations (L858R or Ex19Del) in their PD cfDNA samples. Among them, 15 had acquired EGFR C797S, all *in cis* with T790M, and with no enrichment for L858R or Ex19Del (6 and 9, respectively). The median time of C797S detection from plasma was 2.8 (1.2-8.4) months prior to PD. EGFR L718Q, I744T, C775Y, G796S/D, T854I mutations, or amplification were found in 11 patients. Aberrations in bypass tracks including AKT2, ALK, DDR2, ERBB2/3, HRAS, JAK1/2, KRAS, MET, NTRK1, PIK3CA, RIT1, *etc.* were observed in 45 patients. Clearance of EGFR sensitizing mutations at weeks 3 of treatment was associated with favorable ORR (78.7% *vs.* 33.3%), PFS (9.6 *vs.* 4.0 months, p<0.001) and OS (21.5 *vs.* 11.7 months, p<0.001). Clearance of EGFR sensitizing mutations at weeks 6 of treatment was also associated with favorable ORR (80.0% *vs.* 36.8%) and PFS (8.3 *vs.* 4.2 months, p<0.001). Presence of T790M at PD was correlated with longer PFS (12.3 *vs.* 5.5 months, p<0.001) and OS (21.3 *vs.* 13.2 months, p=0.045). Acquired or enriched TP53 alterations at PD were associated with worse PFS (4.2 *vs.* 8.3 months, p=0.008). **Conclusion:** Our study revealed diverse resistance mechanisms to osimertinib in Chinese NSCLC patients and urged for new drug discovery or combination strategies to overcome this clinical challenge.

Keywords: non-small cell lung cancer, osimertinib, resistance mechanisms

OA11.01 ROLE OF POST-OPERATIVE RADIATION IN DIFFERENT HISTOLOGIC SUBGROUPS OF THYMOMA: RESULT BASED ON NATIONAL CANCER DATA BASE (NCDB)

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Background: Thymoma and thymic carcinoma are rare neoplasms that occur in the anterior mediastinum. According to WHO classification, thymomas are classified into 5 different subgroups based on their clinical behavior. The role of post-operative radiation (PORT) has been studied well based on the stage grouping. However, the benefit of PORT on different histologic subtypes is not well defined. We analyzed role of PORT in 5 different subgroups of thymomas using NCDB data base. **Method:** From 2004-2014, using C37.9 topographic code, 6532 patients were identified with a diagnosis of thymoma or thymic carcinoma. The median age was 60 years. 48.6% were male. 78.5% (n=5127) patients underwent surgery and 52.4% (n=3425) did not receive any radiation. Patients with no surgery and with thymic carcinoma histology were excluded. Patients with thymoma who had radiation dose between 40-60 Gy were included for the final survival analysis. Overall survival (OS) was calculated using Kaplan Meier method with log rank test for comparison analysis. IBM SPSS (v24) was used for statistical analysis; p-value of <0.05 was considered statistically significant. **Result:** Thymic carcinoma was the most frequent subtype (20.6%) followed by AB subtype (14.4%). Type A was least frequent subtype (7.7%) while 22.3% did not have any subclassification. 48.1% (n=3139) had no residual cancer, 12% had microscopic involvement and 2.6% had macroscopic residual cancer. Macroscopic tumors were more frequently seen with thymic carcinoma (3.43%) and B1 (1.23%), B3 (1.43%) subtypes. Median overall survival with surgery was 8 years compared to approximately 10 years with PORT (p<0.0001) for the entire group. Among 5 subcategories, PORT was associated with improved OS for type A (p<0.007), AB (p=0.008) and B3 (p=0.003). For B1, PORT was associated with inferior OS and for B2, PORT was not significant for OS. **Conclusion:** In this analysis PORT was associated with statistically significant improved OS in A, AB and B3 subgroups but not for B2 and B3. Further work is underway to perform multivariable analysis.

Keywords: Thymoma, survival, NCDB

OA11.02 A POPULATION-BASED STUDY OF INCIDENCE AND SURVIVAL TRENDS OF 1,588 THYMIC MALIGNANCIES: RESULTS FROM THE CALIFORNIA CANCER REGISTRY

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Background: Thymic malignancies (TM) are rare with sparse population-based epidemiologic literature. According to data collected by the National Cancer Institute from 1973 to 2006, the incidence of thymomas is 0.13 per 100,000 person-years in the United States. **Method:** We used data from the California Cancer Registry (CCR), a comprehensive population-based state registry to examine TM incidence and survival trends in California from 1988 to 2015. Cases were specified by site (thymus), histology (thymic carcinoma and thymoma), and behavior (malignant). Primary endpoints were cause-specific survival (CSS) and overall survival (OS). Age-adjusted incidence rates were calculated in SEER*Stat, and Joinpoint regression was used to analyze incidence trends. Hazard ratios (HR) for CSS and OS were calculated using a Cox proportional hazards regression model controlling for relevant baseline variables including age, gender, stage, and year of diagnosis, among others. **Result:** We identified 1,588 TM cases in California from 1988 to 2015 with an annual percent increase of 2.08% (95% CI: 1.3%, 2.9%; p < 0.0001). The incidence of TM in 2015 was 0.277 per 100,000. Thymic carcinoma histology was associated with worse CSS across all stages, including localized (HR 7.56, 95% CI 1.44, 39.78), regional (HR 4.23, 95% CI 2.55, 7.01), and remote (HR 2.09, 95% CI 1.37, 3.19) disease. Compared to no treatment, surgery with or without radiation was associated with improved CSS in localized (surgery: HR 0.05 (95% CI 0.01 to 0.35), surgery + radiation: HR 0.12 (95% CI 0.02 to 0.84)) and regional disease (surgery: HR 0.11 (95% CI 0.04 to 0.29), surgery +

radiation: HR 0.15 (95% CI 0.06 to 0.36)). Chemotherapy and radiation was also associated with improved CSS in regional disease (HR=0.22 (95% CI 0.07 to 0.63) and remote disease (5.16 (0.37, 71.94)), though the latter was not statistically significant. **Conclusion:** This is a population-based study of TMs from the CCR that identifies baseline variables significantly associated with CSS. TM incidence appears to be increasing over time. Advanced stage and thymic carcinoma were found to be associated with worsened CSS, which is consistent with previous studies. Treatment incorporating surgery was associated with improved CSS in local and regional disease, as was chemoradiation in regional disease. Improvement in CSS trended towards significance in patients with remote thymic neoplasms treated with chemoradiation. These findings provide a more contemporary database for future TM outcomes research.

Keywords: thymic malignancies incidence, thymic malignancies CSS

OA11 THYMIC AND OTHER THORACIC TUMOURS: TARGETED THERAPIES, BIOMARKERS AND NEO/ADJUVANT RADIOTHERAPY
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

OA11.04 A COMPARATIVE STUDY OF PD-L1 IMMUNOHISTOCHEMICAL ASSAYS WITH FOUR RELIABLE ANTIBODIES IN THYMIC CARCINOMA

T. Sakane[1], H. Haneda[1], K. Okuda[1], K. Yokota[1], T. Tatematsu[1], R. Oda[1], T. Watanabe[1], Y. Saito[2], T. Yamada[3], R. Nakanishi[1]

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Background: Currently, programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) targeted therapy has not been established for thymic carcinoma (TC) yet, and limited information is available regarding the expression pattern of PD-L1 in TC. Four immunohistochemical assays are registered with the US Food and Drug Administration to detect the expression of PD-L1. We investigated the PD-L1 expression in thymic carcinomas using these four diagnostic assays. **Method:** The clinicopathological data of 53 TC patients were reviewed and their specimens were subjected to four PD-L1 assays with different antibodies (22C3, 28-8, SP142, and SP263). We examined tumor proportion scores (TPS) in each case and the cutoff values were settled at 1% for 22C3, 1% for 28-8, 1% for SP142, and 25% for SP263. Date were correlated to clinicopathologic parameters and outcomes. **Result:** The study population included 32 male patients and 21 female patients (median age, 61 years). In the TPS, the four assays showed similar scores in each case. Pairwise analyses of the TPS for the four assays showed high concordance among the four assays (the Spearman's rank correlation coefficients were all >0.9). Histopathologically, high TPS was observed in squamous cell carcinomas (SqCCs). Using cutoffs, 34 cases (64.2%) with 22C3, 41 cases (77.4%) with 28-8, 43 cases (81.1%) with SP142, and 26 cases (49.1%) with SP263 were detected as PD-L1 positive. In SqCCs, the high expression of PD-L1 (TPS ≥50%) were associated with early stage cancer when evaluated with 22C3 (p=0.0205), 28-8 (p=0.0448), and SP263 (p=0.0486), respectively. However the high expression of PD-L1 were not associated with sex, age, tumor size, and curability. The SqCC patients with high expression of PD-L1 tended to show longer overall survival; p=0.0250 in 22C3, p=0.0719 in 28-8, p=0.1064 in SP142, and p=0.0675 in SP263. **Conclusion:** The present study revealed that the TC patients, especially SqCC patients, showed high PD-L1 positivity and that the staining pattern showed high concordance among the four assays. High expression of PD-L1 might be a prognostic predictor, though observed effect was independent on the assay. Our results suggest that the PD-1/PD-L1 pathway is a potential immunotherapeutic target in TC.

Keywords: PD-L1, Immunohistochemistry, Thymic carcinoma

OA11 THYMIC AND OTHER THORACIC TUMOURS: TARGETED THERAPIES, BIOMARKERS AND NEO/ADJUVANT RADIOTHERAPY
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

OA11.05 PHASE II STUDY OF SUNITINIB IN PATIENTS WITH THYMIC CARCINOMA PREVIOUSLY TREATED WITH PLATINUM-BASED CHEMOTHERAPY (KOSMIC TRIAL)

S.H. Kim[1], Y.J. Kim[1], C. Ock[2], M. Kim[2], B. Keam[2], T.M. Kim[2], D. Kim[2], D.S. Heo[2], J.S. Lee[1]

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Background: Only one prospective study in western population suggests sunitinib is an effective treatment for thymic carcinoma (TC). We evaluated the clinical efficacy and toxicity of sunitinib in Korean patients with metastatic TC after platinum-based chemotherapy. **Method:** Between Sep 2015 and May 2017, we enrolled 25 patients with histologically confirmed platinum-refractory TC at three academic hospitals in Korea. Patients were eligible if they had progressive disease after one or more cytotoxic chemotherapy including platinum-based regimen, at least one measurable disease by RECIST (v1.1) and adequate organ function. Patients received 50mg of sunitinib on an alternative schedule (2weeks of treatment followed by 1 week without treatment) until objective progression of disease or unacceptable toxicity of treatment. The primary endpoint was objective response rate and tissue and blood specimen were collected for NGS panel analysis (170 genes, Hybrid capture based method). This trial was registered with Clinicaltrials.gov, number NCT 02623127. **Result:** A total of 25 patients were enrolled in this trial. Median age was 62 (39-75) and 19 (76%) patients were male. Most patients (20 patients, 80%) received sunitinib as 2nd line treatment. Two patients discontinued treatment earlier than first tumor assessment due to toxicity and excluded from efficacy analysis. Among 23 evaluable patients, 5 (21.7%) patients had partial response and 16 (69.6%) patients achieved stable disease. Disease control rate (PR+SD>6m) was 56.5%. Median progression-free survival (PFS) was 15.2 months and 6 patients had ongoing responses at the time of analysis. Most common treatment-related adverse events were mucositis (12 patients, 48%), fatigue (9 patients, 36%), and hand-foot syndrome (9 patients, 36%). The most common grade 3/4 toxicity was thrombocytopenia (4 patients, 16%). Seventeen (68%) patients needed at least one dose reduction due to adverse events. Genomic profiling with NGS cancer panel revealed 2 patients with pathogenic KIT mutation (c.1879+1G>A and c.1671 G>C) who had PFS of 21.3m and 9.3m, respectively. In 15 patients with tumor tissue gene panel results, high tumor mutation burden (TMB) was significantly associated with longer PFS (median PFS not reached in TMB ≥30/MB vs. 3.45m in TMB <30/MB, P=0.03). **Conclusion:** Sunitinib with 2/1 schedule is an active treatment for TC after platinum-based chemotherapy.

Keywords: Thymic carcinoma, TMB, Sunitinib

OA11 THYMIC AND OTHER THORACIC TUMOURS: TARGETED THERAPIES, BIOMARKERS AND NEO/ADJUVANT RADIOTHERAPY
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

OA11.06 TWO BRM PROMOTER POLYMORPHISMS DO NOT PREDICT SUSCEPTIBILITY OR PROGNOSIS OF THYMOMA

M.J. Lee[1], N. Kuehne[2], K. Hueniken[2], D. Shepshelovich[2], S. Soldera[2], S. Shakik[2], D. Patel[2], D. Cheng[2], Z. Chen[2], L. Eng[3], M.C. Brown[2], A. Bezjak[4], S. Keshavjee[5], D. Reisman[6], W. Xu[2], G. Liu[2]

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Background: Brahma (BRM) is a critical protein subunit in chromatin remodeling, and insertions/deletions at its two polymorphic promotor sites (BRM-741 and BRM-1321) have been reported as susceptibility and/or prognostic markers in lung, head and neck, esophageal, pancreatic, and liver cancers. There is also early evidence of potential association with immune-related diseases such as ulcerative colitis and rheumatoid arthritis. As epigenetic silencing of BRM can be pharmacologically reversed, BRM polymorphisms in cancer might have therapeutic implications. Thymoma is a unique cancer in that it has immunological disease associations. We evaluated whether BRM-741 and BRM-1321 polymorphisms influence overall risk, survival, and time-to-progression of thymoma. **Method:** Thymoma cases and matched healthy controls were recruited in a comprehensive cancer centre. Study participants' peripheral blood samples were collected and genotyped for BRM promoter polymorphisms. Multivariable logistic regression assessed risk of thymoma in case-control analyses. Association of BRM variants with overall survival (OS) and time-to-progression or recurrence (TTP) was assessed by multivariable Cox regression. **Result:** Of 237 cases of histologically diagnosed thymoma and 948 age- and gender-matched healthy controls, thymoma patients had median age of 53 (range: 17-84) years; 121 (51%) were male; 76 (32%) had a history of myasthenia gravis. Median follow-up time was 7 years. 79% of patients were recurrence- and progression-free at 10-year follow-up (95% CI: 74-86%), and 81% of patients were alive at 10 years post-diagnosis (95% CI: 75-87%). Frequency of homozygous variants for either gene was not significantly different between thymoma cases and controls: homozygous BRM-741genotype (OR=1.0; 95%CI:0.6-1.8; P=0.95), homozygous BRM-1321 (OR=0.59; 95%CI:0.3-1.0; P=0.07) or double homozygous variants in both loci (OR=0.69; 95%CI:0.3-1.4; P=0.29). No association between BRM-741/BRM-1321 and OS and TTP was detected

(For homozygous BRM-741, OS P=0.74, TTP P=0.93; for homozygous BRM-1321 OS P=0.39, TTP P=0.93). Consistently, there was also no association between double homozygous variants and OS and TTP (Double homozygous, OS P=0.64, TTP P=0.48). Heterozygous variants were also not associated with either risk or outcome. **Conclusion:** Results of this study do not support use of BRM promoter polymorphisms as susceptibility or prognostic markers for thymoma. Molecular biologic mechanisms of risk and prognosis remain elusive in malignant thymoma.

Keywords: Epigenetic, Thymoma, BRM

OA12 NOVEL THERAPIES IN MET, RET AND BRAF
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

OA12.01 PHASE II DATA FOR THE MET INHIBITOR TEPOTINIB IN PATIENTS WITH ADVANCED NSCLC AND MET EXON 14-SKIPPING MUTATIONS

E. Felip[1], H. Sakai[2], J. Patel[3], L. Horn[4], R. Veillon[5], F. Griesinger[6], R. Bruns[7], J. Scheele[7], P. Paik[8]

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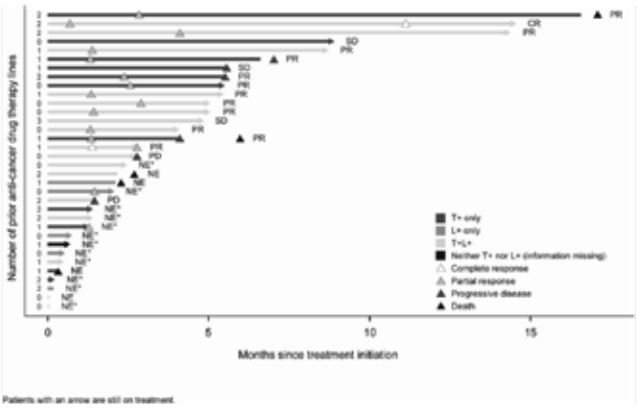
Background: A subset (3%) of NSCLCs harbor mutations of the *MET* proto-oncogene that cause MET exon 14 skipping (*METex14*) and accumulation of active MET lacking a juxtamembrane domain. We report interim data from a single-arm phase II trial (NCT02864992) investigating the efficacy and safety of the potent, selective tyrosine-protein kinase MET inhibitor tepotinib in patients with *METex14*-skipping mutation-positive (*METex14+*) NSCLC. **Method:** Recruitment of ≤120 adult patients with advanced *METex14+* NSCLC without *EGFR*-activating mutations or *ALK* rearrangements is ongoing. *METex14+* mutations are identified in FPE tumor (T) material and/or plasma (L; 60 patients each, overlap anticipated) by a central laboratory. Patients receive tepotinib 500mg QD until disease progression, intolerable toxicity, or withdrawal. Primary endpoint: objective response rate (ORR). Secondary endpoints include safety. **Result:** Forty-one patients have been treated to date; data are available for 34 (median age 73.5 years; 23 male; 24/8 Caucasian/Asian; prior lines of therapy: 0, n=12; 1, n=11; 2, n=10; 3, n=1; stage IVA, n=4; stage IV, n=29; stage IIIB, n=1). Treatment is ongoing in 24 patients. Based on investigator assessment, 13/22 (59.1%) evaluable patients responded: 1 had a confirmed complete response; 12 had a confirmed partial response (PR); 3 (13.6%) had stable disease for ≥12 weeks (SD). Based on independent review, 9/22 (40.9%) had a confirmed PR; 5 (22.7%) had SD. Duration of response >12 months in 2 patients. Twenty (58.8%) patients have experienced tepotinib-related treatment-emergent adverse events (TRTEAEs), including serious TRTEAEs in 3 (8.8%): pneumonia =1, generalized oedema=1, interstitial lung disease=1, and grade ≥3 TRTEAEs in 6 (17.6%): generalized oedema=1, pneumonia=1, ALT increased=1, AST increased=1, amylase increased=2, gamma GT increased=1, lipase increased=1, hyperkalemia=1; no TRTEAEs were grade ≥4 or led to death. Five (14.7%) patients have died.

Figure: Time on treatment and duration of response for tepotinib-treated patients (investigator assessment)



Conclusion: Tepotinib 500mg QD has promising activity in *METex14+* NSCLC, with a favorable safety profile.

Keywords: tepotinib, MET inhibitor, non-small cell lung cancer

OA12 NOVEL THERAPIES IN MET, RET AND BRAF
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

OA12.02 UPDATED ANTITUMOR ACTIVITY OF CRIZOTINIB IN PATIENTS WITH MET EXON 14-ALTERED ADVANCED NON-SMALL CELL LUNG CANCER

A. Drilon[1], J. Clark[2], J. Weiss[3], S. Ou[4], D.R. Camidge[5], B. Solomon[6], G. Otterson[7], L. Villaruz[8], G. Riely[1], R. Heist[2], G. Shapiro[9], D. Murphy[10], S. Wang[10], T. Usari[11], S. Li[10], K. Wilner[10], P. Paik[1]

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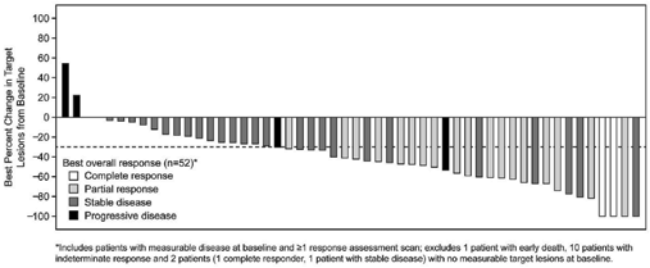
Background: *MET* exon 14 alterations occur in ~3% of non-squamous non-small cell lung cancer (NSCLCs) and 20–30% of sarcomatoid lung carcinomas. Here we present updated antitumor activity for crizotinib in patients with advanced NSCLC whose tumors are positive for *MET* exon 14 alterations (hereafter *MET* exon 14-positive NSCLC), including updated biomarker analyses in circulating tumor DNA (ctDNA). **Method:** Patients with *MET* exon 14-positive NSCLC by local molecular profiling were treated with 250 mg crizotinib BID in an expansion cohort of the ongoing PROFILE 1001 study (NCT00585195). Responses were based on derived investigator assessment per RECIST v1.0. Prospective plasma profiling for *MET* exon 14 alterations in plasma ctDNA was performed (PlasmaSELECT-R64; Personal Genome Diagnostics, Boston, MA). **Result:** As of Jan 31, 2018, 69 patients (65 response-evaluable) with *MET* exon 14-positive NSCLC had been treated. Median age was 72 y (range: 34, 91). Tumor histology was: 84% adenocarcinoma, 9% sarcomatoid adenocarcinoma, 4% squamous cell carcinoma and 3% adenosquamous carcinoma. 61% were former-smokers, 38% never-smokers and 1% a current smoker. Median duration of treatment was 7.4 mo (95% CI: 5.5, 9.1), with 29% of patients ongoing. Confirmed responses were 3 CRs and 18 PRs (ORR, 32% [95% CI: 21, 45]); 29 patients had SD as their best overall response (Figure).



Median time to response was 7.6 weeks (range: 3.7, 16.3). Median DOR was 9.1 mo (95% CI: 6.4, 12.7). Median PFS was 7.3 mo (95% CI: 5.4, 9.1). *MET* exon 14 alterations were detected in ctDNA from 18/37 (49%) patients with analyzable samples. **Conclusion:** In patients with *MET* exon 14-positive advanced NSCLC, crizotinib treatment led to objective responses that were rapid and durable, with CRs in some cases. Plasma ctDNA profiling detected *MET* exon 14 alterations in a subset of patients who harbor *MET* exon 14 alterations by tumor testing.

Keywords: non-small cell lung cancer, crizotinib, MET

OA12 NOVEL THERAPIES IN MET, RET AND BRAF
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OA12.03 ACTIVITY OF CRIZOTINIB IN MET OR ROS1 POSITIVE (+) NSCLC: RESULTS OF THE ACSÉ TRIAL.

D. Moro-Sibilot[1], N. Cozic[2], M. Pérol[3], J. Otto[4], J. Mazieres[5], P. Souquet[6], R. Bahleda[2], M. Wislez[7], S. De Guibert[8], B. Mennecier[9], C. Chouaid[10], R. Sabatier[11], S. Bota[12], R. Gervais[13], V. Verriele[14], V. Haddad[3], G. Ferretti[1], F. Nowak[15], C. Mahier - Ait Oukhatar[16], G. Vassal[2]

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Baclesse, Caen/FR, [14]Institut de Cancérologie de L'Ouest Paul Papin, Angers/FR, [15]Institut National Du Cancer, Boulogne Billancourt/FR, [16]Unicancer, Paris/FR

Background: Crizotinib was registered for ALK+ NSCLC in 2013 and recently for ROS1+ stage IV NSCLC. To generate high evidenced-based knowledge and to prevent off-label use, the French National Cancer Institute (INCa) launched the AcSé Program: equal access to tumor molecular diagnosis including an exploratory phase II trial. AcSé allows nationwide safe and controlled access to crizotinib off-label. **Method:** Biomarkers were identified with INCa molecular genetic platforms. Patients with amplification [amp] MET or mutation [mut] MET or translocation [tlc] ROS1 advanced NSCLC and not eligible for any other trial, were proposed crizotinib 250 mg BID. Tumor response was evaluated every 2 months (mo) using RECIST v1.1. The primary endpoint was the objective response rate (ORR) at 2 mo (complete + partiale response). A two-stage Simon design was applied to each cohort. Median and 95% confidence interval (CI) was estimated through Kaplan-Meier for progression-free survival (PFS), overall survival (OS), and response duration. Response duration was the delay between CR/PR and first progression/death or last follow-up. **Result:** From 08/2013 to 03/2018, 5407 patients from 186 centers entered the biomarker program. Tumor alterations found in patients were: ROS1 tlc in 77/4050; MET amp (≥6 copies/diploid genome) in 251/4171; MET mut in 76/1007. Overall, 90 patients (median age, 63 years [30–92]) received crizotinib 250 mg BID.

Cohorts NSCLC	Patients analyzed	At two cycles		PFS Median [95% CI]	OS Median [95% CI]	Response duration Median [95% CI]
		CR/PR	ORR % [95% CI]			
MET AMP	25	7	28 [10 - 46]	3.4mo [1.9-5.5]	7.7 mo [4.6-15.7]	N=14 ; 11 [6.6-23.3]
ROS1 TLC	37	20	54 [38 - 70]	5.5mo [4.6 -9.1]	17.2mo [6.8-32.8]	N=22; 13 [6.4-19.3]
MET MUT	28*	5**	18 [4 -32]	2.6mo [1.6 – 6.2]	8.1mo [4.1-12.7]	N=17 ; 11 [5.5-13.6]

* *Including 4 patients with mutation MET on other exon than exon 14*
** *patients with mutation MET exon 14*

73 grade ≥3 adverse events (AEs) or SAE were reported in 70/90 patients. Grade ≥3 AEs were: hematologic toxicities (23%) including neutropenia (11%), and general disorders (16%) including fatigue (10%). **Conclusion:** This study confirms the excellent response rate of crizotinib in the ROS1+ population. Response rate in the MET mut population is comparable to the MET amp population. In addition, the response rate to crizotinib in the MET mut population is lower than that in the PROFILE 1001 study. The tolerance profile is good as previously reported.

Keywords: crizotinib, NSCLC, MET or ROS1 alterations

OA12.05 VEMURAFENIB IN PATIENTS HARBORING V600 AND NON V600 BRAF MUTATIONS: FINAL RESULTS OF THE NSCLC COHORT FROM THE ACSÉ TRIAL.

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Background: *BRAF* mutations are found in 2-3% of NSCLC. *BRAF* inhibitors reportedly have antitumor activity. The French National Cancer Institute (INCa) launched a program giving nationwide access to vemurafenib for cancer patients with *BRAF*-mutated tumors and supported molecular screening. We herein report the NSCLC cohort results. **Method:** *BRAF* mutational status was assessed on INCa molecular genetic centers by direct sequencing or NGS. Patients with mutated *BRAF* (V600E and others mutations) progressing after ≥1 standard treatment were proposed vemurafenib 960 mg BID. Objective Response Rate (ORR) was assessed using RECIST v1.1 every 8 weeks. A sequential Bayesian approach was planned to allow early stopping using an inefficacy bound for ORR of 10%. If no early stopping occurred, the treatment was considered worthy for further evaluation if there was a 90% probability that the estimated ORR is ≥30%, the efficacy bound. **Result:** From 10/2014 to 10/2017, 118 NSCLC patients were enrolled: 101 with *BRAF* V600E and 17 with other potentially activating mutations (4 G466, 4 G469, 1 G596, 5 K601, and 3 N581). Median age was 68 years (range 34–85), 71% smokers, 48% females, 100% non-squamous histology, and 20% with ECOG PS 2. Most frequent grade ≥3 adverse events (AEs) were asthenia (9% of patients), epidermoid carcinoma (6%), dermatitis (5%), and increased GGT (5%). Three toxic deaths were reported: 1 nausea and vomiting leading to dehydration, 1 pneumonia, and 1 neutropenic sepsis.

	Included N=118	Analyzed N=115[1a]	Best overall response: CR	PR	SD	PD	Death (before any assessment)	Not evaluable (no tumor assessment)	Mean ORR [95% CI]	Bayesian Analysis conclusion	Median duration of response [95% CI]	mPFS [95% CI]	mOS [95% CI]
NSCLC V600 mutated	101	100	0	43	21	16	12	8	44.9% [35.2; 54.8]	**Efficacy boundary reached:** P(ORR≥30%) ≥ 90%	6.5 months [5.1-7.3]	5.2 months [3.8; 6.9]	9.3 months [6.8;14.9]
NSCLC Non-V600 mutated	17	15	0	0	1	10	2	2	5.9% [0.2; 20.6]	**Stop for inefficacy:** P(ORR≤10%) ≥80%	NA	1.8 months [1.4; 2.1]	5.2 months [2.8; 24.6]

[1a] *Three patients without treatment.*

Nine patients were still on treatment at the cut-off date, 106 had stopped vemurafenib (65 PD, 26 AEs, 3 deaths, 1 doctor's decision, 11 patient's decisions). **Conclusion:** Vemurafenib provided reasonable response rate and extended PFS in pretreated NSCLC patients with *BRAF* V600E mutations but was not effective in those with other *BRAF* mutations. These results emphasize the need of integrating *BRAF* V600E in routine biomarkers screening.

Keywords: NSCLC, Vemurafenib, BRAF mutation

OA12.06 MUTATIONAL LANDSCAPE OF BRAF V600E POSITIVE LUNG CANCER PATIENTS FOLLOWING BRAF DIRECTED THERAPY FAILURE

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Background: *BRAF* V600E mutation is identified as molecular drivers in 1-2% of lung adenocarcinomas and predicts response to combination BRAF and MEK inhibitors. Little is known about molecular mechanisms of acquired resistance to these therapies for lung cancer patients with *BRAF* V600E mutations, partially due to a lack of representative cancer models. **Method:** We identified patients with *BRAF* V600E mutated lung cancer who were progressing after initial response to a BRAF/MEK inhibitor combination in 5 academic institutions in the US. Potential molecular mechanisms of resistance were explored by comparing pre- and post-therapy results from comprehensive tissue and/or the Guardant360 and FoundationACT plasma-based next generation sequencing assays. **Result:** We identified 6 patients. Prior to treatment with a BRAF/MEK inhibitor combination, four patients had received at least one line of chemotherapy and immune checkpoint inhibitor monotherapy, one had received chemotherapy only and one was treatment naïve. Five patients received dabrafenib/trametinib and one vemurafenib/cobimetinib combination. All 6 patients achieved a partial response. Progression free survival (PFS) ranged from 3 to 15 months (median 9.5 months). At the time of progression, all patients had the *BRAF* V600E mutation re-identified in their samples. Additionally, there was one patient with a new *AKT1* E17K and a new *KRAS* G12A mutation, one patient with a new *VHL* R167Q mutation and one patient with a new *TP53* splice site indel mutation at the time of progression. Another two patients had *AKT1* E17K mutations that were present prior to BRAF/MEK inhibitor therapy. They both had oligoprogression, one in lymph nodes and one in the brain after 5.2 and 3 months, respectively; both continued on dabrafenib and trametinib combination therapy after radiation treatment to the progressing sites. Interestingly, co-occurrence of *AKT1* E17K and *BRAF* V600E mutations is rare in the TCGA data, but was identified in three of six patients in our case series. Finally, we have established a *BRAF* V600E positive lung adenocarcinoma cell line from a TKI naïve patient for further functional studies of drug resistance. **Conclusion:** Comprehensive molecular testing can identify potential resistance mechanisms following progression of *BRAF* V600E positive lung cancer to TKI therapy. *AKT1* mutations were common as co-alterations in *BRAF* V600E mutated lung adenocarcinoma before and after targeted therapy and may contribute to drug resistance. The development of patient-derived cell line models may assist in the identification and validation of drug resistance mechanisms, and may help devise strategies to overcome drug resistance.

Keywords: BRAF V600E, AKT1 E17K, drug resistance

OA12.07 CLINICAL ACTIVITY OF LOXO-292, A HIGHLY SELECTIVE RET INHIBITOR, IN PATIENTS WITH RET FUSION+ NON-SMALL CELL LUNG CANCER

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Background: *RET* kinase gene fusions are actionable drivers that occur in ~2% of non-small cell lung cancers (NSCLC). However, the clinical activity of multikinase inhibitors (MKIs) with anti-RET activity in *RET* fusion+ NSCLC patients has been limited. LOXO-292 is a highly selective RET inhibitor, with preclinical activity against diverse *RET* fusions, potential acquired resistance mutations, and against brain metastases. **Method:** LIBRETTO-001 is a multicenter global phase 1/2 study (26 sites, 9 countries) enrolling patients w/ advanced solid tumors (NCT03157128) including *RET* fusion+ NSCLC. Patients are dosed orally in 28-day cycles with dose escalation following a 3+3 design. The primary endpoint is MTD/recommended dose determination. Secondary endpoints include safety, overall response rate (ORR, RECIST 1.1) and duration of response (DoR). Initial data were presented at the ASCO 2018 Annual Meeting. **Result:** As of 02-April 18, 82 solid tumor patients (including 38 RET fusion+ NSCLC) were treated at 8 doses (20 mg QD-240 mg BID). The MTD was not reached. AEs (≥10% of patients) were fatigue (20%), diarrhea (16%), constipation (15%), dry mouth (12%), nausea (12%), and dyspnea (11%); most were grade 1-2. 2 TEAEs ≥ grade 3 were attributed to LOXO-292 (Gr3 tumor lysis syndrome, Gr3 increased ALT). Of the 38 *RET* fusion+ NSCLC pts, 30 had at least 1 post-baseline assessment or discontinued LOXO-292 prior to such assessment. 26 of 30 patients (87%) had >20% radiographic tumor reduction (range: -21 to -72%). The ORR was 77% (23/30, 3 responses pending confirmation) with a confirmed ORR of 74% (20/27, excluding 3 patients with unconfirmed responses). The response rate was similar regardless of prior MKI treatment (12/15 MKI-naïve, 11/15 MKI pretreated). Responses occurred independent of upstream fusion partner when known (13/16 *KIF5B* vs 9/11 other) and included patients w/ baseline brain metastases. Most patients remained on treatment (33/38), including all responders. The median DoR was not reached (longest response was the first responder: >10+ months). Rapid plasma clearance of *RET* variants was observed, with complete clearance by day 15 in 10 of 17 (59%) NSCLC patients with assessable baseline and day 15 ctDNA. **Conclusion:** LOXO-292 was well-tolerated and had marked antitumor activity in *RET*-fusion+ NSCLC patients, including those w/ resistance to prior MKIs and brain metastases. Phase 2 cohorts are now open globally (160 mg BID). Updated safety and efficacy data as of 19 Jul 2018 will be presented.

Keywords: RET, LOXO-292, fusion

OA13 THERAPEUTICS AND RADIATION FOR SMALL CELL LUNG CANCER
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

OA13.01 THE IMPACT OF [^{18}F]FLUDEOXYGLUCOSE PET/CT IN SMALL-CELL LUNG CANCER: ANALYSIS OF THE PHASE 3 CONVERT TRIAL

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Background: The role of ^{18}fludeoxyglucose (^{18}F-FDG) PET/CT in the management of limited stage small-cell lung cancer (LS-SCLC) is uncertain. Previous studies have shown that ^{18}F-FDG PET/CT upstages up to 30% of LS-SCLC patients. Data from the CONVERT trial was analysed to investigate the impact of ^{18}F-FDG PET/CT in the management of LS-SCLC. The prognostic significance of pre-treatment ^{18}F-FDG PET parameters was also investigated in an exploratory analysis. **Method:** CONVERT is an international multi-centre phase III trial that randomly assigned fit patients to receive either twice-daily (45Gy in 30 fractions) or once-daily (66Gy in 33 fractions) radiotherapy starting on day 22 of chemotherapy cycle 1 (NCT00433563). Chemotherapy consisted of 4-6 cycles of cisplatin and etoposide. Prophylactic cranial irradiation was offered, if indicated. Contrast-enhanced thorax and abdomen CT and brain imaging (with/without bone scintigraphy according to clinical indication) were mandated for all CONVERT participants (conventional imaging). Staging with ^{18}F-FDG PET/CT was allowed but not mandated. The primary endpoint was overall survival. Pre-treatment ^{18}F-FDG PET metabolic parameters were investigated in a subset of patients (n=96) including standardised uptake values (max, mean and peak), volumetric and heterogeneity parameters. **Result:** Of 547 patients recruited to CONVERT, 540 patients with data on staging investigations and outcome were included in this analysis. The use of staging ^{18}F-FDG PET/CT was variable in the 8 countries recruiting to CONVERT (range, 41-100%). Compared to patients who underwent conventional imaging (n=231), patients who were also staged with ^{18}F-FDG PET/CT (n=309) had smaller gross tumour volume (p=0·003), were less likely to have elevated pre-treatment serum lactate dehydrogenase (p=0·035), and received more chemotherapy cycles (p=0·026). There were no other significant differences in baseline and treatment characteristics between the two groups. There were no significant differences in overall (hazard ratio 0·87 [95% CI 0·70-1·08]; p=0·192) and progression-free survival (hazard ratio 0·87 [95% CI 0·71-1·07]; p=0·198) between patients staged with ^{18}F-FDG PET/CT in addition to conventional imaging or with conventional imaging alone. These results were observed irrespective of treatment group (once-daily and twice-daily radiotherapy). Pre-treatment ^{18}F-FDG PET parameters were also not prognostic. **Conclusion:** In CONVERT, survival outcomes were not different in LS-SCLC patients staged with or without ^{18}F-FDG PET/CT. This was despite those patients staged with ^{18}F-PET/CT having more favourable baseline and treatment characteristics. Our findings suggest that conventional imaging is sufficient to select LS-SCLC patients for concurrent chemoradiotherapy.

Keywords: PET/CT, SCLC, CONVERT

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OA13.02 TWO NOVEL IMMUNOTHERAPY AGENTS TARGETING DLL3 IN SCLC: TRIALS IN PROGRESS OF AMG 757 AND AMG 119

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Background: Small cell lung cancer (SCLC) is an aggressive neuroendocrine tumor characterized by initial response to chemotherapy and radiotherapy followed by relapse or progression with chemoresistant disease. Delta-like ligand 3 (DLL3) is an inhibitory Notch ligand that is specifically upregulated in SCLC. IHC profiling of tumor samples showed DLL3 expression in 86% of SCLC tumors and minimal expression in normal tissue.

We are conducting clinical trials of two novel immunotherapy agents that target DLL3. AMG 757 is a half-life extended bispecific T cell engager (BiTE®) antibody construct that is designed to transiently crosslink DLL3-positive SCLC cells to CD3-positive T cells and induce T cell–mediated tumor cell lysis and concomitant T cell proliferation. AMG 119 is an adoptive cellular therapy that consists of a patient's autologous T cells that have been genetically modified ex vivo to express a transmembrane chimeric antigen receptor that targets DLL3 on the surface of SCLC cells. Both AMG 119 and AMG 757 showed potent killing of SCLC cell lines with a broad range of DLL3 expression in vitro and inhibition of tumor growth in the SHP-77 human SCLC xenograft model in vivo. AMG 757 was well tolerated in a preclinical multi-dose GLP toxicology study, with no evidence of tissue damage at weekly doses as high as 4.5 mg/kg.

Method: NCT03319940 is an open label, phase 1 study evaluating the safety, tolerability and pharmacokinetics of AMG 757 that will initially enroll adult patients with SCLC who have progressed or recurred following platinum-based chemotherapy. Key inclusion criteria: ECOG PS 0–2, life expectancy ≥12 weeks, at least 2 measurable lesions per modified RECIST 1.1 criteria, and adequate organ function. The study will later enroll patients with extended disease SCLC with ongoing clinical benefit following no more than 6 cycles of first-line platinum-based chemotherapy. AMG 757 will be administered as an intravenous infusion once every 2 weeks.

NCT03392064 is an open-label, phase 1 study evaluating the safety, tolerability and efficacy of AMG 119 in adult patients with SCLC whose disease has progressed or recurred after at least one platinum-based regimen. Key inclusion criteria: ECOG PS 0–1, at least 2 measurable lesions per modified RECIST 1.1 criteria, no evidence of CNS metastasis, and adequate organ function. AMG 119 will be administered as a one-time intravenous infusion.

Both of these studies are currently enrolling patients. For more information, please contact Amgen Medical Information: medinfo@amgen.com.

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WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

OA13.03 ANLOTINIB AS THIRD-LINE OR FURTHER-LINE TREATMENT IN RELAPSED SCLC: A MULTICENTRE, RANDOMIZED, DOUBLE-BLIND PHASE 2 TRIAL

Y. Cheng[1], Q. Wang[2], K. Li[3], J. Shi[4], L. Wu[5], B. Han[6], G. Chen[7], J. He[8], J. Wang[9], H. Qin[10], X. Li[11]

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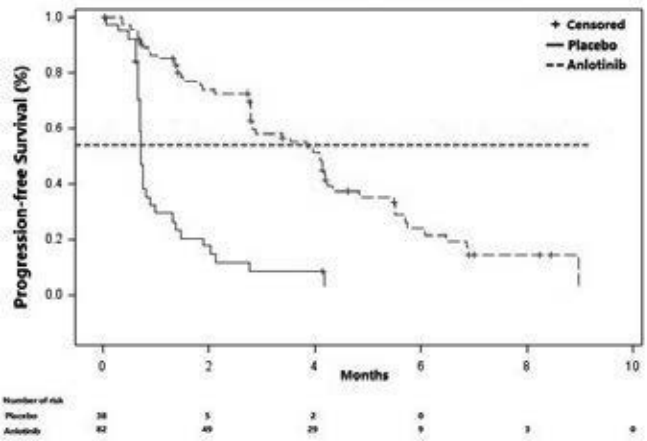
Background: Treatment for patients with relapsed small cell lung cancer (SCLC) who failed ≥ 2 lines of chemotherapy have high unmet needs. Anlotinib is a novel TKI with highly selective inhibition effects on multi-targets, especially on VEGFR, c-Kit, PDGFR, FGFR. Here we report results of a phase 2 study of anlotinib for the third-line and further-line treatment of SCLC. (ALTER1202, NCT03059797). **Method:** Eligible either limited- or extensive-stage SCLC patients with disease progression after ≥ 2 lines of chemotherapy were randomized 2:1 to anlotinib or placebo (12 mg PO QD from day 1 to 14, every 3 weeks). The primary endpoint was PFS and secondary endpoints was OS, ORR, DCR, quality of life and safety. **Result:** Between March 2017 and May 2018, 120 patients from 11 centers were randomized to either anlotinib arm (n=82) or placebo arm (n=38). Until the data cutoff date (30 Jun 2018), median PFS was 4.1 months (95%CI, 2.8 to 4.2 months) in anlotinib arm and 0.7 months (95% CI, 0.7 to 0.8 months) in placebo arm (HR, 0.19; 95% CI, 0.12 to 0.32, p<0.0001). OS data were not sufficiently mature for analysis. Although ORR was similar, considerable improvement in DCR was observed in

anlotinib arm (71.6% vs 13.2%, p<0.0001). Treatment-related adverse events (TRAEs) occurred more frequently in anlotinib arm than that in placebo (87.7% and 74.4%). The most common TRAEs were hypertension, anorexia, fatigue, and hand-foot syndrome. Grade ≥3 TRAEs occurred in 29 (35.8%) of patients in anlotinib arm and 6 (15.4%) in placebo arm, respectively.



Conclusion: ALTER 1202 study demonstrates anlotinib should be considered a treatment option for patients with relapsed SCLC who have experienced treatment failure with two lines of chemotherapy. The safety profile was consistent with the previous report and no newly adverse events were identified.

Keywords: Anlotinib, 3rd line, relapsed SCLC

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OA13.05 PROPHYLACTIC CRANIAL IRRADIATION (PCI) FOR LIMITED-STAGE SMALL-CELL LUNG CANCER: RESULTS FROM THE PHASE 3 CONVERT TRIAL

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Background: PCI is considered standard of care in limited-stage small-cell lung cancer (LS-SCLC) patients. However the impact of the dose and fractionation of thoracic radiotherapy (RT) on the risk of developing brain metastasis (BM) has not been evaluated prospectively. **Method:** CONVERT is an international, phase 3 trial that randomly assigned patients to receive twice-daily (BD 45Gy in 30 fractions) or once-daily (OD 66Gy in 33 fractions) RT starting on day 22 of chemotherapy (CT) cycle 1 (NCT00433563). PCI was offered, if indicated. Data on thoracic and brain RT delivery and timing, rate of BM and overall survival (OS) in patients treated with PCI was analysed. The association of the risk of developing BM/OS and predictor variables, using a competing risk regression model developed by Fine and Gray for BM or the standard Cox proportional hazards model for OS, was investigated. **Result:** Of 547 patients recruited to the study, 449 (82%) received PCI after completion of CTRT. PCI was delivered to 220/273 participants (81%) in the BD group and 229/270 in the OD group (85%; p=0.49). Pre-CTRT brain imaging consisted of CT-scan in 356/449 patients (79%) and MRI in 83/449 (18%) patients. Total median PCI dose was 25 Gy in both BD and OD groups (p=0.74). PCI was delivered later after CT in the OD group compared to the BD group (median days post CT 37 vs. 35 days, respectively; p=0.04). In patients who received PCI, 75 (17%) developed BM (35 [8%] in OD and 40 [9%] in BD) and 173 (39%) other extracranial progression. In the univariate analysis, GTV was associated with an increased risk of BM (HR: 1.37 [95%CI 1.09-1.73]; p=0.007) or other radiological progression events (HR: 1.43 [95%CI 1.11-1.85]; p=0.006), whereas in a multivariate analysis both GTV and PS were associated with either progression type. The median OS of patients treated with PCI was 29 months (95%CI 25.8-35.7). Median OS was 28 months in BD (95%CI 22-35) and 31 months in OD (95%CI 27-52; p=0.1). In the univariate analysis of OS, PCI timing from end of CT, weight loss >10%, and thoracic GTV were prognostic factors associated with OS. In the multivariate analysis, only thoracic GTV was associated with OS. Delay between end of CT and PCI was not associated with OS (p=0.2). **Conclusion:** Patients receiving OD or BD thoracic RT have the same risk of developing BM. Larger tumours are associated with a higher risk of BM.

Keywords: small-cell lung cancer, prophylactic cranial irradiation, CONVERT trial

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OA13.06 FINAL REPORT OF A PROSPECTIVE RANDOMIZED STUDY ON THORACIC RADIOTHERAPY TARGET VOLUMES WITH RADIATION DOSIMETRIC AND PATHOLOGIC ANALYSES

X. Hu[1], Y. Bao[2], Y. Xu[1], H. Zhu[3], J. Liu[4], L. Zhang[5], X. Yu[6], Y. Fan[6], Y. Zhang[6], W. Sun[3], W. Mao[7], M. Chen[8]

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This abstract is under embargo until September 26 at 10:30 Eastern Time.

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WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

OA13.07 SURVIVAL OUTCOMES AFTER WHOLE BRAIN RADIOTHERAPY FOR BRAIN METASTASES IN ELDERLY PATIENTS WITH NEWLY DIAGNOSED METASTATIC SMALL CELL CARCINOMA.

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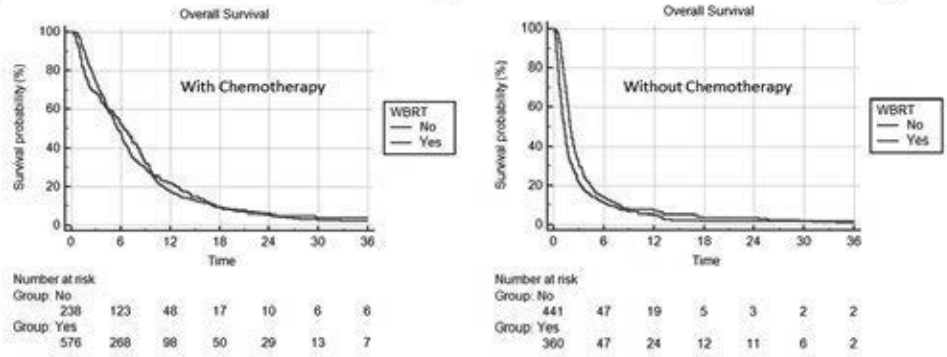
Background: Small cell lung cancer (SCLC) is an aggressive malignancy with a tendency to affect the elderly and to metastasize to the brain. However, elderly patients tolerate whole brain radiotherapy (WBRT) poorly with potentially detrimental effects on quality of life. Accordingly, the survival benefit of WBRT in this population is unclear. We utilized the national cancer database (NCDB) to evaluate the survival outcomes following WBRT in elderly patients with SCLC and brain metastases. **Method:** We analyzed 1615 patients ≥75 years old diagnosed with SCLC and brain metastases at diagnosis. Patients were categorized by type of therapy: chemotherapy + WBRT (n=576), chemotherapy alone (n=238), WBRT alone (n=360) and no chemotherapy or WBRT (n=441). Clinical and demographic characteristics were reported for each treatment cohort with a subsequent multivariable regression analysis for survival. Propensity score-matching analysis was used for balance between comparison groups. **Result:** Median patient age was 79 years. 51% had brain-only metastatic disease. Whole brain radiation median dose delivered was 30 Gy (1.8-40 Gy). Median follow up was 2.8 months (0.03-68.01) for all patients. Of the patients included in this study, 1530 had died at time of analysis yielding a median OS of 2.9 months with 6 month and 1 year survivals of 31% and 12%, respectively. For patients without chemotherapy, median OS with WBRT was 1.9 months compared to 1.2 months without WBRT (p<0.0001). For patients receiving chemotherapy with, and without WBRT, median OS was 5.6 months and 6.4 months, respectively (p=0.43). Multivariable cox regression revealed age >80, extracranial disease, male sex, and rural location as predictors of increased risk of death.

(See next page)

Figure 1. Overall Survival With WBRT in Elderly Patients With and Without Chemotherapy



Conclusion: In elderly patients 75 years old or greater with SCLC brain metastasis, WBRT was associated with a modest increase in survival in patients not fit for chemotherapy, and there was no association with increased survival over chemotherapy alone.

Keywords: small cell lung cancer, brain metastases, elderly

MA01 EARLY STAGE LUNG CANCER: QUESTIONS AND CONTROVERSIES
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

MA01.01 PROPOSAL ON INCORPORATING LYMPHOVASCULAR INVASION AS A T-DESCRIPTOR FOR STAGE I NON-SMALL CELL LUNG CANCER

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Background: Lymphovascular invasion (LVI) and Visceral Pleural Invasion(VPI) have been reported to be risk factors for stage I Non-Small Cell Lung Cancer (NSCLC). However, only VPI was incorporated into the current 8th Tumor–Node–Metastasis(TNM) classification. This study aimed at exploring the prognostic impact of LVI on TNM staging in Pathological Stage I NSCLC. **Method:** We retrospectively reviewed 2600 consecutive p-stage I NSCLC patients in the Shanghai Chest Hospital (2008-2012). By using the Kaplan–Meier method and Cox proportional hazard regression model, we identified the correlations between LVI, VPI and clinical outcomes in p-stage I NSCLC. **Result:** Of all p-stage I NSCLC 2600 patients, 221 were pathologically diagnosed with LVI and 815 pathologically with VPI, respectively. It was observed that patients with LVI had an unfavorable lung cancer specific survival (LCSS) (hazard ratio [HR]: 1.883; 95% confidence interval [CI]: 1.351-2.625; P < 0.001) and recurrence-free survival (RFS) (HR: 2.025; 95% CI: 1.560-2.630; P < 0.001). The 5-year RFS rates of patients with LVI was significantly worse than those without LVI (61.2% VS 82.7%, P< 0.001). Patients with LVI exhibit similar prognosis (HR: 2.538; 95% CI: 1.570-4.098; P < 0.001) compared with that of VPI in pN0 non-small-cell lung cancer and a tumor diameter of 3cm or smaller. When tumor size was between 3-4cm, patients with LVI and VPI were associated with inferior prognosis than those with only LVI or VPI (P < 0.001). **Conclusion:** The presence of LVI independently and significantly affects LCSS and RFS in patients with stage I NSCLC. Our results suggest that stage T1a-1c(IA) patients with LVI should be upstaged to T2a(IB), meanwhile, stage T2a(IB) patients coexist with LVI and VPI should be upstaged again in the TNM classification.

Keywords: TNM classification, lymphovascular invasion, visceral pleura invasion

MA01 EARLY STAGE LUNG CANCER: QUESTIONS AND CONTROVERSIES
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

MA01.02 HISTOLOGIC SUBTYPING IN PATHOLOGIC STAGE I LUNG ADENOCARCINOMA PROVIDES RISK-BASED STRATIFICATION FOR SURVEILLANCE

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Background: Current national practice guidelines (NCCN, ACCP, ESMO) recommend a uniform follow-up protocol with intensive surveillance within the first two years following lung resection for stage I NSCLC. We hypothesize that the recurrence hazard following lung resection for stage I lung adenocarcinoma (ADC) varies according to histologic subtype. **Method:** A total of 1572 patients with resected pathologic stage I lung ADC were investigated. Two thoracic pathologists reviewed all tumor H&E slides (range 1-8, median 3) for histologic subtyping and percentage of each subtype. Recurrence hazard was estimated using the Kernel-Epanechnikov smoothing procedure. Association between recurrence hazard and high-grade histologic subtypes (micropapillary [MIP] and solid [SOL]) was assessed. **Result:** Presence (≥5%) of these high-grade subtypes (MIP and/or SOL) was associated with significant increase of recurrence hazard compared to high-grade pattern negative (<5%) tumors (Figure): 1) patients with presence of either MIP or SOL had significant recurrence hazard peaks within two years after surgery; 2) SOL was associated with early hazard peak at the first year after surgery especially in distant recurrence hazard; 4) one-third of patients (515/1572, 33%) had no high-grade subtypes, in which the recurrence hazard was consistently very low (<2% risk each year) during the 10-year period after surgery without any hazard peak (red arrow).

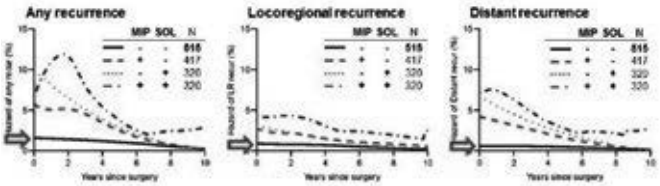

Figure. Hazard function of recurrence for MIP and SOL combination patterns is shown. In 515 patients (33%) without MIP and SOL, the recurrence hazard is consistently very low (<2% hazard in each year) during the 10-year period after surgery without any hazard peak (red arrow).

Conclusion: Our data suggest the utility of histologic subtyping for identifying patients with very low recurrence hazard, and provide foundation for establishing risk-based follow-up protocols. A potential option for low-risk patients may be omission of intensive follow-up during the first two years after surgery.

Keywords: follow up, micropapillary, hazard function

MA01 EARLY STAGE LUNG CANCER: QUESTIONS AND CONTROVERSIES
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

MA01.03 AN EXTERNALLY VALIDATED NOMOGRAM FOR PREDICTING DISTANT METASTASIS AFTER SBRT FOR EARLY STAGE NON-SMALL CELL LUNG CANCER

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Background: SBRT is a standard option for patients with early stage NSCLC who are medically inoperable. While SBRT is associated with excellent local control, distant metastases (DM) represent the primary pattern of failure. Adjuvant systemic therapy has not traditionally been used in this patient population due to medical comorbidities. With the advent of immunotherapy that may be better tolerated, there has been a renewed interest in identifying patients that may derive benefit. We developed and internally validated a nomogram to predict the likelihood of DM after SBRT for early stage NSCLC which was then externally validated. **Method:** Our lung SBRT registry was queried for patients with early stage NSCLC treated with definitive intent from 2003-2017 and 1002 patients were identified for analysis to develop the model. A dataset from an external institution was used to similarly identify patients and 737 were used for the validation cohort. Random Survival Forest was used to assess importance, interactivity, and overall predictive ability with respect to DM for 14 variables. A Fine-Gray competing-risks regression model was formulated where apparent interactions were examined with likelihood-ratio tests. Backward variable selection was implemented to reduce to a parsimonious model. The concordance probability (C-index) of the model was internally validated with 10-fold cross validation. **Result:** The median overall survival was 1.71 years internally and 1.92 years externally. Median follow-up was 18.3 months and 21.1 months. 1-year incidence of DM was 16% and 12.1% in the internal and external cohorts, respectively. Random Forest analysis suggested that tumor size and PET SUV are the most important predictors of distant failure. The 1-year cumulative incidence (CI) of DM was 18.5% for PET SUV ≥4.1 vs 8.4% for <4.1. 1-year CI for tumor size >3 cm was 26% vs 12.6% for ≤3 cm. The median time to DM was 0.86 years internally and 1.1 years externally. The final nomogram included tumor size, histology, PET SUV, age, KPS, and active smoking status, and had a cross-validated C-index of 0.62. The nomogram provides predictive value for probability of DM at 1-year between 10 and 70%. **Conclusion:** This novel nomogram with external validation can be used to predict the 1-yr DM risk after SBRT for patients with early-stage NSCLC, accounting for the competing risk of death. This nomogram may help define patient subsets for stratification in future clinical trials to help identify who may benefit from adjuvant systemic therapy after SBRT to reduce the incidence of DM and disease-related death.

Keywords: Immunotherapy, Distant failure, SBRT

MA01.05 OPIOIDS AND SLEEP MEDICATION USE AFTER SURGERY FOR EARLY STAGE LUNG CANCER: A SEER-MEDICARE ANALYSIS

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Background: More than 50% of patients undergoing surgery for early stage lung cancer experience persistent post-operative pain, which can prevent their returning to normal daily activities and cause disruptions in sleep. Whether Video-Assisted Thoracoscopic Surgery (VATS), a minimally invasive surgical technique, reduces long-term opioid and sleep medication use compared to traditional open surgery has not yet been established. **Method:** The Surveillance, Epidemiology and End Results data linked to Medicare data (SEER-Medicare) database was queried to identify patients with stage I primary non-small cell lung cancer (NSCLC) who had VATS or open resection between 2007 to 2013, and had no record of opioid medication in the 30 days before surgery. Long-term opioid and sleep medication use were defined as having fulfilled one or more prescriptions in the first 90 days after surgery as well another prescription in the 90-180 days post-surgery. Logistic regression was used to investigate the associations between surgical type and long-term opioid and sleep medication use. Models were adjusted for relevant clinical and socioeconomic covariates. **Result:** There were 3,900 NSCLC patients included in this analysis; 1,987 (51.0%) VATS and 1,913 (49.0%) open surgery patients; 15.5% of patients had a record of opioid use and 9.7% of sleep medication use long-term postoperatively. In the adjusted model, patients were less likely to use opioids long-term if they had VATS (OR_{adj} 0.69, 95% CI: 0.57-0.84), were older (ORadj 0.96, 95% CI: 0.94-0.98), diagnosed in a later year (OR_{adj} 0.86, 95% CI: 0.82-0.90), and had higher income (OR_{adj} 0.77, 95% CI: 0.60-0.99). Long-term opioid use was more likely in those with a higher comorbidity score (OR_{adj} 1.10 , 95% CI: 1.05-1.16), large cell histology (OR_{adj} 1.88, 95% CI: 1.17-3.00), using sleep medication before surgery (OR_{adj} 1.72, 95% CI: 1.28-2.32) and with a previous psychiatric condition (OR_{adj} 1.64, 95% CI: 1.28-2.09). After adjustment, only those with a previous psychiatric condition (OR_{adj} 1.95, 95% CI: 1.40-2.71) and previous sleep medication use (OR_{adj} 37.36, 95% CI: 27.92-50.00) were more likely to use sleep medications long-term; no significant difference were observed with type of surgery (OR_{adj} 1.01, 95% CI: 0.76-1.33). **Conclusion:** Patients who were not previous opioid users became long-term opioid users after surgery. VATS might offer NSCLC patients a better quality of life than open surgery, and therefore minimize the risk of longer-term opioid use.

Keywords: VATS, NSCLC, Opioids

MA01.06 EVALUATION OF SAFETY AND EFFICACY IN SURGICAL TREATMENT FOR OCTOGENARIAN LUNG CANCER PATIENTS BY MULTICENTER PROSPECTIVE STUDY: JACS1303

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Background: The percentage of octogenarian lung cancer patients have increased on the background of the aging of Japan's demographics. Although some retrospective studies reported clinicopathological scoring systems for predicting postoperative complications and survival outcomes for elderly lung cancer patients, optimized scoring systems remain controversial. This study (JACS1303) aims to evaluate the clinical factors to develop a comprehensive operative risk scoring (RS) system for octogenarian patients with lung cancer. **Method:** JACS conducted a nationwide multicenter prospective cohort and enrolled a total of 1,019 octogenarians with medically operable lung cancer. Details of the clinical factors, comorbidities, and comprehensive geriatric assessment were recorded for 895 patients to develop a comprehensive risk scoring (RS) system capable of predicting severe complications. **Result:** Operative (30 days) and hospital mortality rates were 1.0% and 1.6%, respectively. Complications were observed in 308 (34%) patients, of whom 81 (8.4%) had grade 3–4 severe complications. Pneumonia was the most common severe complication, observed in 27 (3.0%) patients. The following five predictive factors: gender, comprehensive geriatric assessment $(CGA)7_5$: memory, Simplified Comorbidity Score (SCS): diabetes mellitus, Alb, and %VC were identified as independent predictive factors for severe postoperative complications (odds ratio = 2.73, 1.86, 1.54, 1.66, and 1.61, respectively) through univariate and multivariate analyses. A 5-fold cross validation was performed as an internal validation to reconfirm these five predictive factors (average AUC: 0.70). We developed a simplified RS system as follows: RS = 3 (Gender: male) + 2 (CGA75: memory: yes) + 2 (Alb: <3.8 ng/ml) + 1 (%VC: ≤90) + 1 (SCS: Diabetes mellitus: yes). **Conclusion:** The current study shows that octogenarians can be successfully treated for lung cancer with surgical resection with an acceptable rate of severe complications and mortality. We propose a simplified RS system to predict severe complications in octogenarian patients with medically operative lung cancer.

Keywords: Octogenarian, lung cancer, Surgery

MA01.07 VALIDATION OF RTOG 0813 NORMAL TISSUE CONSTRAINTS FOR PULMONARY TOXICITY IN SBRT FOR CENTRAL NON-SMALL CELL LUNG CANCER

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Background: Stereotactic body radiation therapy (SBRT) yields excellent local control rates for medically inoperable early stage "central" non-small cell lung cancer. Normal tissue constraints provided in RTOG 0813, which tested safety and efficacy of lung SBRT for central tumors, were largely based on expert estimates, and clinical validation of constraints is limited. We sought to identify the sensitivity and specificity of the current RTOG constraints for predicting pulmonary toxicity in a large institutional data set. **Method:** We identified 136 lesions within 2 cm of the proximal bronchial tree (PBT), treated from 2005 to 2014 from a prospective registry of 1,462 patients. Dose was 50 or 60 Gy given in 5 fractions. Pulmonary toxicity was categorized as pneumonitis or non-pneumonitis (fistula, bronchial stenosis or necrosis, atelectasis, hemoptysis, or clinically significant pleural effusion). A series of dose endpoints for the PBT was generated based on dose volume histograms, where dose levels ranged from 0 Gy to 80 Gy in increments of 0.1 Gy, and volumes ranged from 0.03 cc to 50 cc in increments of 0.03cc. A total of 1,333,600 dosimetric endpoints were analyzed. The sensitivity and specificity of these endpoints in predicting pulmonary toxicity was calculated. The optimal dosimetric endpoint was chosen by identifying the highest F-score. **Result:** We observed nine Grade 2 pneumonitis and 10 Grade ≥ 2 non-pneumonitis toxicities, of which three were Grade 5 (broncho-pleural fistula, left mainstem bronchus necrosis, and bronchial stenosis). The optimal dosimetric endpoint to avoid Grade 2-5 non-pneumonitis toxicity was D0.03cc<50 Gy to the PBT, with 90% sensitivity and 77% specificity. The optimal point dose to avoid Grade 3-5 non-pneumonitis toxicity was D0.3cc<46.5 Gy, with 100% sensitivity and 85% specificity. Applying PBT RTOG constraints to our dataset achieved 18% sensitivity and 91% specificity for D4cc<18 Gy and 29% sensitivity and 93% specificity for D0.03cc<52.5 Gy. **Conclusion:** Clinical results from this large institutional data set validate current RTOG constraints for PBT as predictive for pulmonary toxicity. The results also suggest that RTOG constraints D4cc<18 Gy and D0.03cc<52.5 Gy to PBT have moderate sensitivity but excellent specificity for pulmonary toxicity. We identified D0.03cc <50 Gy to PBT as having the largest sensitivity and specificity for toxicity prediction, and this value parallels current RTOG constraint of D0.03cc <52.5 Gy. This analysis suggests that an additional volume/dosimetric constraint of D0.3cc<46.5 Gy may be considered for avoidance of Grade 3-5 non-pneumonitis pulmonary toxicity.

Keywords: toxicity, SBRT, central

MA01.09 RISK FACTORS OF RADIATION-INDUCED LYMPHOPENIA (RIL) AND ITS PROGNOSTIC SIGNIFICANCE IN SMALL LUNG CANCER PATIENTS TREATED WITH STEREOTACTIC BODY RADIATION THERAPY

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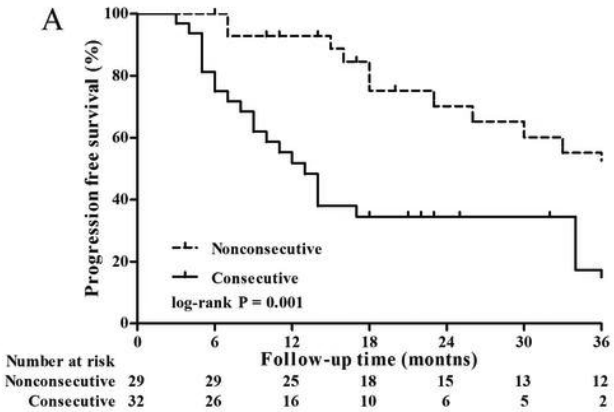
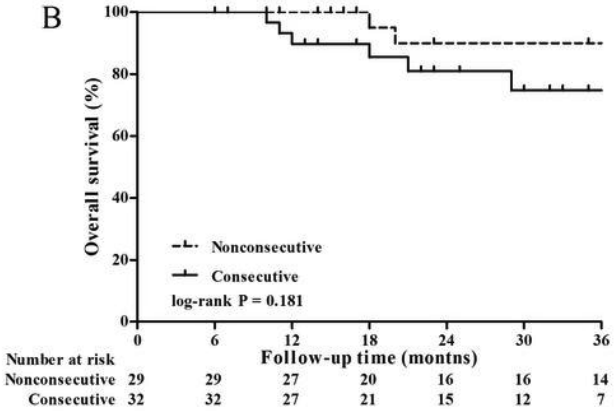
Background: The decrease in peripheral blood lymphocytes induced by radiation lessens the antitumour effect of the immune response, which might cause immunosuppression. This reduction might be affected by fractionation scheme. The purpose of this study was to assess the effect of fractionation scheme (consecutive daily fractions or nonconsecutive fractions) of SBRT on clinical outcomes in early-stage peripheral non-small cell lung cancer (NSCLC). We also analyzed the different effect of these two fractionation schemes in reducing peripheral blood lymphocytes during SBRT treatment period. **Method:** Data from a total of 61 early-stage peripheral NSCLC patients who had received SBRT were retrospectively analyzed. A total dose of 50 Gy in 5 fractions over 5-7 days was delivered for all patients. Peripheral blood lymphocytes were measured before and after SBRT. We used the Kaplan-Meier method, the log-rank test, and Cox proportional hazards regression to determine whether radiation treatment schedule associated with clinical outcomes. **Result:** Figure 1 showed Kaplan–Meier estimates for progression free survival (PFS) (Figure A) and overall survival (OS) (Figure B) for entire cohort stratifying for fractionation regimen. Multivariate analysis showed that nonconsecutive fractionation was an independent predictor of a longer PFS (P = 0.002). OS trended toward improvement in the non-consecutive group, but this was not statistically significant (P = 0.181). Development of any grade 3 or higher toxicity was not significantly different between the two groups (P = 0.813). The average circulating lymphocyte counts of consecutive group patients significantly declined after RT (1977.27 versus 1368.18 cells/μl, P < 0.001) while the nonconsecutive group patients did not (1700.00 versus 1450.00 cells/μl, P = 0.155).





Conclusion: Five-fraction SBRT delivered over non-consecutive days achieved superior clinical outcomes and similar toxicity compared to consecutive fractionation. Consecutive daily fractions of SBRT might cause worse immunosuppression by the more severe damage of peripheral lymphocytes.

Keywords: fractionation scheme, Stereotactic body radiation therapy, non-small cell lung cancer

MA01.10 TOXICITY AND LOCAL CONTROL IN "ULTRA-CENTRAL" LUNG TUMORS TREATED WITH SBRT OR HIGH-DOSE HYPOFRACTIONATED RT

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Background: Stereotactic body radiation therapy (SBRT) for central lung tumors has been associated with higher rates of severe toxicity. Data suggests that tumors with specific high-risk features, namely GTV abutting proximal bronchial tree (PBT), trachea or PTV intersecting esophagus ("ultra-central" tumors), are at risk of severe complications. We sought to evaluate toxicity and efficacy for high-risk lung tumors treated with SBRT in our institution. **Method:** All patients treated with SBRT for central lung tumors during 2008 to 2017 were reviewed to identify ultra-central tumors. Patients who received more than 4 Gy per fraction and $BED_{10} \geq 84$ were included in the analysis. The primary endpoint was grade 3+ adverse events potentially attributable to RT, based on CTCAE 4.0. Secondary endpoints were local control (LC) and overall survival (OS) for primary lung cancer patients, Kaplan-Meier analysis was used to estimate LC and OS. **Result:** We identified 88 patients who met the inclusion criteria (76 with abutment of PBT, 8 with abutment of trachea, 22 with overlap of esophagus, and 17 with multiple structures at risk). The median follow-up was 21.5 (95%CI, 12.5 to 30.5) months. Forty-six patients had primary NSCLC, 7 had locally recurrent NSCLC and 35 had lung metastases. The prescription doses were 400cGy x 15 (n=21), 750cGy x 8 (n=13), 1000cGy x 5 (n=29) and 900cGy x 5 (n=25). Eight patients (9.1%), all abutting the PBT, experienced fatal complications potentially related to RT. Four patients developed fatal pulmonary hemorrhage. Maximum point doses to PBT were 54.9Gy, 51.4Gy, 49.4Gy (in 5 fractions) and 63.8Gy (8 fractions) and 2 of them had received bevacizumab in close proximity to RT. Four patients developed fatal pneumonia/radiation pneumonitis (all had pre-existing COPD). No Grade 4 toxicity was identified. Grade 3 overall toxicity rate was 12.5%. Only 3 of 22 (13.6%) patients whose PTV overlapped with esophagus had Grade 3 toxicity. The 1-year and 2-year LC for the whole cohort were 87.5% and 79.1%, respectively. The 1, 2-year OS for primary NSCLC patients were 77.8% and 62.6%, respectively. **Conclusion:** To our knowledge, this is the largest reported series of patients who received SBRT for ultra-central tumors. RT achieves high rates of local control in these patients, but the rate of severe or fatal toxicity is substantial. Further studies are needed to establish the relationship between SBRT and toxicity in these patients.

Keywords: Ultra-central, SBRT, lung cancer

MA01.11 SALVAGE SBRT FOR LOCAL RECURRENCE AFTER PRIMARY SURGICAL RESECTION OF EARLY STAGE NON-SMALL CELL LUNG CANCER

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Background: To report on the patient, tumor and treatment characteristics of patients treated with salvage lung SBRT (sSBRT) for non-metastatic NSCLC that has relapsed after previous surgical resection, and the resulting clinical outcomes. **Method:** We surveyed our IRB-approved prospective lung SBRT registry for patients who received sSBRT for local recurrence after previous resection of an early stage NSCLC. Following sSBRT, outcomes of interest included local control (LC), overall survival (OS), and treatment-related toxicity graded per CTCAE version 4.0. **Result:** For the interval 2004-2017, 50 (3.4%) pts, of a total of 1,461 lung SBRT cases, met criteria for analysis. Pre-sSBRT surgical approaches were: 23 (46%) wedge resection, 2 (4%) segmentectomy, 20 (40%) lobectomy, 2 (4%) bilobectomy, 1 (2%) pneumonectomy and 1 (2%) with unspecified surgery. At the time of resection, disease stage

was: 34 (68%) stage I, 4 (8%) stage II, 5 (10%) stage III and for 3 (6%) pts, pre-operative stage was unknown. Median time to local recurrence after surgery was 27.45 months. At sSBRT, 38 (76%) pts had biopsy-proven recurrence while 12 (24%) had recurrence diagnosed only by radiographic findings. Forty seven (94%) pts could not have surgical salvage due to pulmonary (60%), cardiac (2%), technical unresectability (4%), poor KPS (2%), or multifactorial reasons (26%), with 3 (6%) refusing re-resection. Median age and KPS at salvage treatment was 74 years (range 50-89) and 80 (range 60-100) respectively. The most common sSBRT schedule was 50Gy in 5 fractions (68%), with all schedules having a BED of at least 100 Gy_{10}. Median follow up after sSBRT was 22.2 months (3.8-108.8 months). Eight pts subsequently experienced local or lobar failure (16%), and 9 patients had nodal failure (18%). Median time to local failure after sSBRT was 12.5 months (2-66.1 months). At analysis, 11 (22%) pts remain alive and free from disease progression. At 24 months, LC and OS were 83.6% (95% CI 71.1-96) and 66.7% (95% CI 53.3-80.1). Median OS after sSBRT was 29.3 months. Twenty one (42%) pts failed distantly at a median time of 11.4 months and 12 (24%) pts received systemic therapy following distant failure. 74% of pts experienced no toxicity after sSBRT and three patients (6%) developed grade III toxicity (cough, atelectasis or soft tissue necrosis). **Conclusion:** Similar to SBRT for primary early stage NSCLC, sSBRT for local relapse following initial surgical resection of NSCLC offers high rates of LC with limited toxicity. Distant failure remains the primary pattern of failure.

Keywords: Salvage SBRT, local recurrence, early stage NSCLC

MA02 IMPROVING OUTCOMES FOR PATIENTS WITH LUNG CANCER
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

MA02.01 ROS1 GENE REARRANGEMENTS ARE ASSOCIATED WITH AN EXAGGERATED RISK OF PERI-DIAGNOSIS THROMBOEMBOLIC EVENTS

T. Ng[1], D. Smith[2], R. Mushtaq[1], T. Patil[1], A. Dimou[1], S. Yang[3], Q. Liu[3], X. Li[4], C. Zhou[5], F. Yan[6], I.A. Bowman[7], S. Liu[8], R. Doebele[9], D. Aisner[10], S. Ren[11], R. Camidge[12]

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Background: Based on clinical observation, we hypothesized that ROS1 gene-rearranged non-small cell lung cancer (ROS1+ NSCLC) has a higher than expected thromboembolic event (TEE) rate. A multicenter, retrospective cohort study of TEE in advanced ROS1+, KRAS+, ALK+ and EGFR+ NSCLC was conducted. **Method:** Venous (DVT / PE) and arterial (MI/TIA/CVA) TEE within +/- 365 days of diagnosis of ROS1+, KRAS+, ALK+ or EGFR+ advanced NSCLC at 4 academic centers in USA and China from October 2002 to January 2018 were captured. The primary endpoint was the incidence of TEE in ROS1+ compared to KRAS+ NSCLC as a control group within +/- 90 days of diagnosis. Secondary endpoints compared TEE incidence between ROS1+ and ALK+, and ROS1+ and EGFR+. Fine-Gray Model was used to detect differences in TEE incidence while accounting for death as a competing risk. **Result:** 105 ROS1+, 101 ALK+, 112 EGFR+, and 114 KRAS+ NSCLC patients were enrolled. Incidence rate of TEE within +/- 90 days of diagnosis was 30.5% (32/105), 12.9% (13/101), 7.1% (8/112), and 12.3% (14/114) in the respective molecular cohorts. Compared to the ROS1+ cohort, the risk of TEE was significantly lower in the three other cohorts (KRAS+ HR 0.334, 95% CI: 0.18-0.62, p=0.001; ALK+ HR 0.357, 95% CI: 0.188-0.68, p=0.002; EGFR+ HR 0.193, 95% CI: 0.089-0.421, p<0.001) (**Figure 1**). First event TEEs were venous as opposed to arterial in 59.5% (22/37) ROS1+, 87.1% (27/31) ALK+, 80.6% (25/31) EGFR+, and 80% (16/20) KRAS+ cases. The median time (Interquartile Range) to TEE from the time of diagnosis for ROS1+/ALK+/EGFR+/ KRAS+ was 0 days (-6.75 to 7.0), 0 days (-20.0 to 35.0), 0.50 days (-43.7 to 21.3), and 13 days (0.49 to 32.0), respectively. **Conclusion:** Among common molecular subtypes of NSCLC, ROS1+ oncogene is associated with a significantly higher risk of developing TEE within +/- 90 days of advanced NSCLC diagnosis.

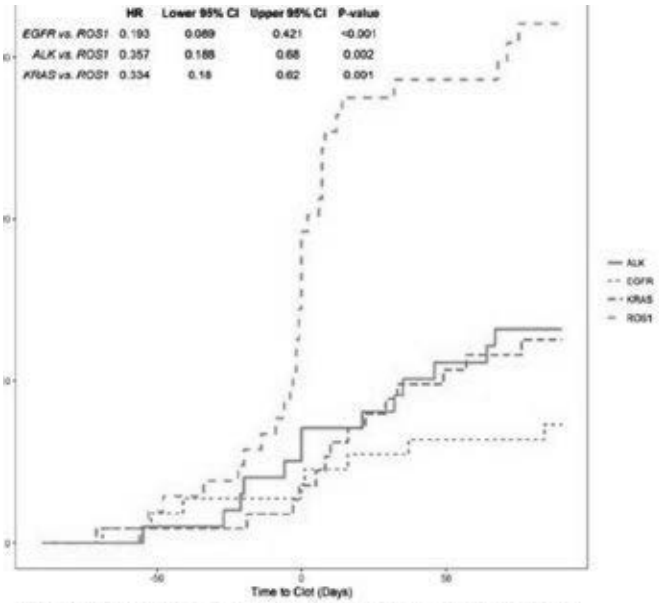

Figure 1. Cumulative incidence of clotting events by molecular driver group. Time 0 is stage IIIB or IV diagnosis.

Keywords: non-small cell lung cancer, thromboembolic events, ros1

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MA02.02 MULTISTATE HEALTHCARE NETWORK UNDERUTILIZES VALUABLE END-OF-LIFE RESOURCES IN STAGE IV NON-SMALL CELL LUNG CANCER

J. Rayburn[1], C. Wilshire[1], C. Gilbert[1], R. Weerasinghe[2], B. Louie[1], R. Aye[1], A. Farivar[1], E. Vallieres[1], J. Gorden[1]

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Background: Early implementation of outpatient palliative care (OPC) in stage IV non-small cell lung cancer (NSCLC) patients has been associated with increased survival, improved quality of life and reduction in unnecessary health care. However, medical systems have struggled with the adoption of end-of-life resources. We aimed to determine the utilization of OPC services in stage IV NSCLC patients within our multistate, community-based healthcare network. **Method:** We reviewed 4,298 stage cIV NSCLC patients diagnosed between 1/2013-12/2017, in a community-based healthcare network encompassing 34 centers in Alaska, California, Montana, Oregon and Washington. We excluded 899 patients managed at 9 sites without OPC services, and 92 patients who received inpatient palliative care only. Eligible patients were stratified by whether or not they received OPC; then further by early OPC, which was defined as within 11 weeks of diagnosis. Survival was compared using Kaplan-Meier with log rank tests. **Result:** Of the 3,307 patients reviewed, only 8% (252/3,307) received OPC and 6% (182/3,307) early OPC. Median time from diagnosis to death was significantly longer for OPC patients (347 days, 95% CI 273-421) versus no PC (151 days, 95% CI 138-164), $p<0.001$; and similarly for early OPC (216 days, 95% CI 167-265) versus no PC, $p=0.008$. Documentation of advance directive/living will/ power of attorney was low in all categories, with rates of documentation at 32%, 31% and 27% for patients receiving OPC, early OPC and no OPC, respectively.

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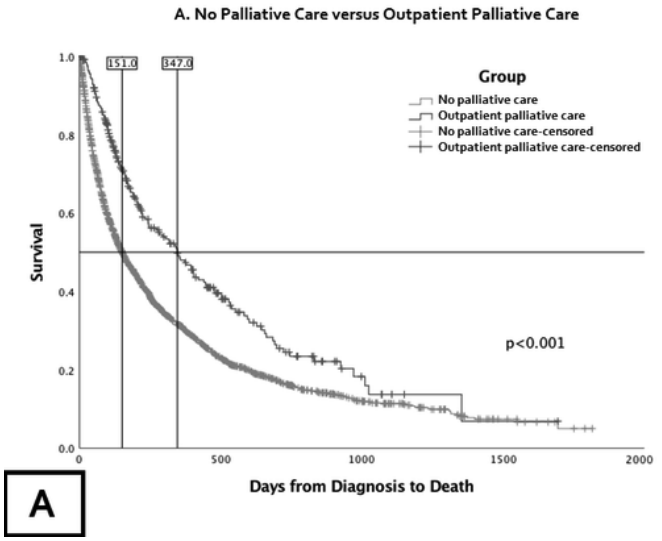

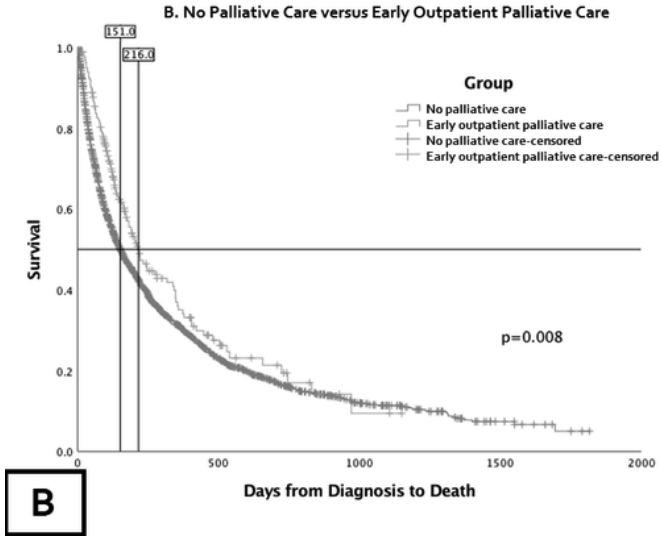

Conclusion: We identified that OPC services are broadly underutilized in stage cIV NSCLC patients across our multistate, community-based healthcare network. In addition, end-of-life documents were rarely completed in all clinical settings regardless of OPC. We confirmed prolonged survival associated with OPC in the community setting, but greater utilization is required to increase this benefit. These findings, as well as the additional benefits/value of OPC, require further study.

Keywords: palliative care, Stage IV NSCLC, outpatient palliative care

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MA02.03 ASTRIS: A REAL WORLD TREATMENT STUDY OF OSIMERTINIB IN PATIENTS WITH EGFR T790M-POSITIVE NSCLC

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Background: Osimertinib is a third-generation, CNS-active EGFR-TKI that potently and selectively inhibits both EGFR-TKI sensitizing and EGFR T790M resistance mutations. We report results from a second planned protocol, optimal interim analysis of the ongoing ASTRIS study (NCT02474355). **Method:** Eligible patients receive osimertinib 80 mg once daily. Inclusion criteria: stage IIIB/IV T790M-positive non-small cell lung cancer (NSCLC); T790M status confirmed locally by validated test, not restricted by sample type; prior EGFR-TKI therapy received; WHO performance status (PS) 0–2; acceptable organ and bone marrow function and no history of interstitial lung disease (ILD) or QTc prolongation. Asymptomatic, stable CNS metastases are permitted. The primary efficacy outcome is overall survival (OS). **Result:** From Sept 18, 2015, first patient in, to Oct 20 2017 data cut-off (DCO), 3014 patients were enrolled across 16 countries and received ≥1 dose of osimertinib (full analysis set [FAS]): median follow-up 7.9 months (range <1–24), median age 62 yrs (27–92), 64% female, 69% Asian, 30% White, 11% WHO PS 2, 45% prior chemotherapy, 34% prior radiotherapy. All patients had T790M-positive status, identified from tissue in 1610 patients (53%), plasma ctDNA in 1241 patients (41%) and from other sources in 162 patients (5%). At DCO, 1276 patients (42%) had discontinued treatment (1738 [58%] ongoing); median duration of exposure 7.4 months (<1–25); 1289 patients (43%) had a progression-free survival (PFS) event, 1276 (42%) had a time to treatment discontinuation (TTD) event, and 593 (20%) had died. In patients evaluable for response, the investigator-assessed clinical response rate was 56.6% (1625/2872; 95% confidence interval [CI] 54.7, 58.4). In the FAS, estimated median PFS was 11.0 months (95% CI 10.6, 11.1), median TTD was 12.6 months (95% CI 12.2, 13.7), and median OS was not reached (OS at 12 months was 75.8% (95% CI 73.7, 77.8). Adverse events (AEs) leading to dose modification and treatment discontinuation were reported in 321 patients (11%) and 147 patients (5%), respectively. Serious AEs were reported in 505 patients (17%). ILD/pneumonitis-like events were reported in 41 patients (1%), and QTc prolongation in 48 patients (2%). **Conclusion:** ASTRIS, the largest reported study of osimertinib in T790M-positive NSCLC, demonstrates clinical activity similar to that observed in the osimertinib clinical trial program with no new safety signals.

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MA02.05 A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED PHASE 3 NONINFERIORITY STUDY OF DARBEPOETIN ALFA FOR ANEMIA IN ADVANCED NSCLC

R. Nagarkar[1], P. Gascón[2], M. Šmakal[3], K. Syrigos[4], C. Barrios[5], J. Cárdenas Sánchez[6], L. Zhang[7], D. Tomita[8], J. Park[8], C. De Oliveira Brandao[8]

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Background: The effect of erythropoiesis-stimulating agents on overall survival (OS) in patients with chemotherapy-induced anemia has long been debated. This study (NCT00858364) evaluated noninferiority of darbepoetin alfa (DAR) versus placebo for OS and progression-free survival (PFS) in anemic patients with NSCLC treated to a 12.0-g/dL hemoglobin ceiling. **Method:** Adults with stage IV NSCLC expected to receive ≥2 cycles of myelosuppressive chemotherapy, life expectancy >6 months, ECOG 0–1, and hemoglobin ≤11.0 g/dL were randomized 2:1 to DAR (500 µg SC) or placebo Q3W. Patients were stratified by region, histology, and hemoglobin. Primary endpoint was OS; a Cox proportional hazards model, stratified by randomization factors, was used to evaluate noninferiority (margin based on upper confidence limit [CL] for hazard ratio [HR] <1.15). Secondary endpoints were PFS (noninferiority) and incidence of transfusions or hemoglobin ≤8.0 g/dL from week 5 to end of efficacy treatment period (EOETP). **Result:** 4161 patients were screened, 2549 enrolled, and 2516 included in the primary analysis set: 1680 randomized to DAR and 836 to placebo. The study was stopped early per independent DMC recommendation. Patients were well matched between arms for age (mean 61.8 years), sex (66.0% male), and race (47.5% white). DAR was noninferior to placebo for OS (HR_{adj} 0.92; 95%CL 0.83–1.01) and PFS (HR_{adj} 0.95; 95%CL 0.87–1.04). DAR was superior to placebo for transfusion or hemoglobin ≤8.0 g/dL from week 5 to EOETP (OR 0.70; 95%CL 0.57–0.86; *P*<0.001). Objective tumor response was similar between arms (DAR 36.2%; placebo 32.6%). Incidence of serious adverse events was the same in both arms (31.1%). No unexpected adverse events or cases of antibody-mediated PRCA were observed (**Table**).

	DAR (n=1685) %	Placebo (n=833) %
All treatment-emergent adverse events	84.5	86.3
Serious adverse events	31.1	31.1
Fatal adverse events	12.2	13.6
Adverse events leading to discontinuation of blinded drug	2.8	4.2
Adverse events of interest (standardized MedDRA query)		
CNS vascular disorders	1.5	1.0
Hypersensitivity	10.6	9.0
Severe cutaneous adverse reactions	2.1	1.3
Embolic and thrombotic events	5.3	4.1

Conclusion: DAR dosed to a 12.0-g/dL hemoglobin ceiling was noninferior to placebo for OS and PFS and significantly reduced odds of transfusion or hemoglobin ≤8.0 g/dL in anemic patients with NSCLC receiving myelosuppressive chemotherapy.

Keywords: overall survival, darbepoetin alfa, chemotherapy-induced anemia

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MA02.06 A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF CHEMOTHERAPY COMBINED WITH YANGZHENG XIAOJI IN ADVANCED NSCLC

L. Xing[1], J. Wang[2], L. Li[3], Z. Ma[4], C. Hu[5], H. Zhang[6], L. Shan[7], Z. Chen[8], J. Zhang[9], Q. Zhou[10], S. Gao[11], X. Ma[12], P. Sun[13], Q. Ren[14], M. Wu[15], J. Wu[16], J. Li[17], J. Yao[18], H. Ma[19], W. Wang[20], W. Yao[21], D. Wang[22], J. Kang[23], G. Li[24], X. Wang[25], W. Zhu[1], J. Wang[26], J. Yu[1]

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Background: *Yangzheng Xiaoji (YZXJ)* is a Chinese medicine formulation made of 16 herbs and used in patients with solid cancers. The aim of this randomized, double-blind and placebo-controlled multi-center trial (YANG-1,ClinicalTrials.gov registration No. NCT02195453) is to evaluate the impact of *Yangzheng Xiaoji* capsule on the quality of life (QoL) and treatment-related side effects in patients with advanced non-small cell lung cancer (NSCLC) receiving chemotherapy. **Method:** Patients with advanced NSCLC and with Eastern Cooperative Oncology Group performance status 0 to 1, who receive first-line chemotherapy (gemcitabine or pemetrexed and cisplatin), were randomized (1:1) to *Yangzheng Xiaoji* (*YZXJ*) or placebo combined with chemotherapy. The primary endpoint was QoL (Functional Assessment of Cancer Therapy-Lung (FACT-L) and Lung Cancer Symptom Scale (LCSS)) after two or four cycles of chemotherapy. The second endpoints included overall response rate, progression free survival and toxicity. **Result:** Between 10/2014 and 4/2017, the trial enrolled and randomized 504 patients from 25 centers in China. 397 patients received at least two cycles of chemotherapy and were included for final analysis. Baseline characteristics, including FACT-L and LCSS scores, were well balanced between two groups. The mean FACT-L scores were significantly changed in both groups from the baseline to that after chemotherapy (97.58 increase to 100.89 in YZXJ/chemotherapy arm, *P*<0.001; 93.83 decrease to 97.93 in placebo arm, P<0.001). The mean score of LCSS from baseline was significantly changed in *YZXJ*/chemotherapy groups(25.84 decrease to 22.31, *P*<0.001), but there was no statistical difference in the placebo group(25.59 *vs*. 26.45, *P*=0.136). The *YZXJ*/chemotherapy arm had a better QoL than the placebo/chemotherapy arm (FACT-L, 3.30 vs. -4.09; *P*<0.001) as well as improved lung cancer symptoms compared with placebo (LCSS, -3.53 *vs*. -0.86; *P*<0.001). There was no statistical difference in chemotherapy completion rate, ORR and PFS between two groups. The most common adverse events were bone marrow toxicity (70.92% *vs*. 67.59%) and gastrointestinal reaction (34.66% *vs*. 63.24%) (*YZXJ vs.* Placebo, P=0.441 and P<0.001, respectively). The rate of fatigue was significantly lower in *YZXJ* group than placebo group (4.38% *vs.* 30.04%, *P*<0.001). **Conclusion:** For patients with advanced NSCLC who received platinum-based chemotherapy, *Yangzheng Xiaoji* Capsule significantly improved the quality of life and symptoms, especially fatigue and gastrointestinal reaction.

Keywords: Yangzheng Xiaoji (YZXJ), chemotherapy, Advanced Non-Small Cell Lung Cancer

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MA02.07 APREPITANT FOR COUGH SUPPRESSION IN ADVANCED LUNG CANCER: A RANDOMIZED TRIAL

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Background: Cough is a distressing symptom in patients with lung cancer. Effective management of cough leads to improvement in quality of life (QoL) and optimal palliative care. Aprepitant, a centrally acting neurokinin-1 inhibitor, has been shown in a pilot study to significantly decrease the cough frequency. **Method:** A randomized open-label study in patients with advanced lung cancer with cough for over 2 weeks despite therapy with a cough suppressant, with an ECOG performance status 0 to 2. Patients were randomized 1: 1 to Arm A: aprepitant 125 mg orally on day 1, followed by 80 mg orally on days 2 to 7 along with physician's choice of antitussive therapy. Patients on Arm B received physician's choice of antitussive therapy. Patients were evaluated at baseline and then on days 3, 7, 9 and 12. Primary efficacy endpoint was subjective improvement in cough, measured with the Visual Analog Scale (VAS) and the Manchester Cough in Lung Cancer Scale (MCLCS). Secondary endpoints included toxicity and QoL, measured by the EORTC QLQ-C30 and LC13. The trial was approved by the` institutional IEC and registered with (CTRI/2017/05/008691). **Result:** Between June 2017 and June 2018, 128 patients were randomized: 64 to each arm. The median age was 53 yrs, 65% male, 64% never-smokers, 82% had adenocarcinoma. 88% had Stage IV disease; 80% had PS 1 and 20% PS 2. The median duration of cough was 90 days. VAS scores at baseline and day 9 was 67.93, 38.50 in Arm A and 63.15, 48.57 Arm B , with p<0.001 and the MCLCS scores at baseline and day 9 was 30.03, 22.32 in Arm A and 27.53, 23.80 Arm B , with p<0.001. Overall, there was no significant difference in the QoL scores in patients in the two arms, however there was a significant improvement in the cough-specific QoL domain in the patients on the aprepitant arm, p=0.017. There was no increase in the grade 3 and higher adverse events in the patients on the aprepitant arm. **Conclusion:** Aprepitant led to a significant improvement in cough in patients with advanced lung cancer, with no increase in severe side-effects. Aprepitant should be considered as one of the treatment options for cough in lung cancer patients.

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MA02.08 THE EFFECT OF NABILONE ON APPETITE, NUTRITIONAL STATUS, AND QUALITY OF LIFE IN LUNG CANCER PATIENTS: A RANDOMIZED, DOUBLE-BLIND CLINICAL TRIAL

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Background: Over one half of the patients diagnosed with advanced lung cancer experience anorexia. In addition to its high incidence, cancer-induced anorexia promotes the development of the anorexia-cachexia syndrome, which is related to poor clinical outcomes. Recently, drugs derived from cannabinoids, such as Nabilone, have been recognized for their appetite improvement properties; however, clinical trials to support their use in cancer patients are necessary. **Method:** This is a randomized, double-blind, placebo-controlled clinical trial to assess the effect of

Nabilone vs. placebo on the appetite, nutritional status, and quality of life in patients diagnosed with advanced Non-small cell lung cancer (NSCLC) (NCT02802540). **Result:** A total of 65 patients from the outpatient clinic at the National Institute of Cancer (INCan) were assessed for eligibility and 47 were randomized to receive Nabilone (0.5 mg/2 weeks followed by 1.0 mg/6 weeks) or placebo. After 8 weeks of treatment, patients who received Nabilone increased their energy intake (342-kcal) and had a significantly improvements in Quality of life parameters.

Figure 1. Difference in energy intake between control and experimental groups throw 8-weeks.

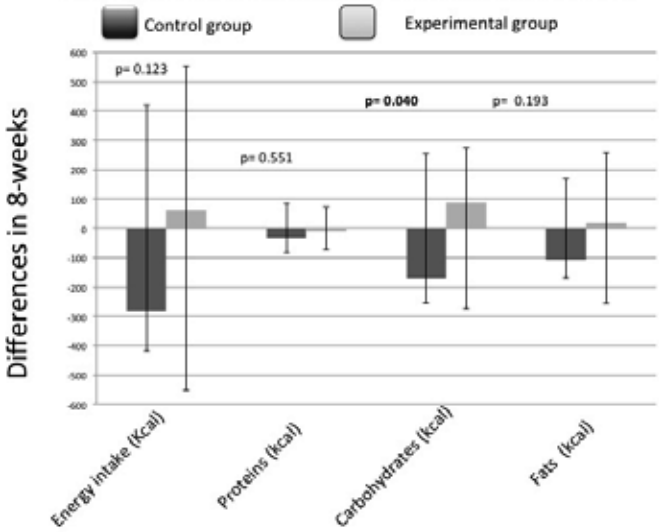
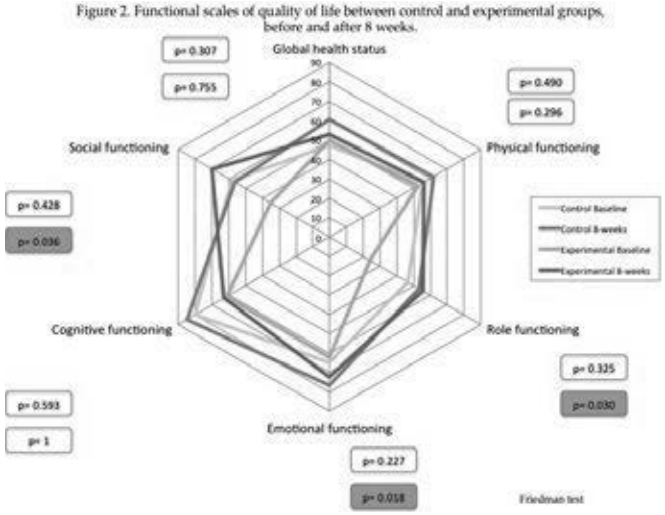


Figure 2. Functional scales of quality of life between control and experimental groups, before and after 8 weeks.



Conclusion: Nabilone is an adequate and safe therapeutic option to aid in the treatment of patients diagnosed with anorexia. Larger trials are necessary in order to draw robust conclusions in regard to its efficacy in lung cancer patients.

Keywords: anorexia, orexigenic agent, lung cancer

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MA02.10 THE FIRST YEAR OF IMPLEMENTING A LUNG CANCER SCREENING PROGRAM IN AN URBAN SAFETY-NET HEALTH SYSTEM

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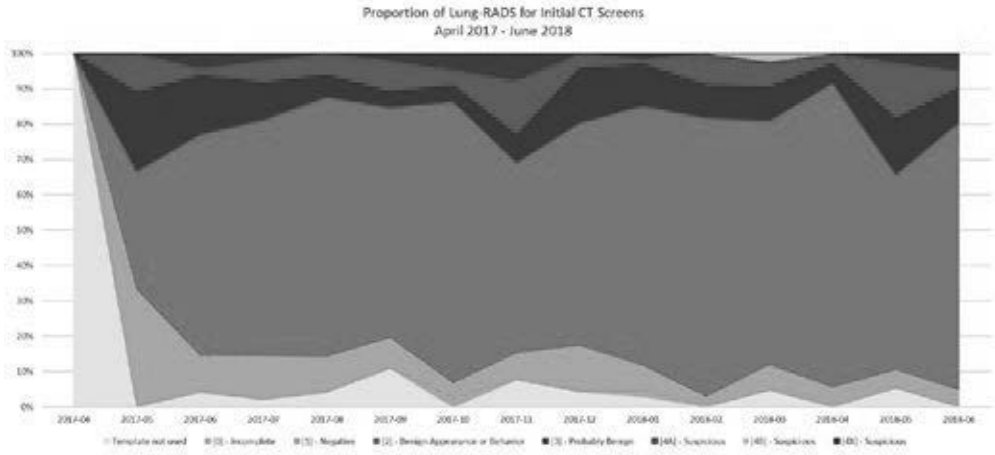
Background: Little is known about implementing low-dose computed tomography (LDCT) -based screening for lung cancer in settings that care for minority and underinsured populations. These patients may benefit most from guideline-based screening but may also be least likely to complete this multi-step process. **Method:** Parkland Health & Hospital system provides care through a combination of federal, state, and county-supported funding for more than one million, racial/ethnically diverse residents of Dallas County, Texas. A systematic protocol for LDCT screening was implemented in February 2017. We report initial screens and follow-up procedures for this first year through June 2018. **Result:** 844 LDCTs were ordered; 528 (63%) were completed, 68 (8%) had been scheduled. We detail demographics of completers and non-completers (Table 1) and proportion of LungRADS scores (Figure 1). For every year older, patients are 3% more likely to complete their scan. Of 249 completers requiring some form of follow-up (47%), only 3 required CT biopsy.

	Completed N=528 n (%)	Not Completed N=316 n (%)	Overall N=844 n (%)	p_value
Age, Years, Mean (STD)				
ageorder	62.05 (6.60)	60.77 (7.20)	61.57 (6.85)	**0.0088**
Sex				
Female	219 (41.5)	146 (46.2)	365 (43.2)	0.1799
Race/Ethnicity				
White	171 (32.4)	95 (30.1)	266 (31.5)	0.4949
Black	262 (49.6)	171 (54.1)	433 (51.3)	
Hispanic	83 (15.7)	41 (13.0)	124 (14.7)	
Other/Unknown	12 (2.3)	9 (2.8)	21 (2.5)	
Language				
English	471 (89.2)	285 (90.2)	756 (89.6)	0.8899
Spanish	47 (8.9)	26 (8.2)	73 (8.6)	
Other	10 (1.9)	5 (1.6)	15 (1.8)	
Language				
English	471 (89.2)	285 (90.2)	756 (89.6)	0.6503
Spanish/Other	57 (10.8)	31 (9.8)	88 (10.4)	
Marital Status				
Single	228 (43.2)	134 (42.4)	362 (42.9)	0.6826
Married/Common Law	128 (24.2)	75 (23.7)	203 (24.1)	
Divorced/Legally Separated	132 (25.0)	78 (24.7)	210 (24.9)	
Widowed	36 (6.8)	23 (7.3)	59 (7.0)	
Other/Unknown	4 (0.8)	6 (1.9)	10 (1.2)	
Marital Status				
Married/Common Law	128 (24.2)	75 (23.7)	203 (24.1)	0.8672
All Others	400 (75.8)	241 (76.3)	641 (75.9)	
Insurance				
Medicare	196 (37.1)	115 (36.4)	311 (36.8)	0.1561
Charity	155 (29.4)	82 (25.9)	237 (28.1)	
Medicaid	112 (21.2)	62 (19.6)	174 (20.6)	
Commercial	25 (4.7)	17 (5.4)	42 (5.0)	
Self-Pay	40 (7.6)	40 (12.7)	80 (9.5)	
Insurance				
Commercial/Medicare/Medicaid	333 (63.1)	194 (61.4)	527 (62.4)	0.6266
Charity/Self-pay	195 (36.9)	122 (38.6)	317 (37.6)	
Deceased?				
Yes	4 (0.8)	3 (0.9)	7 (0.8)	0.7662

(See next page)



Conclusion: While a systematic screening program in an urban safety-net setting generates high volume, a significant percentage of patients do not complete their initial screen. Of those who complete, many require follow-up procedures. More long-term data are needed to understand non-completion trends and subsequent annual screening.

Keywords: safety-net health system, implementation, lung cancer screening

MA02 IMPROVING OUTCOMES FOR PATIENTS WITH LUNG CANCER
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

MA02.11 ACHIEVING VALUE IN CANCER DIAGNOSTICS: BLOOD VERSUS TISSUE MOLECULAR PROFILING - A PROSPECTIVE CANADIAN STUDY (VALUE)

D. Ezeife[1], J. Agulnik[2], R. Juergens[3], J. Laskin[4], S. Laurie[5], L. Le[1], D. Hao[6], G. Bebb[7], J. Law[1], S. Skrzypczak[8], D. Juri[1], R. Lanman[8], N. Leighl[9]

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Background: Cell-free DNA (cfDNA) next-generation sequencing (NGS) has emerged as an effective molecular profiling technique that is potentially faster and cost-saving in comparison to standard-of-care (SOC) tumour biopsy and tissue-based profiling. In a public payer system, the added value of cfDNA blood-based profiling compared to SOC remains unknown. This study will determine the incremental clinical utility and cost of cfDNA NGS versus SOC genotyping in patients with advanced non-squamous non-small cell lung cancer (NSCLC). **Method:** This multicentre, non-randomized, longitudinal study will be conducted at 6 sites across Canada (BC, Alberta, Ontario, Quebec). The Guardant360® assay will be used to perform plasma-based cfDNA testing, and includes mutations, rearrangements and copy number variations in 73 known cancer associated genes. Two patient cohorts will be recruited: (1) treatment naïve patients with ≤10 pack year smoking history; and (2) patients with known abnormalities of *EGFR, ALK, ROS-1* or *BRAF* after disease progression on all standard targeted therapies. SOC tissue profiling will be performed for all patients per institutional standards. The study will begin recruiting in May 2018, with estimated completion in 12 months. The primary endpoints are comparison of response rate (RR), progression-free survival (PFS) and time-to-treatment failure (TTF) using cfDNA versus tissue genomic testing. Secondary endpoints include time to treatment initiation, number of actionable genomic abnormalities identified, result turnaround time, potentially avoidable repeat tissue biopsies, costs, patient-reported quality of life (EQ-5D) and willingness-to-pay. Exploratory analyses of treatment outcomes in selected molecular subgroups will also be undertaken, including response to immunotherapy in those with *KRAS/STK11* co-mutations. A decision-analytic model will be developed to perform cost-consequence analyses using a cfDNA versus tissue-based approach. **Result:** A total of 210 patients will be recruited across Canada, (Cohort 1 N=150, Cohort 2 N=60). Based on testing with either blood-based GUARDANT360™ or tissue-based profiling, the costs and benefits of blood-based profiling either at initial diagnosis or upon TKI progression will be determined versus initial or repeat tumour biopsy and tissue-based profiling. Data from patients accrued until 08/2018 will be presented at the meeting. **Conclusion:** This study will determine the added value of cfDNA blood-based genotyping compared to SOC from the perspective of a public payer system (Canada).

Keywords: cell-free DNA, value

MA03 LUNG CANCER SCREENING - NEXT STEP
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

MA03.01 MANCHESTER LUNG CANCER SCREENING: RESULTS OF THE FIRST INCIDENCE SCREENING ROUND

H. Balata, P. Crosbie, M. Evison, R. Booton

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Background: The European position on lung cancer (LC) screening has recommended planning for implementation to commence throughout Europe (1). The Manchester lung cancer screening pilot is one of the first real world implementation projects to take place in Europe and to publish baseline results (2). In this abstract we share, for the first time, the results from the first incidence screening round of the Manchester pilot. **Method:** The methodology and results of the baseline round of the Manchester screening pilot have been published previously (2). In brief, ever smokers, aged 55-74, from deprived areas of Manchester were invited to a free 'Lung Health Check' (LHC) in mobile units located at their local shopping centres. The $PLCO_{m2012}$ LC risk stratification model was incorporated into the LHC and those at high risk of LC ($PLCO_{m2012}$ ≥1.51%) were offered immediate LDCT in a co-located mobile scanner. At baseline, 75% of attendees were ranked in the lowest deprivation quintile; 56% were at high risk and 1384 screened with LDCT. 3% had LC diagnosed of which 80% were early stage (I+II) and 90% offered curative treatment. In this round of screening, all high risk individuals screened at baseline with no subsequent diagnosis of LC (screening or non-screening) were invited back for an annual LDCT scan at the same community locations. Exclusion criteria included death, other malignancies under follow-up and CT thorax within 3-months of due screening date. National and GP specific registries were checked for interval LC diagnosis. **Result:** A total of 1,194 LDCT scans were performed as part of the first incidence round of screening. Overall 28 (2.3%) individuals received a positive scan result and were referred to the MDT. Of these, 18 (1.5%) individuals were diagnosed with LC of which 78% (n=14/18) were lower stage (I-II) and 89% (n=16/18) offered curative treatment. The false positive rate was 0.8% of the screened population as a whole and 36% of those with a positive scan result. There were no interval LCs diagnosed at one year. The cumulative LC detection rate over the first 12 months of the programme was 4.3% (n=60/1384) of which 80% (n=51/64) were stage I-II. **Conclusion:** Annual LDCT screening of high risk individuals in this real world lung cancer screening implementation project continues to identify a significant number of early stage lung cancers amenable to curative treatment. No

interval lung cancers were diagnosed at one year suggesting the baseline selection criteria for screening was appropriate.

Keywords: Screening, early diagnosis, implementation

MA03 LUNG CANCER SCREENING - NEXT STEP
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

MA03.02 PROSPECTIVE EVALUATION OF THE CLINICAL UTILITY OF THE INTERNATIONAL LUNG SCREEN TRIAL LUNG NODULE MANAGEMENT PROTOCOL

S. Lam[1], R. Myers[1], S. Atkar-Khattra[1], R. Yuan[1], J. Yee[2], J. English[3], K. Grant[4], A. Lee[4], A. Mcguire[4], A. McWilliams[5], F. Brims[6], E. Stone[7], V. Chin[8], L. Chantrill[8], M. Connellan[8], M. Plitt[8], H. Marshall[9], I. Yang[9], R. Bowman[9], K. Fong[10], J. Mayo[11]

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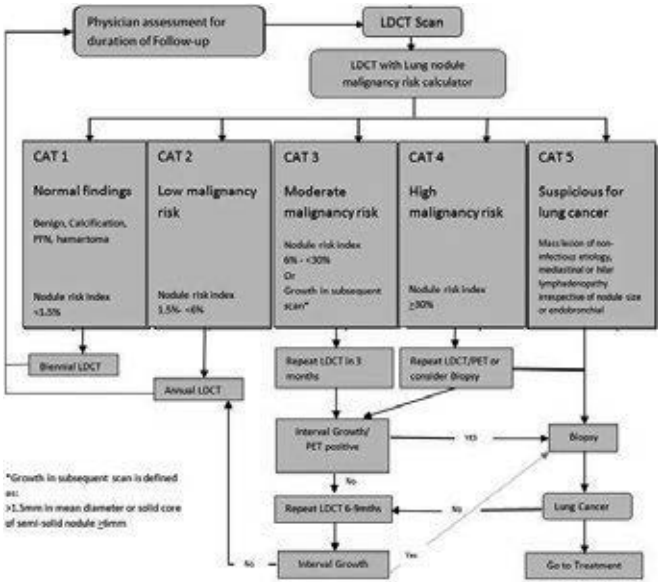
Background: Several protocols are available to guide management of lung nodules identified by low-dose screening CT. It is important to objectively assess their clinical utility in order to weigh the potential harm versus potential beneficial impacts of the following: early recall imaging studies/biopsy and health care resource utilization. We aimed to prospectively evaluate clinical utility of the PanCan lung nodule management protocol in the International Lung Screen Trial (ILST). **Method:** Ever smokers age 55 to 80 years were enrolled into ILST if they has a ≥30 pack-years smoking history and smoked within 15 years or if their $PLCO_{m2012}$ 6 year lung cancer risk was ≥1.51%. Figure 1 shows the ILST lung nodule management protocol based on the PanCan nodule malignancy risk calculator (NEJM 2013;369:908 & BMJ 2014;348:g2253). **Result:** Since July 2016, 757 ever smokers (mean age 65 years, 44% female, 15% non-Caucasian) had been enrolled. The distribution of malignancy risk categories (CAT) were: CAT1 70%, CAT2 15%, CAT3 11%, CAT4 3.5%, CAT5 0.4%. CT biopsy or bronchoscopic biopsy for diagnosis/staging was done in 16/26 CAT 4 (62%) and 7/84 CAT 3 (8%) participants. Lung cancer was confirmed in 15/757 (2%). Thus far, surgery was performed in 9 CAT 4 and 2 CAT 3 participants, with one benign resection (9%) for a growing FDG avid nodule. Of the 3 CAT5 participants, one was found to have granulomatous changes in an enlarged paratracheal lymph node and two had segmental atelectasis due to mucoid impaction. **Conclusion:** The ILST protocol triaged 70% of the screening cohort with low malignancy risk to biennial screening instead of annual repeat screening. Participants with high malignancy risk (CAT 4+5) were triaged to a diagnostic pathway (4%). Our preliminary results suggest the ILST protocol may decrease resource utilization and potentially minimize risk of screening for participants.



Keywords: nodule management, Screening

MA03 LUNG CANCER SCREENING - NEXT STEP
MONDAY, SEPTEMBER 24, 2018 - 10:30-12:00

MA03.03 PROLONGED LOW-DOSE COMPUTED TOMOGRAPHY (LDCT) SCREENING BEYOND 5 YEARS REDUCES OVERALL AND LUNG CANCER SPECIFIC MORTALITY

U. Pastorino[1], F. Sabia[1], S. Sestini[1], M. Silva[1], M. Boeri[2], A. Cantarutti[3], N. Sverzellati[4], G. Sozzi[5], G. Corrao[3], A. Marchianò[6]

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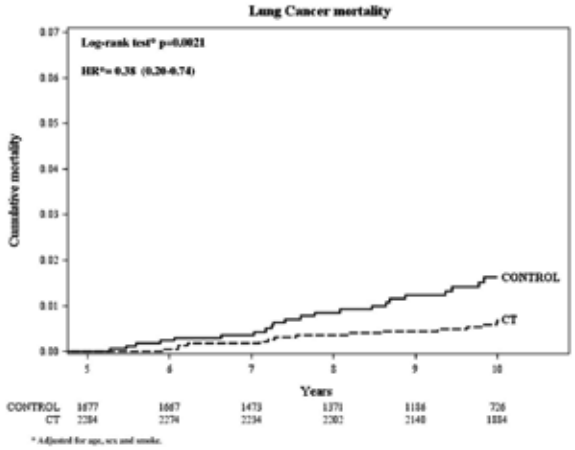
Background: The National Lung Screening Trial (NLST) showed that lung cancer screening (LCS) by low-dose computed tomography (LDCT) improves the overall survival. The NLST and most of the LCS trials were limited to a 5-year period, therefore there is no prospective evidence about the optimal duration of LCS. The aim of this study was to assess the potential benefit of long term LC screening beyond 5 years, notably its effect in 10-year overall and LC specific mortality. **Method:** The Multicenter Italian Lung Detection (MILD) trial prospectively enrolled 4,099 participants, randomized to either LDCT arm (n=2,376) or control arm (n=1,723); 38,561 person-years of follow-up were accumulated between 2005 and March 2017. The primary outcomes were 10-year overall and LC specific mortality. Moreover, a Landmark Analysis was used to test the long-term effect of LCS, beyond 5 years (notably by selective exclusion of events that occurred < 5 years). Cumulative mortality were evaluated using Kaplan-Meier estimator and differences among groups were tested using Log-rank test, adjusted for sex, age and pack-years. The prognostic value of assigned arm in predicting mortality was investigated by Cox's proportional-hazard's regression adjusted for the above variables. **Result:** In the whole 10-year LCS, LDCT arm showed a protective non-statistically significant trend for reduction of overall mortality (HR: 0.82, 95% CI 0.63 to 1.07) and a significant 41% reduced risk of LC mortality (HR 0.59, 95% CI 0.38 to 0.92), compared to the control arm. Beyond the 5th year of screening, LDCT arm showed a significant 29% reduction of overall mortality (HR: 0.71, 95% CI 0.50 to 0.99), and a significant 62% reduced risk of LC mortality (HR 0.38, 95% CI 0.20 to 0.74) (**Figure 1**).

Figure 1. Cumulative lung cancer mortality for the control group and the CT group of the Multicentric Italian Lung Detection study over 5-year follow-up.



Conclusion: Prolonged LDCT screening beyond 5 years reduces overall mortality, and it is most beneficial in further reduction of LC specific mortality.

Keywords: mortality, lung cancer screening, outcome

MA03.05 NEW SUBSOLID PULMONARY NODULES IN LUNG CANCER SCREENING: THE NELSON TRIAL

M. Heuvelmans[1], J. Walter[1], U. Yousaf-Khan[2], M. Dorrius[1], E. Thunnissen[3], A. Schermann[1], H. Groen[4], C. Van Der Aalst[2], K. Nackaerts[5], R. Vliegenthart[6], H. De Koning[7], M. Oudkerk[1]

[1]Center for Medical Imaging North-East Netherlands, Department of Radiology, University of Groningen, University Medical Center Groningen, Groningen/NL, [2]Department of Public Health, Erasmus MC, Rotterdam/NL, [3]Department of Pathology, VU University Medical Center, Amsterdam/NL, [4]Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen/NL, [5]Department of Pulmonary Medicine, Ku Leuven - University Hospitals Leuven, Leuven/BE, [6]Department of Radiology, University of Groningen, University Medical Center Groningen, Groningen/NL, [7]Public Health, Erasmus MC, Rotterdam/NL

Background: A central challenge in low-dose computed tomography (LDCT) lung cancer screening is the identification of clinically relevant lung cancer, while preventing overdiagnosis and overtreatment. Subsolid nodules are particularly challenging as they carry a relatively high malignancy rate but possess a slow growth rate. Current guidelines propose a watchful waiting approach with CT surveillance. While new solid nodules after baseline screening have a high lung cancer probability at small size and require lower size cutoff values than baseline nodules, there only is limited evidence on management of new subsolid nodules. Aim of this study was to assess the occurrence and lung cancer frequency of new subsolid nodules and to determine whether a more aggressive follow-up approach is necessary for new subsolid nodules. **Method:** Within the Dutch-Belgian randomized controlled LDCT lung cancer screening trial (NELSON), 7557 participants underwent baseline screening between April 2004 and December 2006. Three incidence screening rounds took place 1 year, 3 years, and 5.5 years after baseline screening. Participants with new subsolid nodules detected after the baseline screening round were included. A nodule was classified as (pre-) malignancy when it was diagnosed as lung cancer during diagnostic workup including histologic assessment. **Result:** In the three incidence screening rounds 60 new subsolid nodules not visible in retrospect (43 [72%] part-solid, 17 [28%] nonsolid) were detected in 51 participants (0.7% [51/7295] of participants with at least one incidence screening). Eventually, 6% (3/51) of participants with a new subsolid nodule was diagnosed with a (pre-)malignancy in such a nodule. The (pre-) malignancies were adenocarcinoma (in situ) and diagnostic work-up (referral 950, 364, and 366 days after first detection respectively) showed favorable staging (stage I). Overall, 65% (33/49) of subsolid nodules with follow-up screening were resolving. **Conclusion:** Less than 1% of participants in LDCT lung cancer screening presents with a new subsolid nodule after baseline. Contrary to new solid nodules, new subsolid nodules do not require a more aggressive follow-up approach than baseline nodules.

Keywords: lung nodule, subsolid, lung cancer screening

MA03.06 DESCRIPTIVE EPIDEMIOLOGY OF SIGNIFICANT INCIDENTAL FINDINGS IN A LARGE CLINICAL LUNG CANCER SCREENING PROGRAM

A. Borondy Kitts[1], S. Regis[2], A. Mckee[2], C. Lamb[2], K. Christ[2], J. Sands[3], B. Mckee[2]

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Background: The identification and reporting of significant incidental (non-lung cancer) findings in CT lung screening (CTLS) has not been standardized, though there is an available modifier in the LungRADS structured reporting system to identify a scan as including a significant incidental finding. In this study, we describe the significant incidental findings and follow-up in a large, established clinical CTLS program. **Method:** We retrospectively reviewed all of the clinically significant or potentially significant non-lung cancer findings, which we will refer to as significant incidental findings, for patients undergoing clinical CTLS in our program from January 2012 through December 2016 with follow-up through December 2017. Significant incidental findings were defined as any unexpected new and/or unknown non-lung cancer finding requiring clinical or imaging evaluation prior to the next CTLS exam. Given the high prevalence of coronary artery calcifications and emphysema in the CTLS population, these findings were not classified as significant incidentals. We describe the site of the incidental finding, the follow-up intervention, and the outcome. We also calculate the cancer detection rate for non-lung cancers. **Result:** Of the 6482 scans performed during the study window, 286 (4.4%) reported a significant incidental finding. These findings were reported in 276 (9.4%) of the 2927 patients screened during that time. Nine patients had more than one CTLS exam with a significant incidental finding. The majority of incidental findings were found in the kidneys (18%), liver (14%), and thyroid (11%). There were 15 non-lung cancers diagnosed for a cancer detection rate of 5.4%. The most common intervention, 43%, involved additional imaging, while 26% had a follow-up phone call or consult with a physician. Biopsy was performed in 9.1% and 6.7% had surgery. Surveillance was recommended for 43.4% of the findings, medical intervention was required for 12.3% of non-cancer findings and 12.9% of findings required no additional follow-up. There were 25 (8.7%) significant incidental findings with unknown follow up and outcomes and 31 (10.8%) that resulted in not finding anything on follow-up to explain the finding seen on the CTLS. **Conclusion:** Only 4.4% of all scans in our CTLS program reported a significant incidental finding. Almost 70% of the 286 significant incidental findings identified conditions requiring medical treatment, surgical intervention, or surveillance. There was one non-lung cancer diagnosis for every 7.5 lung cancers diagnosed in our screening program.

Keywords: Incidental finding, CT lung screening, lung cancer

MA03.07 DEVELOPMENT AND VALIDATION OF DEEP LEARNING MODELFOR RECOGNITION OF HISTOLOGIC SUBTYPE OF LUNG ADENOCARCINOMA FROM CT IMAGES

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[1]Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai/CN, [2]Shanghai Pulmonary Hospital, Shanghai/CN

Background: The clinical decision to either follow-up or resection from radiologic features for lung adenocarcinoma (atypical adenomatous hyperplasia [AAH], adenocarcinoma in situ [AIS], minimally invasive adenocarcinoma [MIA] and invasive adenocarcinoma [IA]) appearing as Sub-solid nodules (SSNs) is still challenge, and currently more relies on measures of diameter, solid component ratio. With the successful application of deep learning neuro-network (DLNN) for the classification of skin or common treatable blinding retinal diseases, we hypothesized that DLNN might help the histologic subtype classification of SSNs from CT images. The purpose of this study is to develop and validate a deep neuro-network model to classify AAH, AIS, MIA and IA or define a feasible classification for follow-up or treatment decision. **Method:** A total of 869 patients with 1344 pathologic confirmed nodules (AAH: 75, AIS: 340, MIA:321, IA: 608) were enrolled into this study. Two 3D mixed-scale dense-connected convolutional neuro network models (3D MS-DenseNet) were developed for 2 classification tasks: 4-class (AAH, AIS, MIA, IA), 3-class (AAH, AIS/MIA, IA). Eighty percent of whole datasets were randomly selected for training set, while other 20% were used for testing set. The nodules were firstly selected using a bounding box in 3D Slicer, and then cropped into 128 x 128 x 128 matrix size as the input to MS-DenseNet, and the output layer from the network was a 4-node or 3-node softmax classifier. Confusion matrix were used for the performance evaluation of both models and the classification accuracy for each class were reported. **Result:** The classification accuracy of AAH, AIS, MIA, IA in testing set were 0.75, 0.45, 0.52, 0.85 respectively by 4-class, suggesting that the differentiation between AIS and MIA from CT images by neuro-network is challenge. While in the 3-class classification task with purpose of decision supporting for treatment, the classification accuracy of AAH, AIS/MIA, IA were 0.70, 0.73, 0.88 in the same testing set. **Conclusion:** The DLNN showed potential capability in differentiating AAH, IA from other adenocarcinoma subtypes, while failed to differentiate AIS and MIA. When combing AIS and MIA for reclassify adenocarcinoma subtypes from the perspective of treatment, the DLNN achieved reasonable performance, suggesting that DLNN might be useful in supporting clinical treatment decision whether to follow-up or take different resection for SSNs.

Keywords: lung adenocarcinoma, Deep learning, Sub-solid nodule

MA03.09 TRANSCRIPTOME-WIDE ASSOCIATION STUDY REVEALS CANDIDATE CAUSAL GENES FOR LUNG CANCER

A. Clemenceau[1], M. Lamontagne[1], R. Carreras Torres[2], M. Obeidat[3], W. Timens[4], P. Joubert[1], C. Amos[5], J. Mckay[2], Y. Bossé[6]

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Background: Genome-wide association studies have identified robust susceptibility loci associated with lung cancer. As part of the OncoArray-TRICL consortium, we have recently completed the largest GWAS on lung cancer including 29,266 cases and 56,450 controls of European descent. The goal of this study is to integrate the complete GWAS results with a large-scale expression quantitative trait loci (eQTL) mapping study in human lung tissues (n=1,038) to identify candidate causal genes for lung cancer. **Method:** Transcriptome-wide association study (TWAS) was used to integrate GWAS and lung eQTL signals and identify genes whose levels of expression in lung tissue are causally related to lung cancer. TWAS was performed on six histological and smoking subgroups, namely overall lung cancer, adenocarcinoma, squamous cell carcinoma, small cell carcinoma, never-smokers, and ever-smokers. **Result:** As expected, the main TWAS signal for all histological subtypes and ever-smokers was on chromosome 15q25. The genes most strongly associated with lung cancer at this locus were *IREB2*(P_{TWAS}=4.97E-104), and to a lower extent, *CHRNA5*(P_{TWAS}=5.26E20) and *HYKK*(P_{TWAS}=2.04E-17). TWAS identified causal genes were different from those reported in GWAS including *JAML*on 11q23.3 in overall lung cancer (P_{TWAS}=1.39E-6) and adenocarcinoma (P_{TWAS}=2.09E-8),*NOTCH4*on 6p21.32 in squamous cell carcinoma (P_{TWAS}=1.24E-12), *ZNRD1*on 6p22.1 in overall lung cancer (P_{TWAS}=3.41E-14) and ever-smokers (P_{TWAS}=1.29E-9), *HIST1H2BD*on 6p22.2 for small cell carcinoma (P_{TWAS}=1.54E-6), and *NEXN*on 1p31.1 in never-smokers (P_{TWAS}=2.64E-5). In addition, a new small cell carcinoma susceptibility locus was identified on 4q32.2 and associated with the expression levels of *TMA16*(P_{TWAS}=4.2E-6). **Conclusion:** In conclusion, lung tissue TWAS on lung cancer, histological subtypes and smoking subgroups revealed novel causal genes in GWAS-nominated loci. A new locus for small cell carcinoma (4q32.2-*TMA16*) was also identified and will require further validation.

Keywords: TWAS, lung cancer, Genomics

MA03.10 POPULATION-BASED RELATIVE RISKS FOR LUNG CANCER BASED ON COMPLETE FAMILY HISTORY OF LUNG CANCER

L. Cannon-Albright[1], W. Akerley[2], S. Carr[3]

[1]Internal Medicine, University of Utah, Salt Lake City/UT/US, [2]Huntsman Cancer Institute, Salt Lake City/UT/US, [3]Thoracic Surgery, University of Maryland School of Medicine, Baltimore/MD/US

Background: Published risk estimates for diagnosis of lung cancer based on family history are typically focused on close relatives, rather than a more diverse or complete family history. This study provides relative risks (RR) for lung cancer based on comprehensive family history data obtained from a statewide Cancer Registry linked to a high quality genealogy data resource. Risk estimates presented avoid common recall, recruitment, ascertainment biases, and are based on an individual's (proband's) lung cancer family history constellation (pattern of lung cancer affected relatives). **Method:** A population-based genealogical resource linked to a statewide electronic SEER cancer registry estimated relative risk (RR) for lung cancer for an individual based upon their lung cancer family history. Family history data available for a proband included degree of relationship (first to third-degree), paternal or maternal family lung cancer history, number of lung cancer affected relatives and age at diagnosis of affected relatives. Over 1.3M probands probands with specific constellations of lung cancer were analyzed. To estimate RRs, the observed number of lung cancer cases among probands with a specific family history constellation was compared to the expected number using internal cohort-specific rates. **Result:** 5,048 lung cancer cases were identified. Significantly elevated RR was observed for any number of lung-cancer-affected relatives among first-, second-, or third-degree relatives. RRs for lung cancer were significantly elevated for each additional lung cancer first-degree relative (FDR) ranging from RR=2.57 (2.39, 2.76) for >= 1 FDR to RR=4.24 (1.56, 9.23) for ≥3 FDRs affected. In an absence of FDR family history, increased risk for lung cancer was significant for increasing numbers of affected second-degree relatives (SDR) ranging from 1.41 (1.30, 1.52) for ≥ 1 SDR to 4.76(1.55, 11.11) for ≥ 4 SDRs. This was also seen in the absense of FDRs and SDRs for affected third-degree relatives (TDR) ranging from 1.18 (1.11, 1.24) for ≥1 affected TDR to 1.55 (1.03, 2.24) for ≥ 4 affected TDRs. RRs were significantly increased with earlier age at diagnosis of a first degree relative, and equivalent risks for maternal compared to paternal history were observed. **Conclusion:** This study provides unbiased, population-based estimates of lung cancer risk based on a proband's complete family history that can be 2-5+ times increased. Estimates of RR for lung cancer based on family history are arguably very relevant clinically. The constellation RR estimates presented could serve in individual decision making to direct resource utilization, and could be pivotal in decision making for screening, treatment, and post treatment surveillance.

Keywords: Family history, lung cancer, Individualized Relative Risk

MA03.11 TRAINED DOGS CAN IDENTIFY MALIGNANT PULMONARY NODULES IN EXHALED GAS

A. Guirao[1], L. Molins[1], I. Ramon[2], G. Sunyer[3], N. Vinolas[4], R. Marrades[5], D. Sanchez[6], J.J. Fibla[7], J. Hernandez[7], M. Boada[6], R. Guzman[1], A. Libreros[6], A. Agusti[8]

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This abstract is under embargo until September 24 at 10:30 Eastern Time.

MA04.01 CEMIPLIMAB, A HUMAN MONOCLONAL ANTI-PD-1, ALONE OR IN COMBINATION WITH RADIOTHERAPY: PHASE 1 NSCLC EXPANSION COHORTS

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Background: Cemiplimab (REGN2810), a human monoclonal anti-PD-1, has exhibited substantial antitumor activities in patients with advanced malignancies in a first-in-human study. We report interim results of the Phase 1 expansion cohorts (ECs 1 and 2) of cemiplimab, alone or plus radiotherapy, in advanced NSCLC (NCT02383212). **Method:** Patients with advanced NSCLC who had relapsed after, or were refractory to, at least, first-line therapy received cemiplimab 200 mg Q2W in EC 1, or cemiplimab 3 mg/kg Q2W plus radiotherapy (9 Gy × 3 times/week 1 week after first dose of cemiplimab) to a single lesion in EC 2. For EC 2, patients were required to have NSCLC for which palliative radiation therapy was indicated. Planned treatment duration was up to 48 weeks in both ECs. The co-primary objectives were to evaluate the safety, tolerability, and efficacy of cemiplimab, alone or plus radiotherapy. Tumor measurements (of non-irradiated lesions) were performed by RECIST 1.1 Q8W. **Result:** As of Sept 1, 2017, 20 patients (13 M/ 7 F; median age 64.0 years [range,

50–82]) and 33 patients (22 M/ 11 F; median age 67.0 years [range, 47–82]) were enrolled in EC 1 and EC 2, respectively. ECOG performance status 1 versus 0 was 80.0% versus 20.0% and 66.7% versus 30.3%, respectively, for ECs 1 and 2, and missing in one in EC 2; 75.0% (EC 1) and 48.5% (EC 2) had received prior radiotherapy. Investigator-assessed overall response rate (ORR; complete response [CR] + partial response [PR]) was 40.0% (1 CR and 7 PRs) and 18.2% (6 PRs) in EC 1 and EC 2, respectively. Disease control rate (ORR + stable disease [SD]) was 60.0% (1 CR + 7 PRs + 4 SDs) and 72.7% (6 PRs + 18 SDs) in EC 1 and EC 2, respectively. The most common treatment-emergent adverse events (TEAEs) of any grade were arthralgia, asthenia, cough, and dyspnea (each 20.0%) in EC 1, and decreased appetite (30.3%), fatigue (27.3%), cough (24.2%), asthenia and back pain (each 21.2%) in EC 2. Grade ≥3 TEAEs occurring in ≥2 patients were pneumonia (10.0%) in EC 1; and anemia (12.1%), hypophosphatemia and urinary tract infection (each 6.1%) in EC 2. One patient in EC 2 experienced TEAE of pneumonitis with an outcome of death, considered related to study drug. **Conclusion:** Cemiplimab monotherapy demonstrated substantial antitumor activity in pretreated NSCLC patients. The safety profiles were comparable with other anti-PD-1 agents and radiotherapy.

Keywords: cemiplimab, Anti-PD-1, NSCLC

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MA04.02 RESPONSES AND DURABILITY IN NSCLC TREATED WITH PEGILODECAKIN AND ANTI-PD-1

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Background: Responses in NSCLC to agents targeting the PD-1/PD-L1 axis are correlated with PD-L1 expression by immunohistochemistry (IHC), tumor mutational burden (TMB), interferon-associated mRNA expression profile (GEP), and the absence of liver metastases. Anti-PD-1 impedes the inhibition of T cells while pegilodecakin (AM0010) stimulates the survival and expansion of intratumoral, antigen-activated CD8+ T cells (Mumm et al, 2010). This provides a rationale for combining anti-PD-1 agents with pegilodecakin. **Method:** Pretreated NSCLC subjects (N = 34) received pegilodecakin (10-20 µg/kg QD, SC) with pembrolizumab (2 mg/kg, Q3W, IV; n = 5) or nivolumab (3 mg/kg, Q2W, IV; n = 29). Median follow-up is 31.2 months (range, 28.3-33+ months) and 17.5 months (range, 8.3-25.9+ months), respectively. Responses were assessed by irRC. Twenty subjects had sufficient tissue for PD-L1 testing with the 22C3 IHC assay (CLIA) and 10 subjects had sufficient tissue for TMB evaluation by whole exome sequencing (WES) and pretreatment GEP by NanoString. **Result:** In 26 subjects evaluable for response, the ORR was 41% (11 PRs). Another 12 subjects (46%) had SD as best response. As investigators were asked to preferentially enroll PD-L1–negative patients, PD-L1 expression was <1% in 12 of 20 PD-L1–evaluable subjects with 4 achieving a PR. Ten subjects had sufficient tissue for TMB and GEP, including 6 PRs. Five of the 8 who tested low to intermediate for TMB (≤243 mut) had a PR as did 2 of 6 GEP-negative subjects. In addition, 5 of 8 subjects with liver metastasis had a PR. The mPFS and mOS of the 5 NSCLC subjects (4/4 tested PD-L1 <1%) treated with pegilodecakin + pembrolizumab was 10.9 and 32.2 months, respectively. The mPFS and mOS for the pegilodecakin + nivolumab cohort (8/16 tested PD-L1 <1%) has not been reached. **Conclusion:** Pegilodecakin, when added to anti-PD-1 therapy in advanced NSCLC patients, was associated with response rates and durability of benefit greater than has been seen with anti-PD-1 alone. Responses were seen in settings in which anti-PD-1 therapy has demonstrated limited benefit, such as absent PD-L1 expression, low TMB, and/or the presence of liver metastasis. These preliminary findings support further studies of pegilodecakin with anti-PD-1 therapies.

Keywords: PD-1, IL-10, NSCLC

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MA04.03 IMMUNOTHERAPY FOR NON-SMALL CELL LUNG CANCERS (NSCLC) WITH ONCOGENIC DRIVER MUTATIONS: NEW RESULTS FROM THE GLOBAL IMMUNOTARGET REGISTRY

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Background: Prospective data on immunotherapy for NSCLC with oncogenic driver mutations are limited. We recently reported first results from the global IMMUNOTARGET registry (Mazières, ASCO 2018). Here, we present new data for PD-L1 and mutation subgroups. **Method:** In 2017, we started an international retrospective registry study ("IMMUNOTARGET") for patients with advanced NSCLC, known driver mutations (KRAS, EGFR, ALK, ROS1, BRAF, HER2, MET and RET) and PD-L1 immune checkpoint inhibitor therapy. The registry is approved by University of Toulouse and Swissethics, and funded by University of Toulouse and Cantonal Hospital of Lucerne. Anonymized real-world data submitted to the coordinating center include: patient and tumor characteristics, mutation test methods and results, systemic therapy lines, immune related adverse events, best response by RECIST, survival, and tumor PD-L1 expression (optional). Statistical calculations including best response, median PFS and OS are done at University of Toulouse. **Result:** In April 2018, the registry included 551 pts from Europe, USA, Israel and Australia. Patients were 50% male/female, 28% current smokers, median age 60 years (range 28-83), 85% had PS0/1. Most (73%) tumors were stage IV at diagnosis, almost all (96%) were adenocarcinomas. Molecular classification by dominant driver mutation: KRAS=271 (49%), EGFR=125 (23%), BRAF=43 (8%), MET=36 (7%), HER2=29 (5%), ALK=23 (4%), RET=16 (3%), ROS1=7 (1%), 1 (0.2%) not classified (ALK+RET+MET). Most pts received nivolumab (466) or pembrolizumab (48) and were treated with immunotherapy in second or third line (67%). The median number of cycles was 5 (range 1-68). Fifty (11%) pts had grade 3-5 toxicity. Median OS from start of immunotherapy was 13.3 months, median PFS was 2.8 months. Best response was PR/CR in: KRAS=26%, BRAF=24%, ROS1=17%, MET=16%, EGFR=12%, HER2=7%, RET=6%, ALK=0%. Percentage of PD-L1 positive cells was available for 177 pts: 0%=71 (40%), 1-49%=46 (26%), 50-100%=60 (34%). Median % of positive cells was highest for ROS1 (90%), BRAF (50%), MET (30%) and RET (26%) mutant tumors. PD-L1 positivity was predictive for improved PFS in KRAS and EGFR mutant tumors. PD-L1 status was known in 18 tumors with ALK, ROS1 or RET rearrangements: 5 had 0%, 4 had 1-49% and 9 had 50%-100%. No tumor remissions were observed in this subgroup. The registry remains open, updated results will be presented at the conference. **Conclusion:** Although response rates were lower than in KRAS mutant NSCLC, individual tumors with other driver mutations responded to immunotherapy. PD-L1 expression may not accurately predict clinical benefit from immunotherapy in some molecular subgroups, better markers are needed.

Keywords: mutations, NSCLC, Immunotherapy

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MA04.05 OUTCOMES IN NSCLC PATIENTS TREATED WITH FIRST-LINE PEMBROLIZUMAB AND A PD-L1 TPS OF 50-74% VS 75-100% OR 50-89% VS 90-100%

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Background: Among patients with NSCLC and a PD-L1 tumor proportion score (TPS) ≥50%, the response rate to the PD-1 inhibitor pembrolizumab is ~45%. Whether certain subsets of patients with a PD-L1 TPS ≥50% are more likely to benefit from treatment with a PD-1 inhibitor is currently unknown. We compared outcomes among NSCLC patients treated with first-line pembrolizumab and different PD-L1 TPS groupings: 50-74% vs 75-100% or 50-89% vs 90-100%. **Method:** We retrospectively analyzed patients who received commercial pembrolizumab as first-line treatment for NSCLC with a PD-L1 TPS of ≥50% from the Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, and Massachusetts General Hospital. Clinicopathologic characteristics and clinical outcomes were compared among patients with a PD-L1 TPS of 50-74% vs 75-100% or 50-89% vs 90-100%. Event-time distributions were estimated using Kaplan-Meier and compared with the log-rank test. **Result:** 172 patients were identified for inclusion in this study. In the entire cohort, the overall response rate (ORR) to pembrolizumab was 33.9%, median progression-free survival (mPFS) was 4.8 months, and median overall survival (mOS) was 20.6 months. Compared to patients with TPS 50-74% (N=68, 39.5%), patients with TPS 75-100% (N=104, 60.5%) had a significantly higher ORR (45.2% vs 20.6%, P=0.001), a significantly longer mPFS (5.3 vs 2.5 mo, HR=0.61 [95% CI: 0.41-0.90], P=0.008), and a trend towards improved mOS (33.6 vs 20.6 mo, HR=0.60 [95% CI: 0.34-1.04], P=0.056). Compared to patients with TPS 50-89% (N=99, 57.6%), patients with TPS 90-100% (N=73, 42.4%) had a significantly higher ORR (50.7% vs 24.2%, P<0.001), a significantly longer mPFS (6.4 vs 2.8 mo, HR=0.52 [95% CI: 0.36-0.76], P<0.001), and a significantly longer mOS (33.6 vs 18.0 mo, HR=0.46 [95% CI: 0.27-0.79], P=0.008). There were no significant differences in smoking history, histology, sex, and age between patients in each TPS cutoff group. **Conclusion:** Among NSCLCs with a PD-L1 TPS ≥50% treated with first-line pembrolizumab, higher PD-L1 TPS levels above 75% and 90% are associated with improved clinical outcomes compared to NSCLCs with lower PD-L1 levels.

Keywords: Immunotherapy, pembrolizumab, PD-L1

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MA04.06 PD-1 BLOCKADE PROMOTES HYPERPROGRESSIVE DISEASE IN NSCLC THROUGH MACROPHAGES ACTIVATION VIA ANTIBODY-FC/FCR INTERACTION

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Background: In a subset of patients, named hyperprogressors (HPs), immunotherapy seems to paradoxically boost tumor growth. However, neither pathological and clinical features nor the underlying biological mechanism have been identified. We dissected the role of tumor-myeloid cells crosstalk as possible players. **Method:** HPs were defined on the basis of clinical and radiological features. Baseline histological samples from patients treated with immune checkpoints inhibitors (ICI) were evaluated by immunohistochemistry for myeloid and lymphoid markers. We tested the effect on tumor growth of murine and human ICI in T-cell deficient mice injected with human lung cancer cell lines and PDXs bearing different genotypes (EGFR+, KRAS+, STK11+ and wt). Innate immune microenvironment was evaluated by FACS analysis and immunohistochemistry. In vitro studies of ICI binding functional modulation were performed in human myeloid cells from patients and healthy donors. **Result:** In a clinical series of 187 patients treated with ICI, hyperprogression was observed in 40 (26.3%) cases. All available HP pre-treatment tissue samples (11 cases) showed CD163+CD33+PD-L1+Arginase-A1+ clustered epithelioid macrophages infiltrating the tumor foci also expressing FcRs including CD32b. No differences in T cell compartment were observed. Murine and human PD1 blocking mAbs induced a boost of tumor growth in H460 xenografs in imunocompromised mice. A similar effect was observed in EGFR+ but not in KRAS+ and wt PDXs treated with human anti-PD1. Notably, no hyperprogression was observed after treatment with murine and human anti PD-1 F(ab)2. Hyperprogressive tumors were enriched in arginase+ myeloid-macrophage cells and fibrotic features. ICI bind in vitro to human macrophages and monocytes via Fc/FcR interactions, likely involving CD32b (FcgRIIb) and triggering functional polarization. **Conclusion:** Our results provide evidence that FcR triggering on macrophages by ICI delivers a signaling cascade promoting a functional reprogramming of these cells toward a more aggressive pro-tumorigenic behavior eventually inducing hyperprogression in a subset of patients with distinctive immune and genetic profile. A validation prospective study in ongoing.

Keywords: Hyperprogression; Immune checkpoint inhibitor; macrophages

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MA04.07 MICRORNA-BASED LIQUID BIOPSY COMBINES WITH PD-L1 TUMOR EXPRESSION TO PREDICT RESPONSE TO IMMUNOTHERAPY IN ADVANCE NSCLC PATIENTS

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Background: The advent of the new immune checkpoint inhibitors (ICIs) targeting the PD-1/L1 axis drastically improves survival of advance non-small-cell lung cancer (NSCLC) patients. However, only a limited subset of patients actually benefits of ICIs treatment and PD-L1 as predictive biomarker has a limited efficacy. We have previously identified a plasma microRNA-signature classifier (MSC) reflecting a circulating tumor-host interaction with diagnostic and prognostic value in low-dose computed tomography (LDCT) lung cancer screening trials. **Method:** The tumor immune contexture of 40 LDCT-screening detected lung tumors was characterized by the "cell-type identification by estimating relative subsets of RNA transcripts" (CIBERSORT) software. In a consecutive series of 84 advanced lung cancer patients treated with ICIs, both plasma and tissue samples were collected and prospectively analyzed. Both 2-years progression free (PFS) and overall survival (OS) in strata of plasma MSC risk level alone or combined with tumor PD-L1 expression were evaluated in univariate and multivariate analysis by log-rank test and Cox proportional hazards models. **Result:** A pro-tumorigenic immune contexture was identified in tumors of MSC high risk patients. Lower levels of cytotoxic CD8+ and CD4+ T cells and increased levels of Tregs, γδ T Cells, M2 macrophages characterized these tumors. In addition, genes differentially expressed according to MSC risk level (high vs. intermediate and low) were associated with 5-years OS in the screening series (p-values=0.02), as well as in additional 1000 cases from The Cancer Genome Atlas database (p-values<0.01). In the 84 advanced NSCLC patients treated with ICIs, the PFS hazard ratio ranged from 0.44 (95%CI: 0.25-0.75) of PD-L1 (adjusted p-value=0.005) and 0.38 (95%CI:0.2-0.73) of MSC (adjusted p-value=0.004) alone, to 0.25 (95%CI: 0.14-0.45) if combined (adjusted p-value<0.0001). In the subgroup of 45 patients with both plasma and tumor tissue available, the combination of MSC and PD-L1 stratified patients in three groups with 2-years PFS ranging from 25%to 10% and 0% (p-value=0.01) according to the presence of 2, 1 or 0 favorable markers, respectively. Similar results were obtained when considering OS, where the median survival time for patients with no favorable markers was 5.6 months (p-value<0.0001). **Conclusion:** Overall, these findings suggest that a circulating microRNA-based risk level, reflecting an altered tumor immune contexture, could implement PD-L1 tumor tissue expression as predictive biomarkers of response to immunotherapy.

Keywords: Immunotherapy, Biomarkers, microRNA

MA04.09 NEOADJUVANT ATEZOLIZUMAB IN RESECTABLE NON-SMALL CELL LUNG CANCER (NSCLC): UPDATED RESULTS FROM A MULTICENTER STUDY (LCMC3)

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Background: Cisplatin-based chemotherapy, before or after surgery, provides only a 5% benefit in 5yr. OS in resectable NSCLC. A 20 patient study (NEJM April 2018) showed that preoperative immune checkpoint inhibitor therapy yielded a clinically meaningful major pathologic response rate (MPR ≤10% residual viable tumor cells) and did not delay or complicate surgery. This large multicenter trial measures MPR and biomarkers of benefit using neoadjuvant atezolizumab (atezo) [NCT02927301]. **Method:** We planned 2 cycles of atezo (1200mg, days 1, 22) in patients with stages IB -selected IIIB resectable NSCLC prior to surgical resection (day 40 +/- 10). Chest CT, PET were planned pre-atezo and presurgery to assess response. Primary tumor +/- node biopsies and blood samples were obtained before atezo and presurgery for biomarker studies. The primary endpoint was MPR. Secondary endpoints included safety, response by PD-L1, OS, and DFS. **Result:** For this updated efficacy and safety analysis (Feb'18 datacut), we report first 54 of 180 planned pts: 29 males, median age 65 yr, all ECOG 0-1; 17 current, 33 former smokers; 35 non-squamous NSCLC; clinical stages Ib/IIa/IIb/IIIa/IIIb = 5/11/13/20/5. Two pts received one dose of atezo due to treatment related AE (Gr 1 pyrexia, Gr 2 dyspnea) but underwent uncomplicated resection with MPR assessment. There was 1 unrelated Gr 5 AE (sudden cardiac death post surgical resection), 16 Gr 3-4 AEs (3 treatment related). Surgery was delayed in 1 pt due to Gr3 pneumonitis. By RECIST, 3 pts had PR, and 49 had SD. 50 pts underwent surgery and 47 pts had MPR assessment: 2 pts discontinued study preop due to radiographic PD and 2 discontinued due to other reasons; 3 pts had unresectable disease. MPR rate was 10/50 (20%, 95% CI 10-34%) including 3 pts who had pCR (no viable tumor cells) in the primary tumor. Excluding 5 pts who had known driver mutations (4 EGFR+, 1 ALK+), MPR rate was 10/45 (22%, 95% CI 11-37%). PD-L1 status was evaluable in 44/54 pts; 8/10 pts with MPR had PD-L1+ status and 2 had unknown PD-L1 status; 8/28 PDL-1 (+) patients had MPR (29%). **Conclusion:** In a multicenter study, neoadjuvant atezo was well tolerated. MPR rate is encouraging. Clinical and pathological responses are often discordant. Correlative analyses on pre- and post atezo tissues are ongoing. Preliminary correlative analyses in blood samples are included in a separate abstract.

Keywords: neoadjuvant atezolizumab, NSCLC

MA04.10 COMPREHENSIVE PERIPHERAL BLOOD IMMUNOPHENOTYPING AND T-CELL CLONAL ANALYSIS DURING NEOADJUVANT IMMUNOTHERAPY WITH ATEZOLIZUMAB IN NSCLC

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Background: Immune-checkpoint blockade targeting PD-L1/PD-1 to activate anti-tumor immunity is associated with improved response rates and survival compared to chemotherapy in selected metastatic NSCLC patients. Evaluation of the pre-therapeutic immune profile and its treatment-related evolution associated with clinical benefit will guide future immunotherapy development and support clinical decision-making. Here, we present an analysis of peripheral blood (PB) immunophenotyping and T-cell-receptor (TCR) clonality before and after immunotherapy from an ongoing 180-patient phase II study of atezolizumab as neoadjuvant therapy with stage IB-IIIB resectable NSCLC (NCT02927301; LCMC3). **Method:** As of February 5th datacut, the first 54 enrolled and dosed patients are presented. The biomarker evaluable population (BEP) further subset to patients with paired PB samples analyzed within 72 hours after collection and a major pathological response (MPR) assessment. Comprehensive immune cell phenotyping (10-color flow cytometry, IMMUNOME) and TCR-Vß-analysis by flow cytometry were performed. Immunoprofile analyses were correlated with atezolizumab treatment, pathological response and PD-L1 expression. **Result:** In this ongoing analysis, BEP included 31 patients. 5 patients (16%, 95% CI (5%, 34%)) had a MPR; all of which stained positive for PD-L1 by IHC using 22C3 (TPS≥1%) and SP142 (PD-L1 expression on ≥1% tumor cells (TC) and/or tumor infiltrating immune cells (IC)) at baseline. We observed significant increases in natural killer (NK) cells (p=0.005) and CD8+ T-cells (p=0.031) and a Th1-response related dendritic cell (DC) subpopulation (p=0.031) and significant decreases in B-cells (p=0.015) after treatment. Patients who achieved MPR show lower baseline levels of degranulated CD8+ T-cells (p=0.015), late-activated NK-cells (p=0.043), memory CD4+ (p=0.048) and memory CD8+ T-cells (p=0.032); changes in PB NK-cells (p=0.041), a decrease in M-MDSCs and a Th-2 and Th-17-response related DC subpopulation (p=0.043) in response to treatment were noted in patients with MPR versus non-MPR. Among the 16 patients with TC/IC 1/2/3 (> 1% PD-L1 expression) the following significant differences were observed compared to TC0/IC0 (7 patients): higher levels of late-activated CD4+ T-cells (p=0.025) and mid-activated CD8+ T-cells (p=0.044) at baseline, decrease of senescent T-cells (p=0.041), monocytic myeloid-suppressor cell subpopulations (M-MDSCs) and an increase in a Th1-response related DC subpopulation (p=0.026) after treatment. TCR clonality analysis showed expansions in Vß-subtypes after atezolizumab treatment. **Conclusion:** Immunophenotyping and TCR-Vß-repertoire analysis in peripheral blood samples from NSCLC patients treated with neoadjuvant atezolizumab show differences in immune cell subsets in baseline samples and changes after treatment.

Keywords: neoadjuvant immunotherapy, immunophenotyping, NSCLC

MA04.11 NEOANTIGEN TARGETING AND T CELL RESHAPING IN RESECTABLE NSCLC PATIENTS TREATED WITH NEOADJUVANT PD-1 BLOCKADE

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Background: PD-1 blockade is now standard treatment for advanced non-small cell lung cancer (NSCLC) and has recently shown impressive efficacy in promoting major pathologic response (MPR) and delaying relapse in the neoadjuvant setting. The role of tumor mutational burden, and specifically T cells targeting neoantigens derived from these mutations, in facilitating tumor clearance has been demonstrated in advanced NSCLC. However, it is unknown how neoadjuvant PD-1 blockade impacts the frequency and function of tumor specific T cells and their ability to promote major pathologic response, or how these factors may synergize to prevent or delay relapse after surgical resection. **Method:** Whole exome sequencing and neoantigen prediction was performed on pre-treatment tumor biopsies and matched normal tissue from 11 patients with resectable NSCLC treated with neoadjuvant nivolumab as part of a clinical trial (NCT02259621). T cell recognition of peptides representing candidate neoantigens was evaluated using the MANAFEST assay, which identifies T cell receptor clonotypes corresponding to antigen specificities. T cell receptor sequencing was additionally performed on serial peripheral blood T cells, pre-treatment tumor biopsies, and resected post-treatment tissues. A bioinformatic platform was developed to evaluate the dynamics of intratumoral T cell clonotypes, and more specifically neoantigen-specific clonotypes detected before, during, and after treatment and during long-term follow-up. **Result:** High-magnitude, polyclonal neoantigen-specific T cell responses were detected in the peripheral blood and persisted for many months after surgical resection and cessation of treatment. Binding to and stability with cognate HLA I molecules was validated for reactive neoantigens. Significant treatment-

induced systemic perturbations in the tumor-specific T cell repertoire and an influx of peripheral T cell clonotypes into tumor tissue and lymph nodes was observed in patients regardless of pathologic response, whereas peripheral clonotypic reshaping of the anti-tumor repertoire and intratumoral T cell clonality were associated with MPR status. **Conclusion:** We show significant and systemic alterations in the peripheral anti-tumor T cell repertoire in NSCLC patients treated with neoadjuvant anti-PD-1 regardless of MPR status. Notwithstanding, the impaired restructuring of the anti-tumor T cell repertoire in patients without MPR highlights a potential immunological deficiency to overcome in future therapeutic approaches aiming to increase the MPR rate in NSCLC patients treated with neoadjuvant PD-1 blockade.

Keywords: neoantigen recognition, T cell dynamics during checkpoint blockade, Neoadjuvant checkpoint blockade in NSCLC

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MA05.01 E6508: PHASE II STUDY OF IMMUNOTHERAPY WITH TECEMOTIDE AND BEVACIZUMAB AFTER CHEMORADIATION IN UNRESECTABLE STAGE III NS-NSCLC

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Background: Chemoradiation (CRT) is standard of care for unresectable stage III NSCLC. Tecemotide is a MUC1 antigen-specific cancer immunotherapy. Bevacizumab is considered to have a significant role in immune modulation. Immunotherapy in combination with VEGF blockade was tested in this phase II trial combining tecemotide and bevacizumab in patients with stage III NS- NSCLC. **Method:** Subjects with stage III NS-NSCLC suitable for definitive CRT received carboplatin(C) AUC 2 + paclitaxel(P) 45 mg/m2 weekly + 66 Gy/33fx/6.5wk and consolidation C AUC 6 + P 225 mg/m2 q21 days x 2. Patients with CR/PR/SD were then registered onto Step 2 (S2). S2 was 6 weekly tecemotide injections followed by q6 weekly injections and bevacizumab 15 mg/kg q3 weeks for up to 34 doses. The primary endpoint was safety of tecemotide and bevacizumab after CRT and consolidation. The proportion of circulating dendritic cells and their expression of CD40, HLA-DR and CD123 (IL-3R) were analyzed by flow cytometry at various time points. **Result:** 70 patients were enrolled from Dec 2010 to Oct 2014; 68 started therapy, and 39 completed CRT and consolidation therapy. Reasons for discontinuation included progression (11) and toxicity (10). 33 patients were registered to S2. The median number of S2 cycles was 12 (range 2-34). S2 toxicity: gr 3 N=9 (6 hypertension), gr 4 N=1, gr 5 N=1. Among the treated and eligible patients (n=31), from study entry, the median PFS was 14.3 (95% CI 11.0-22.2), OS was 40.1 (95% CI 21.7-NA) months. A correlative trend of increased expression of CD40 and HLA-DR on CD11c+ cells was observed at cycle 7 (week 21) of S2.

Conclusion: This cooperative group trial met its endpoint, demonstrating tolerability of tecemotide and bevacizumab after CRT and consolidation in NS-NSCLC pts. In this select group of patients, therapy with tecemotide and bevacizumab was associated with encouraging PFS and OS.

Keywords: Immunotherapy, Stage III NSCLC, chemoradiation

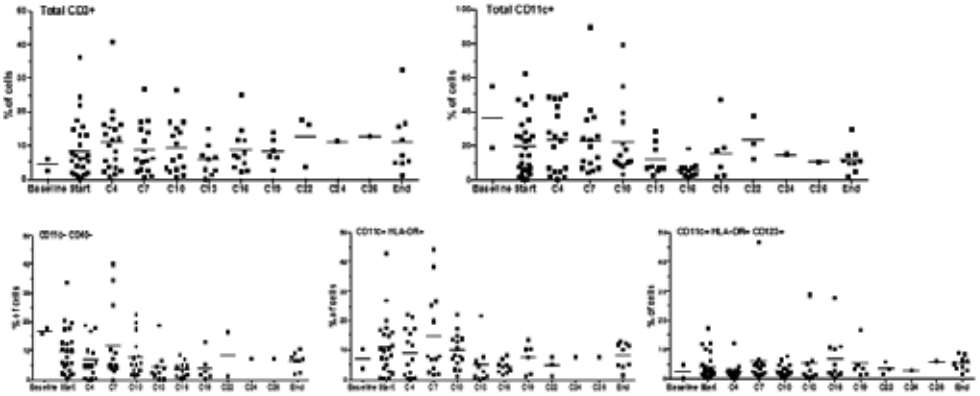

Figure 1. Trend of lymphoid and dendritic cell populations during the course of therapy. Data shown are from the flow analysis of CD3, CD11c, CD40, HLADR and CD123 (IL-3R). A trend of increased expression of CD40 and HLA-DR on CD11c+ cells was observed at Cycle 7.

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MA05.02 PACIFIC SUBGROUP ANALYSIS: PNEUMONITIS IN STAGE III, UNRESECTABLE NSCLC PATIENTS TREATED WITH DURVALUMAB VS. PLACEBO AFTER CRT

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Background: In the Phase 3 PACIFIC study of durvalumab versus placebo in patients with stage III, unresectable non-small cell lung cancer (NSCLC) after concurrent chemoradiotherapy (cCRT), on-treatment pneumonitis or radiation pneumonitis ('pneumonitis') occurred in both arms with similar rates of grade 3/4 pneumonitis (durvalumab, 3.4%; placebo, 2.6%). We performed exploratory analyses to further characterize time to onset and duration of pneumonitis and examine its relationship with underlying risk factors, including patient characteristics and prior CRT. **Method:** PACIFIC (NCT02125461) was a randomized, double-blind study of patients with WHO PS 0/1 without progression after ≥2 cycles of platinum-based cCRT. Patients were stratified by age, sex, and smoking history and randomized (2:1) 1–42 days after completing cCRT to durvalumab 10 mg/kg IV Q2W or placebo up to 12 months. Potential associations between the presence of the AE pneumonitis (investigator assessed with review/adjudication by study sponsor) and baseline characteristics or patient disposition were investigated. **Result:** As of Feb 13, 2017, 709 patients had received treatment; 33.6% on durvalumab and 24.9% on placebo had any-grade pneumonitis. Treatment exposure was similar in patients with or without pneumonitis across both arms. Median time to onset of pneumonitis from treatment start was the same for both durvalumab and placebo, 55.0 days (73.0 and 76.5 days from RT completion). Pneumonitis was self-limited, with median durations of 64.0 and 57.0 days, respectively. Patients with pneumonitis were more likely to be Asian (47.9% vs 17.6%)

or have EGFR mutations (11.0% vs 3.8%); however, the proportions of patients with pneumonitis and these risk factors were numerically lower with durvalumab than with placebo (Asian: 44.4% [71/160] vs 57.6% [34/59]; EGFRm: 10.6% [17/160] vs 11.9% [7/59]), suggesting no apparent interaction with treatment. There were no apparent associations of pneumonitis with baseline respiratory disorders, prior RT dose, or prior cisplatin or carboplatin use. Previous induction CT was more commonly associated with the absence of pneumonitis in both treatment arms (durvalumab: 30.1% vs 17.5%; placebo: 31.5% vs 20.3%). The presence of pneumonitis was associated with greater discontinuation due to AEs (durvalumab: 25.6% vs 10.2%; placebo: 18.6% vs 6.8%) regardless of treatment. **Conclusion:** Rates of pneumonitis were higher in Asian patients and those with EGFRm, as previously reported. Durvalumab did not increase pneumonitis in patients with these risk factors. There were no differences in treatment exposure in patients based on the presence/absence of pneumonitis. Multivariate analyses may further assist in the discernment of etiologic risks.

Keywords: PACIFIC, durvalumab, pneumonitis

MA05 IMPROVING OUTCOMES IN LOCOREGIONAL NSCLC II
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MA05.03 IMMUNE MICROENVIRONMENT AND ITS ASSOCIATION WITH ADJUVANT CHEMOTHERAPY BENEFIT IN LOCOREGIONALLY ADVANCED LUNG ADENOCARCINOMA

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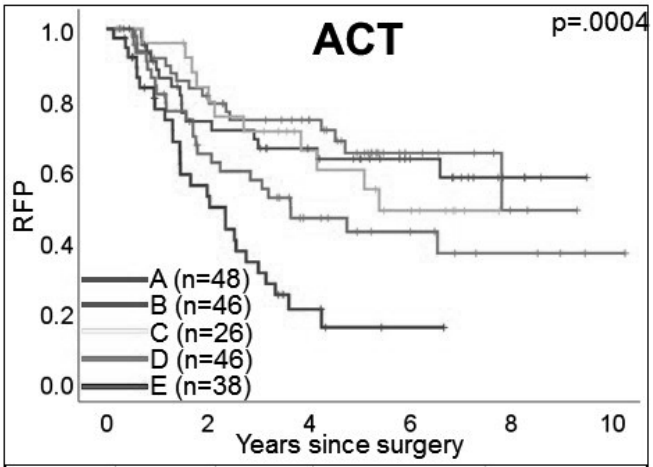
Background: The impact of the tumor immune microenvironment on the effectiveness of platinum-based adjuvant chemotherapy (ACT) in locoregionally advanced (stage II-III) lung adenocarcinoma (ADC) is unknown. We performed an analysis of the cellular components of the tumoral and tumor-associated stromal immune environment in stage II-III lung ADC and examined their association with ACT benefit. **Method:** Tissue microarrays (6 tumor and 3 stromal cores from each tumor) were constructed using resected tissue from patients with pT2-T4N1 lung ADC (n=500, 2000-2012) who did (n=225) and did not (n=214) receive ACT. Multiplex immunofluorescence was used to determine the quantity, localization, and colocalization of 21 types of immune cells and markers (including PD-1, PD-L1, CD3, CD20, CD68, CD163, MPO, and PanCK). The association between immune cell infiltration and recurrence free probability (RFP) was compared using Kaplan-Meier methods, and benefit from ACT by unsupervised hierarchical cluster modeling. **Result:** Overall, increased tumoral infiltration of $CD20^+$ B-cells and $CD3^+$ and $CD4^+$ T-cells was associated with an improvement in 5-yr RFP ($CD20^+$ low vs high: 37% vs 49%, p=.03; $CD3^+$: 39% vs 48%, p=.003; and $CD4^+$: 39% vs 47%, p=.02, respectively) whereas increased stromal MPO^+ neutrophil infiltration was associated with a worse 5-yr RFP (low vs high: 50% vs 38%, p=.003). Among patients who received ACT, cluster modeling revealed 5 risk groups (Groups A-E; Figure) with immune signatures including tumoral B-cells and $CD163^+PD\text{-}1^+$ macrophages as well as stromal $CD57^+$ NK-cells and $CD163^+PD\text{-}L1^+$ macrophages that provided a progressive stratification of RFP following adjuvant treatment.



Group	Str-CD57$^+$	Tu-CD20$^+$	Str-CD163$^+$PDL1$^+$	Tu-CD163$^+$PD1$^+$
A	Low	-	-	-
B	High	High	-	-
C	High	Low	Low	-
D	High	Low	High	High
E	High	Low	High	Low

Top: RFP stratification by group following ACT
Bottom: Group definitions based on immune infiltration signature
Tu-Tumor, Str-Stroma

Conclusion: Immune infiltration analysis can predict benefit from ACT and thereby provide a rationale to select patients for either chemotherapy, immunotherapy, or combination therapy following surgical resection.

Keywords: Immune-cells, chemotherapy, NSCLC

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MA05.05 PHOTON-BASED CARDIAC SPARING VIA VOLUMETRIC MODULATED ARC THERAPY IN THORACIC RADIATION THERAPY FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Increasing radiation dose to the heart is associated with worse survival in stage III non-small cell lung cancer. Techniques to reduce the dose to the heart, including proton beam therapy (PBT), are being evaluated in ongoing clinical trials. However, advanced technologies such as PBT are not readily accessible for most patients. We therefore sought to evaluate the efficacy of volumetric modulated arc therapy (VMAT), a readily available technology in the United States, to spare cardiac substructures and determine how a cardiac optimization treatment planning algorithm influences dose distribution to other thoracic organs at risk (OARs). **Method:** We selected stage III non-small cell lung cancer patients who were treated at our institution with VMAT to 60 Gy in 2 Gy fractions. Cardiac substructures were retrospectively contoured, and included: valves, atrioventricular node (AVN), coronary arteries (CA), chambers, and great vessels. New radiation treatment plans were created to spare these structures while preserving planning target volume (PTV) coverage and maintaining standard dose constraints to OARs. Dosimetry variables—maximum dose (Dmax), mean dose (Dmean), and common clinically relevant dose-volume relationships—for the new cardiac-sparing radiation treatment plans were compared via paired t-test to the original radiation treatment plans. **Result:** Twenty-six patients, treated from July 2013 to September 2017, were included. Statistically significant improvements were demonstrated for all cardiac structures for the new cardiac-sparing plans compared to the original plans, while maintaining appropriate lung, esophagus, and spinal cord constraints, and PTV coverage goals, as demonstrated in Table 1 (significant *P*-values in bold). **Table 1** (See next page)

Dosimetry variable	Cardiac-sparing plan (mean)	Original plan (mean)	P-value*
Cardiac parameters			
Heart Dmax	64.9 Gy	63.6 Gy	0.928
Heart Dmean	12.3	16.1	< 0.001
Heart V5Gy	55.4	64.1	0.003
Heart V30Gy	12.5	18.7	< 0.001
Heart V40Gy	7.9	11.5	< 0.001
Heart V45Gy	6.5	11.5	< 0.001
Heart V60Gy	2.7	3.4	0.001
Aortic valve Dmax	22.9	31.7	< 0.001
Aortic valve Dmean	11.4	31.7	< 0.001
Mitral valve Dmax	24.6	29.4	0.002
Mitral valve Dmean	11.2	16.7	< 0.001
Pulmonic valve Dmax	26.8	35.4	< 0.001
Pulmonic valve Dmean	14.1	25.1	< 0.001
Tricuspid valve Dmax	9.7	16.6	< 0.001
Tricuspid valve Dmean	5.6	10.3	< 0.001
AVN Dmax	13.4	20.4	< 0.001
AVN Dmean	8.1	14.0	< 0.001
Left main CA Dmax	26.4	38.8	< 0.001
Left main CA Dmean	16.4	30.2	< 0.001
Left anterior descending CA Dmax	27.4	34.8	< 0.001
Left anterior descending CA Dmean	14.4	22.6	< 0.001
Left circumflex CA Dmean	32.6	36.8	0.001
Left circumflex CA Dmean	19.3	26.9	< 0.001
Right CA Dmax	18.1	26.1	< 0.001
Right CA Dmean	9.4	15.7	< 0.001
Left atrium Dmax	51.8	54.8	0.091
Left atrium Dmean	17.5	21.0	< 0.001
Left ventricle Dmax	35.7	40.1	< 0.001
Left ventricle Dmean	8.3	11.3	< 0.001
Right atrium Dmax	31.4	36.1	0.004
Right atrium Dmean	11.1	13.9	< 0.001
Right ventricle Dmax	23.7	33.2	< 0.001
Right ventricle Dmean	6.9	12.2	< 0.001
Aorta Dmax	50.8	55.3	0.001
Aorta Dmean	20.4	27.9	< 0.001
Pulmonary artery Dmax	65.2	65.1	0.895
Pulmonary artery Dmean	32.3	37.9	< 0.001
Superior vena cava Dmax	47.4	51.7	0.002
Superior vena cava Dmean	29.4	33.1	0.006
Other OAR parameters			
Lungs V5Gy	56.5	58.2	0.121
Lungs V20	22.4	23.3	0.083
Lungs Dmean	13.6	14.8	0.012
Spinal cord Dmax	28.0	31.1	0.013
Esophagus Dmean	21.2	22.1	0.023
PTV coverage parameters			
PTV Dmax	65.5	67.2	0.189
PTV minimum dose	51.2	52.7	0.019
PTV V100%	95.2%	95.4%	0.195

Conclusion: Dose to the heart and cardiac substructures can be substantially lowered using a cardiac-sparing optimization algorithm with VMAT, without increasing radiation dose other thoracic OARs or compromising PTV coverage. Though time-consuming, delineation of the full complement of cardiac substructures provides an effective means of improving the quality of radiation treatment plans with readily available technologies.

Keywords: Treatment planning, Heart dose, VMAT

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MA05.06 LOCALLY ADVANCED LUNG CANCER RADIOTHERAPY IN DEEP INSPIRATION BREATH HOLD: DOSIMETRIC BENEFITS FROM A PROSPECTIVE TRIAL

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Background: Radiotherapy for locally advanced non-small cell lung (NSCLC) cancer is often complicated by treatment-related toxicity. A toxicity-reducing technique is deep inspiration breath hold (DIBH), where the lungs inflate and the heart is pushed downwards. DIBH is widely applied in breast radiotherapy, but only sporadically in NSCLC. We initiated the INHALE trial, investigating compliance and benefits of DIBH for NSCLC at a single academic institution. **Method:** Patients referred for definitive radiotherapy of locally advanced NSCLC (66Gy/33 fractions) were included from May 2015-Dec 2017. All patients underwent respiratory coaching for voluntary visually guided DIBH and were imaged with PET/CT, 4D-CT and DIBH-CT. Target volumes were defined according to national guidelines. PTV margins were patient- and modality-specific. For all patients, FB and DIBH plans were made with volumetric modulated arc therapy, with equal PTV coverage. The plan with the lowest lung and/or heart dose was chosen for treatment. Normal tissue complication probability for pneumonitis was calculated retrospectively based on a logistic dose response model. **Result:** The treatment intent was maintained in 69 of included 88 patients (2 were downstaged, 12 upstaged, 2 withdrew consent, other causes in 3). 62/69 were DIBH compliant and in 61 patients a FB and a DIBH plan were made (in one patient, 4DCT image quality was not sufficient). In 54/61 patients, the DIBH plan was chosen for treatment. 3/54 patients lost DIBH compliance within the first few fractions. All data is presented as median (range), with p<0.001 (Wilcoxon signed rank). Lung volume increased in DIBH by 55% (20-168%). Compared to FB, DIBH reduced mean lung dose from 14.4Gy (1.2-25.3Gy) to 11.8Gy (1.0-20.4Gy), and lung V20 from 23.7% (1.5-47.8%) to 20.8% (1.2-39.7%). Reduced lung dose translated to reduced pneumonitis risk: from 8.6% (2.3-23.3%) to 6.5% (2.2-14.4%). Lung dose constraints were violated in 5/62 patients in FB and 1/62 patients in DIBH. Mean heart dose was reduced from 3.6Gy (0.1-25.8Gy) in FB to 2.4Gy (0.1-25.3Gy) in DIBH. DIBH reduced mean heart dose in 44/61 patients. The differences between FB and DIBH varied between – 6.6Gy and 8.9Gy, stressing the influence of tumour location on the potential of reducing heart dose with DIBH. **Conclusion:** Benefits of changed anatomy with DIBH were reduced dose to lungs and, for most patients, to the heart. Curative treatment intent could be maintained in more patients. Risk of developing radiation pneumonitis was reduced. Continuous follow up of INHALE patients will reveal how the reduced risk is manifested clinically.

Keywords: deep inspiration breath hold, Radiotherapy, locally advanced lung cancer

MA05 IMPROVING OUTCOMES IN LOCOREGIONAL NSCLC II
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MA05.07 DOSE ESCALATED CHEMO-RT TO 84 GY IN STAGE III NSCLC APPEARS EXCESSIVELY TOXIC: RESULTS FROM A RANDOMIZED PHASE II TRIAL

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Background: Concurrent chemoradiotherapy is the mainstay treatment for NSCLC stage III disease, however, with a rather high probability of locoregional and metastatic recurrence further treatment optimization is warranted. Based on previous one-armed trials with dose escalated radiotherapy, showing feasibility, the Swedish Lung Cancer Study Group aimed to investigate whether dose escalation based on individual normal tissue constraints could improve outcome in this randomized phase II trial. **Method:** NSCLC patients with stage III disease, good performance status (0-1), adequate lung function (FEV1 > 1.0 L and CO diff. > 40%) received three cycles of cisplatin (75 mg/m^2 day 1) and vinorelbine (25 mg/m^2 day 1 and 8) every third week. The radiotherapy started concurrently with the second cycle, with either 2 Gy daily, 5 days a week, to a total dose of 68 Gy (standard arm A) or escalated therapy (B) based on constraints to the spinal cord, esophagus and lungs up to 84 Gy by adding an extra fraction of 2 Gy per week while keeping the total treatment time constant at seven weeks with the same dose to involved nodes and primary tumor. **Result:** A pre-planned safety analysis revealed excessive toxicity and decreased survival in the escalated arm, and the study was stopped. Thirty-six patients were included during 2011-2013 (56% male, 78% with adenocarcinoma, 64% with PS 0 and 53% with stage IIIB). The median progression-free survival (PFS) and overall survival (OS) were 11 and 17 months in the dose escalated group compared to 28 and 45 months in the standard group. The 1-, 3- and 5-year survival rates were 56%, 33% and 17% in the escalated arm and 72%, 61% and 34% in the standard arm. There were four toxicity-related deaths due to esophageal perforations (one in arm A and three in arm B) and three deaths due to pneumonitis (one in arm A and two in arm B). **Conclusion:** Dose-escalated concurrent chemoradiotherapy to 84 Gy to primary tumor and nodal disease is hazardous, with a high risk of excessive toxicity, whereas modern standard dose chemoradiotherapy with proper staging given in the control arm shows a promising outcome with a median survival of 45 months and a 5-year survival of 34%. A possible step forward will be to improve systemic therapy, but future approaches with escalated radiotherapy may include boost techniques to remaining PET positive areas or different escalation schedules to the primary tumor and mediastinal nodes.

Keywords: Chemoradiotherapy, Dose-escalation, Locally advanced NSCLC

MA05 IMPROVING OUTCOMES IN LOCOREGIONAL NSCLC II
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MA05.09 PFS AND CARDIAC-TOXICITY-ADJUSTED-PFS AS PREDICTORS OF OS IN LOCALLY ADVANCED NSCLC TREATED WITH CONCURRENT CHEMORADIATION

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Background: Overall survival (OS) is the gold standard for LA-NSCLC with chemoradiation (CCRT), while the complex relationships among RT dosimetry, systemic therapies, cardiopulmonary toxicity, progression (PD) and OS are also of increasing scientific and clinical interest. **Method:** NRG Oncology RTOG 0617 (NCT00533949) was a randomized phase 3 trial comparing standard (SD, 60 Gy) versus high-dose (HD, 74 Gy) CCRT +/- cetuximab from 11/07-06/11. This secondary analysis includes 469 patients (pts) given ≥50 Gy. A PFS event was defined as the first occurrence of local, regional, distant PD or death w/o documented PD. A CTA-PFS event was the first occurrence of grade 2+ treatment-related cardiac toxicity event or a PFS event. Landmark analyses at 6mo and 12mo were used to minimize the immortal time bias. Cox model with PD or CT/PD as a time-dependent covariate was used to evaluate their predictive roles. Median f/u time for surviving pts was 5.1 years. **Result:** As previously reported, pts treated with HD had significantly lower OS rates (HR=1.28, 95%CI: 1.04-1.58, p=0.018) and CTA-PFS rates (HR=1.24, 95%CI: 1.02-1.51, p=0.035), and marginally lower PFS rates (HR=1.21, 95%CI: 0.99-1.47, p=0.06) than pts treated with SD. Median survival time (MST) among pts having PD within 6mo versus not were 13.4mo (95%CI: 10.0-19.0mo) and 30.7mo (95%CI: 28.0-37.0mo) (p<0.001). MST for pts having PD within 12mo versus not were 20.6mo (95%CI: 18.8-25.0mo) and 60mo (95%CI: 47.6-74.5mo) (p<0.001). Results are similar when using CTA-PFS with 6mo or 12mo cutoff (p<0.001). RT dose was no longer significantly associated with OS (p=0.08 or p=0.15) when PD or CT/PD was included in multivariable analysis (p<0.001), suggesting OS differences in HD/SD may be partially captured by PFS or CTA-PFS. **Conclusion:** Long-term survival results from RTOG 0617 suggest that PFS (or CTA-PFS) status at 6mo or 12mo predicts long-term OS, and may potentially be considered as a surrogate endpoint of OS in clinical trials. Pts who were progression-free at 12mo had a MST of 5 years. Further validation on external datasets and in

the modern era of immunotherapy are needed. Funding: This project was supported by grants NCORP (UG1CA189867), NRG Operations (U10CA180868), NRG SDMC (U10CA180822), IROC (U24CA180803), and CTEP from the National Cancer Institute (NCI).

Keywords: Surrogate endpoint, Locally advanced NSCLC, Progression-free survival

MA05 IMPROVING OUTCOMES IN LOCOREGIONAL NSCLC II
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MA05.10 THE PATHOLOGIC RESPONSE OF LOCALLY ADVANCED NSCLC TREATED WITH CONCOMITANT CHEMORADIATION TO 60 GY IN IMAGE GUIDED RADIATION THERAPY (IGRT)

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Background: Neoadjuvant concomitant chemoradiation (NACCRT) was historically limited to 45 Gy. We recently published data on the safety of a higher radiation dose in this setting. Here we evaluate the pathologic response of locally advanced non small cell lung cancer (LANSCLC) treated with 60Gy NACCRT combined with modern IGRT. **Method:** Our cohort comprised patients that underwent NACCRT followed by surgery during August 2012-December 2017 at our institution. We retrospectively collected the demographic, stage, histology, and treatment details. Radiation was planned using eclipse system to deliver 2 Gy per fraction to a total of 60 Gy Treatment effect was determined from the pathologic specimen in accordance with College of American Pathologists recommendations, based on the modified tumor regression grading: Favorable pathologic responses included major tumor regression (MTR); we also evaluated the average percent of the residual tumor cells seen in the specimen. Statistical analysis was performed to analyze treatment effect on the pathologic response using spearman correlation and Kruskal-Wallis test with SPSS software v.24. **Result:** Our cohort included 70 patients. Mean age was 63 years (range 45–79.7), men n=49 (70%), smoking status: never smokers n=11 (16.2%), past smokers n=10 (14.7%), current smokers n=47 (69.1%). Histology consisted adenocarcinoma n=42 (60%), squamous n=21 (30%) and other n=7 (10). Stage 2 were n=65 (78.3%) and stage 3 n=15 (21.4%). Chemotherapy consisted of platinum-doublet administered to 69 patients (98.5%). A mean radiation dose of 59 Gy (range 46-72 Gy) was delivered with IGRT prior to each fraction. Five patients received lower radiation doses due to toxicity or dose constraints. Surgery comprised of lobectomy n=50 (71.4%), chest wall resection n=9 (12.9%) or pneumonectomy n=11 (15.7%). Negative surgical margins were achieved in n=63 (90%) and positive margins in n=7 (10%). 30-day mortality was n=2 (2.8%) both cases after Right-sided pneumonectomy. MTR was observed in 45 cases (64.3%) including a pathological complete response in 25 (35.7%) and < 10% residual tumor in 20 cases (28.5%). The mean percent of residual tumor cells was 16% and the median 6.5%. Percent of residual tumor cells did not correlate to radiation dose (Rs=0.092), and not to the histology (p= 0.165), and not to type of chemotherapy (p=0.35). **Conclusion:** NACCRT delivered to 60 Gy with modern image-guided radiation therapy is safe. Two thirds of such patients achieve major tumor regression.

Keywords: pathologic regression, chemoradiation, Trimodality

MA05 IMPROVING OUTCOMES IN LOCOREGIONAL NSCLC II
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MA05.11 RADIOMICS ANALYSIS USING SVM PREDICTS MEDIASTINAL LYMPH NODES STATUS OF SQUAMOUS CELL LUNG CANCER BY PRE-TREATMENT CHEST CT SCAN

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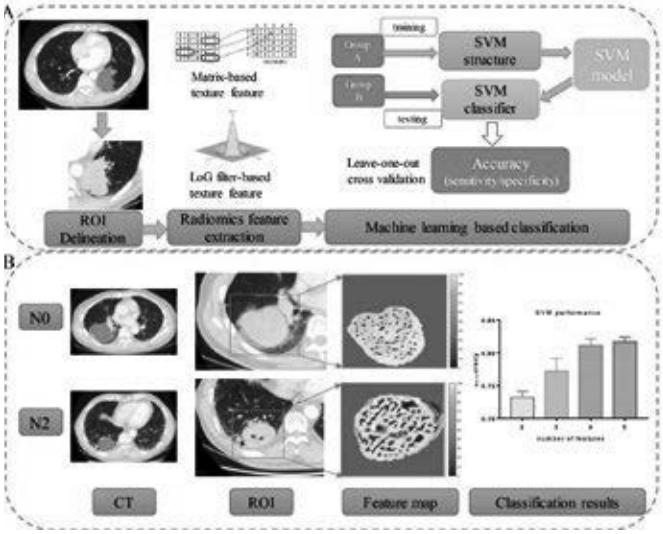
Background: Assessment of mediastinal lymph nodes (N2 station) is essential in staging patients with Non-small-cell lung cancer (NSCLC), for patients with preoperative confirmed N2 status should follow neoadjuvant therapy before surgery, and occult N2 status should be avoided. There are several invasive and non-invasive exams available for preoperative N staging, like EBUS-TBNA and PET-CT scan. Chest CT scan was the basic examination of every patient, while only the length of minor axis could be used to predict lymph node involvement, and the potential value of CT might be underestimated. In this study we aimed to explore the value of radiomics analysis with machine learning in differentiating N2 from N1/N0 subjects using pre-treatment chest CT. **Method:** Ninety-three patients with squamous cell lung cancer, who underwent pre-treatment CT scans were included in this study. By use of Laplacian of Gaussian (LoG) filter and matrix based radiomics models (e.g. gray-level co-occurrence matrix), comprehensive radiomics features were extracted from the regions of interest which were manually delineated on primary tumors. We performed radiomics analysis using support vector machine (SVM) to test texture and heterogeneity features derived from pre-treatment CT images as indicators for the staging of lymph node metastasis, especially N2. The gold standard of N staging is confirmed pathologically after systematic mediastinal lymphadenectomy (N2 subjects=31). **Result:** For the performance evaluation of single image feature, there are 16 features able to differentiate N2 subjects from others (N0 and N1) with p value <0.05. Furthermore, SVM training and classification were performed using 5-feature combinations as inputs. With feature selection, the best performance of N2 prediction is 83% accuracy with 87% sensitivity and 81% specificity.



Conclusion: Radiomics analysis using SVM training can successfully predict N staging by pre-treatment chest CT scan for NSCLC patients, which could diminish the odds of occult N2 status and provide unique information preoperatively for treatment planning.

Keywords: Radiomics, support vector machine training, Squamous cell lung cancer

MA06 PDL1, TMB AND DNA REPAIR
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MA06.01 THE INTRINSIC PD-L1 PROMOTES CELLULAR INVASIVENESS VIA THEIR PD-1 RECEPTOR IN LUNG ADENOCARCINOMA CELLS

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Background: Lung cancer is the most frequent cause of cancer death. Programmed death 1 (PD-1) in T cells and its ligand PD-L1 in tumor cells play a key role in immune checkpoint therapy and had applied to advanced stage lung cancer. Migration and invasion of tumor cells is a prerequisite for tumor cell metastasis. Since intrinsic PD-1 receptor functions promote tumor growth was reported, we will investigate the interaction between PD-1 and PD-L1 in lung adenocarcinoma cell lines, the impact on chemosensitivity, and clinical outcome. **Method:** In vitro experiments, lung adenocarcinoma CL1-5 cells, derived from CL1-0 cells. We prepared PD-L1-overexpression human lung adenocarcinoma cell line,

derived from CL1-0 cells (CL1-0-PD1). Migration and invasion ability were assessed by transwell assay; EMT marker and regulator were evaluated by Western blotting. We also observed the morphology of cells. To explore interaction between PD1 and PD-L1, we added anti-PD-1 antibody into CL1-0, CL1-5, and CL1-0-PDL1 cells, and then test migration, invasion and cellular morphology. We also suppressed PD-1 by siRNA to test whether PD-1/PDL-1 interaction contributed to the EMT change. Further, we evaluated cellular proliferation and chemosensitivity by MTT assay and colony formation assay. We will correlate PD-L1 expression in lung cancer cells with clinical outcome by IHC stain clinically. **Result:** In CL1-5 cells, derived from CL1-0 cells, with high PD-L1 expression possessed higher cellular migration ability than the parental CL1-0 cells with less PD-L1 expression. CL1-0 cells with PD-L1 overexpression had more expression of EMT (epithelial mesenchymal transition) regulator and mesenchymal marker. We also observed that CL1-5 and CL1-0-PDL1, which had more PD-L1 expression, are shaped like spindles; while CL1-0 cells are more rounded. Therefore, PD-L1 up-regulated cell migration and invasiveness in human lung adenocarcinoma cells and promotes EMT. After adding anti-PD1 antibody in CL1-5, CL1-0, and CL1-0-PDL1 cells, migration and invasion ability decreased. These result indicated anti-PD-1 antibody block the link between PD-1 and PD-L1 in cancer cells. The phenomenon was confirmed by PD-1 siRNA. Therefore, PD-1/PD-L1 axis regulated cancer cells migration and invasiveness. PD-L1 expression also decreased cellular proliferation and had little influence on chemsensitivity. Finally, we found that higher PD-L1 expression was correlated with lymph node metastasis in clinical specimen. **Conclusion:** Lung adenocarcinoma cells with higher PD-L1 expression promote cell migration, invasiveness, EMT, and little chemoresistance. PD-L1 expression lowers proliferation rate. PD-1 and PD-L1 interaction on lung adenocarcinoma cells contribute cellular migration and invasiveness.

Keywords: epithelial mesenchymal transition, lung adenocarcinoma, PD-L1

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MA06.02 PROSPECTIVE IMMUNOGENOMIC PROFILING OF NON-SMALL CELL LUNG CANCER: GENOMIC AND IMMUNE PROFILING UPDATES FROM PROJECT ICON

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Background: Our previous work has demonstrated that higher level of genomic complexity is associated with more heterogeneous neoantigen repertoire, suppressed T cell repertoire and postsurgical relapse in localized non-small cell lung cancers (NSCLC) highlighting the complex interaction of tumor molecular and immune landscape and their impact on cancer biology and patient survival. We launched the ICON Project (Immune Genomic Profiling of NSCLC) to prospectively delineate the molecular and immune landscape of early stage NSCLC and their impact on patient survival through a multidisciplinary approach. Here we report the updated genomic and immune analyses. **Method:** Surgical specimens from stage I-III NSCLC were subjected to whole-exome and RNA sequencing for mutational analysis, in silico neoantigen prediction and gene expression analysis as well as T cell receptor sequencing, cytometry by time-of-flight and multiplex immunofluorescence staining. **Result:** From 2016-2018, 127 patients were accrued and 50 surgical samples have undergone WES, RNAseq, TCR sequencing and immune phenotyping. Median age is 66 yrs (range: 39-86), 52% (26/50) were female and 76% (38/50) former smokers. 76% (38/50) are non-squamous carcinomas and 24% (12/50) squamous cell carcinomas. 34% have stage I disease (17/50), 30% stage II (15/50), 34% stage III (17/50) and 2% stage IV (1/50). The majority of patients had upfront surgery (45/50; 90%). With median follow-up of 19 months, 15 patients have relapsed. Median tumor mutational burden is 7.8mut/Mb and predicted neoantigen burden was 10/sample (range: 0-250). Predicted neoantigen burden is significantly correlated with tumor mutational burden (r=0.41, p=0.002). The most commonly mutated genes are TP53, KRAS, CDKN2A, PIK3CA, EGFR, BRAF, GRIN2A and ATM. C->A transversions and C->T transitions were the most common mutational subtypes. PD-1 expression and regulatory T-cell (CD4+/FoxP3+) infiltration are significantly increased in tumor tissue compared to normal tissue (p=0.003 and p=0.02 respectively), while CD3, CD8, granzyme B and CD45RO are decreased in tumor tissue compared to normal lung. **Conclusion:** NSCLC tumors have an immunosuppressive microenvironment compared to tumor adjacent normal lung tissues. Clinical data will be adequate to conduct genomic and immune profiling comparisons across different clinical subgroups. Mutational and neoantigen profiling are consistent with previously reported studies and correlations between molecular and immune landscapes and its impact on patient survival are ongoing.

Keywords: immunogenomic profiling

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MA06.03 PD-1 AND ID-1 COMBINED BLOCKADE IMPACTS TUMOR GROWTH AND SURVIVAL THROUGH PD-L1 EXPRESSION AND TUMOR INFILTRATION BY IMMUNE-RELATED CELLS

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Background: PD-1/PDL-1 inhibitors are approved in advanced non-small cell lung cancer (NSCLC). Long-term survival rates associated to PD-1/PDL-1 blockade have changed treatment paradigm. However, many patients do not benefit from PD-1/PDL-1 blockade. New therapeutic combinations are under investigation. Id1 is involved in proliferation, angiogenesis and immunosuppression. We described Id1 as an independent prognostic factor in NSCLC (Ponz-Sarvise, Clin Cancer Res 2011) and more recently showed Id1's role in lung cancer metastasis (Castanon, Cancer Letters 2017). Here we test a combined therapeutic strategy targeting PD-1 and Id1 in a murine lung cancer model. **Method:** Three in vivo studies evaluated the impact of Id1 inhibition in tumor cells, tumor microenvironment and in both, on tumor volumes and mice survival. A syngeneic tumor model using C57BL/6 and Id1-/- Id3+/- mice was created by subcutaneous injection of Lewis Lung Carcinoma (3LL) cells and Id1 silenced 3LL (Id1Sh) cells. After injection, mice were treated with an anti-PD-1 (RMP-1-14) monoclonal antibody or PBS. Tumor volumes according to mice strain, Id1 status in tumor cells and treatment were quantified. Mice's survival was calculated in those groups. Tumor CD8+ and CD3+ TILs and CD68+ cells were quantified by specific immunostainings. **Result:** Id1 inhibition in the tumor environment and the injected tumor cells, combined with anti-PD-1 treatment, induced a significant tumor growth impairment ($p < 0.0001$) and increased survival ($p = 0.0051$). CD3+ and CD8+ TILs and tumor CD68 + cells were significantly higher in tumors from mice with the combined Id1-PD-1 blockade treated with the anti-PD-1 inhibitor compared to control animals suggesting that tumor increased immune-related cells infiltration exerts the effector phase of the antitumor immune response. Additionally, PD-L1 expression seemed to be higher when Id1 expression was absent in the immune microenvironment ($p = 0.04$). Additional data based on multiplexed immunohistochemistry results will be presented at the meeting. **Conclusion:** Id1 and PD-1 combined blockade in our syngeneic murine lung cancer model significantly impaired tumor growth and increased survival. Increased tumor PD-L1 expression and CD3+ and CD8+ TILs and CD68+ cells may explain these findings.

Keywords: Id-1, Immunotherapy combination, PD-1

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MA06.05 THE MICRO-ENVIRONMENTAL CROSS TALK BETWEEN MAST CELLS AND LUNG CANCER CELLS THROUGH CELL-TO-CELL CONTACT

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Background: Mast cells (MCs) are key effectors in allergic reactions, but are also involved in tissue remodeling, wound healing and protection against pathogens. MCs infiltrate tumors and their number within the tumor microenvironment in certain cancer types, such as lung cancer, have been correlated with poor prognosis. The nature of crosstalk between lung cancer and MCs remain poorly resolved. In this study, we investigated the activation patterns within the MCs following cell-to-cell contact with lung cancer cells showing CD73 involvement and implying metabolic changes. **Method:** Human MCs (HMC-1 and LAD-2) were exposed to Human lung cancer cells (H1299), derived membranes to recapitulate cell contact mediated activation. Lysates of MCs were tested for protein expression and posttranslational modifications (i.e. phosphorylation) by targeted western blotting. We unraveled the intracellular signaling molecules that are necessary for this signaling pathway by a pharmacological approach using several inhibitors. Each condition was repeated at least twice. **Result:** H1299 membrane exposure activated the ERK 1/2 MAP kinases in HMC-1 and in LAD-2 cells. AKT signaling was also activated in LAD-2 cells as a result of this contact. CD73 dephosphorylates AMP to adenosine within the MCs. Interestingly enough, this ERK 1/2 activation was inhibited by CD73 inhibitor and A3 receptor antagonists in HMC-1 cells. ERK 1/2 activation was inhibited by A3 receptor antagonists and PI3K in LAD-2 cells. Furthermore, we discovered that protein kinase C (PKC) inhibitor augments the activation of ERK 1/2 in LAD-2 cells. In contrast, PKC inhibitor inhibits the activation of ERK 1/2 in HMC-1 cells. In addition, we discovered that the AKT activation was inhibited by A3 receptor and PI3K inhibitors but not by CD 73 inhibitors. **Conclusion:** Our results suggest that H1299 membranes activate ERK 1/2 in HMC-1 cells by a mechanism that involves autocrine formation of adenosine and is mediated by CD 73 and A3 receptor. In addition, we discovered that there is an important difference between the ERK 1/2 MAP kinase signal transduction in HMC-1 and LAD-2 cells, PKC is an inhibitor of the H1299 activation of ERK 1/2 in LAD-2 cells. In contrast, the H1299 membrane activation of ERK 1/2 kinase in HMC-1 cells is mediated by PKC. Furthermore, we can conclude that H1299 membranes activate AKT in an A3 receptor dependent mechanism that is mediated by PI3K.

Keywords: lung cancer, mast cells, Cell Communication

MA06 PDL1, TMB AND DNA REPAIR
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MA06.06 AN EX-VIVO PATIENT-DERIVED, IMMUNOCOMPETENT (PDI) CULTURE SYSTEM TO EVALUATE IMMUNOTHERAPEUTIC AGENTS' ANTI-TUMOR EFFICACY

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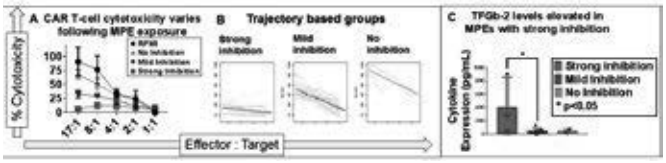
Background: Anti-tumor efficacy of human immunotherapeutic agents, such as antibodies, chimeric antigen receptor (CAR) and T-cell receptor transduced T cells, are currently being investigated in immunodeficient mice prior to clinical translation. We developed and optimized an *ex-vivo* culture system utilizing malignant pleural effusions (MPEs) to compliment these investigations in a human, immunocompetent, tumor-like environment. We hypothesized that CAR T cells' cytotoxicity will vary by the different immune compositions in each MPE, which are conditions unavailable in current efficacy assays. **Method:** Mesothelin-targeted CAR T cells from multiple donors were exposed to MPEs derived from non-small cell lung cancer patients (n=15) and RPMI culture medium. Influence of the MPEs on CAR T-cell efficacy was evaluated by viability and phenotype (flow cytometry), cytotoxicity (chromium release assay), and gene expression (NanoString). Group-based trajectory modeling was used to stratify the inhibitory effect of MPEs. MPE composition (ELISA and Luminex assays) was evaluated to interpret its influence on CAR T cells. **Result:** With the incorporation of our optimized protocols, T cells retain their viability, phenotype (CD4/CD8), and percentage of CAR expression when cultured in MPEs. MPE soluble factor levels remained stable over multiple freeze/thaw cycles. CAR T cells co-cultured in MPE exhibited variable antigen-specific cytotoxicity (**Fig. A**). MPE-induced T-cell inhibition was stratified into groups of strong, mild, or no inhibition. (**Fig. B**). Compared to MPEs with either mild or no inhibition, MPEs with strong inhibition had significantly higher levels of TGFβ-2 (average TGFβ-2 level in strong vs. mild inhibition: 402 vs. 50 pg/mL, p<0.05) (**Fig. C**), IL-6, RANTES, and IL-5.



Conclusion: We present the first human immunocompetent culture system that can be used to evaluate immunotherapeutic agents' efficacy prior to their clinical translation. Furthermore, analyses of the culture system's soluble factors sheds light on their relative influence on T-cell efficacy.

Keywords: car, Malignant plerual effusion, Immunotherapy

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MA06.07 GENETIC AND EPIGENETIC ALTERATIONS ARE ASSOCIATED WITH TUMOR MUTATION BURDEN IN NON-SMALL CELL LUNG CANCER

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Background: Although several studies have indicated that tumor mutation burden (TMB) is associated with non-small cell lung cancer (NSCLC) development and clinical efficacy of immune checkpoint inhibitors (CPIs), identification of factors associated with TMB is still a major biological issue. It is well-known that DNA transcription can be regulated through methylation and demethylation, gene silencing caused by DNA hypermethylation is associated with cancer development. However, the relationship between DNA methylation and TMB in NSCLCs remains unclear. **Method:** The landscape of DNA sequence in Chinese NSCLCs population were surveyed by using whole-exome sequencing (WES) by profiling 178 lung tissues (89 without any systemic anti-cancer therapy tumors and matched normal lung tissues). According to the 104 median-level of TMB in our cohort, high TMB (n=16, 252-465 range mutations per tumor) and low TMB (n=13, 57-79 range mutations per tumor) groups were divded. The NSCLC methylome between high and low TMB was characterized on a genome-wide scale using Illumina Infinium MethylationEPIC arrays combined with the WES data. **Result:** The results show frequently aberrant DNA methylation, abundant chromosomal amplifications and deletions, and mutational signatures in high TMB lung cancer. Combining with clinical data, cigarette smoking associated with high TMB were observed in our cohort. Cancer-specific epigenetic alterations were observed in 294,141 CpG sites, comprising both tumor hyper- (769,38) and hypo- (217,203) methylation in high TMB lung cancer while none in low. These different methylations sites cover 1232 genes including 25 HOX genes. **Conclusion:** Global DNA hypomethylation and TP53 mutation, associated with increased chromosomal instability, were associated with TMB in NSCLCs.The high TMB NSCLCs are characterized by numerous copy number alterations and aberrantly methylated sites and display distinct mutational signatures. 25 hypermethylated HOX genes can be potentially useful as DNA methylation markers for prediction of TMB level. The results provide insights into the epigenetic impact of TMB, which may contribute to improve precison management of NSCLCs.

Keywords: Tumor mutation burden, DNA methylation, non-small cell lung cancer

MA06.09 XRCC6BP1: A DNA REPAIR GENE IN CISPLATIN RESISTANT LUNG CANCER STEM CELLS THAT MAY PREDICT SURVIVAL OUTCOMES IN PATIENTS

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Background: Alterations in the DNA repair capacity of damaged cells is now recognised as an important factor in mediating resistance to chemotherapeutic agents. **Method:** DNA Repair Pathway RT^2 Profiler Arrays were used to elucidate key DNA repair genes implicated in chemoresistant NSCLC cells using cisplatin resistant (CisR) and corresponding parental (PT) H460 cells. DNA repair genes significantly altered in CisR cells were validated at the mRNA and protein level. The translational relevance of differentially expressed genes was examined in a cohort of chemo-naïve matched normal and tumour lung tissues from NSCLC patients. Loss of function studies were carried out using siRNA technology. The effect of XRCC6BP1 gene knockdown on apoptosis was assessed by FACS. Cellular expression and localisation of XRCC6BP1 protein and γH2AX foci in response to cisplatin were examined by immunofluorescence (Cytell™). To investigate a role for XRCC6BP1 in lung cancer stem cells, Side Population (SP) studies were used to characterise stem-like subpopulations within chemoresistant cells. XRCC6BP1 mRNA analysis was also examined in ALDH1$^+$ and ALDH1$^-$ subpopulations. Immunohistochemistry analysis was carried out in resected lung tumour tissues and XRCC6BP1 expression was correlated with survival in addition to a number of clinicopathological parameters such as tumour stage & grade, gender, smoking status and chemotherapy. **Result:** We identified a number of critical DNA repair genes that are differentially regulated between PT and CisR NSCLC cells. XRCC6BP1 mRNA and protein expression was significantly increased H460 CisR cells relative to their PT counterparts. Relative to matched normal lung tissues, XRCC6BP1 mRNA was significantly increased in lung adenocarcinoma patients. Gene silencing of XRCC6BP1 induced significant apoptosis of chemoresistant cells and reduced their DNA repair capacity. Immunofluorescence studies showed an increase in XRCC6BP1 protein expression and gH2AX foci in CisR cells. SP analysis revealed a significantly higher stem cell population in resistant cells, while XRCC6BP1 mRNA expression was considerably increased in SKMES-1, H460 and H1299 CisR cells positive for ALDH1 activity (ALDH1$^+$) compared to ALDH1$^-$ cells. IHC scoring of XRCC6BP1 demonstrated poor survival outcomes for NSCLC patients with high expression of this DNA repair gene. **Conclusion:** Our data highlight the potential of targeting components of the DNA repair pathway, in particular XRCC6BP1, in chemoresistant lung cancer. Furthermore, XRCC6BP1 may play an important role in subsets of lung cancer stem cells which, at least in part, may be responsible for driving and maintaining the cisplatin resistant phenotype in NSCLC.

Keywords: Resistance, dna repair, XRCC6BP1

MA06.10 GERMLINE MUTATION IN ATM AFFECT LUNG CANCER RISK WITH HIGH EFFECT

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Background: Genome wide association studies have identified several lung cancer susceptibility regions and common variants influencing lung cancer risk. However, few previous studies investigated the association between germline mutations and lung cancer risk. **Method:** We analyzed data from a case-control study with 19053 lung cancer cases and 15446 healthy controls of European ancestry in a discovery phase and performed a validation analysis using a case-control study comprising 4261 lung cancer cases and 4152 healthy controls of European ancestry for replication. Logistic regression was used to identify germline mutations with high effect within exome regions associated with lung cancer risk. **Result:** We found rs56009889 in ATM was statistically associated with lung cancer risk in the discovery set (OR = 3.05, P = 3.68×10^{-8}) and was nonsignificantly associated with lung cancer risk in the validation set (OR = 1.83, P = 0.16). Stratified analyses by gender with adjustment for age and smoking status showed that females carrying at least one mutated allele of rs56009889 (T/C + T/T) had an increased risk of lung cancer with ORs being 7.77 (95% CI 3.45 - 17.47) in discovery and 6.73 (95% CI 1.46–30.98) in replication, compared to C/C homozygotes among females. Individuals carrying at least one T allele showed a significant 6.9-fold increased risk for lung adenocarcinoma in discovery (adjusted OR = 6.85; 95% CI 4.37 – 10.75) and approximately a 4.9-fold increased risk in replication (adjusted OR = 4.89; 95% CI 2.01 – 11.91). Never smokers with combined genotypes (T/C + T/T) had a greater than 8-fold increased risk of lung cancer in discovery (adjusted OR = 8.03, 95% CI 4.00 – 16.13), while smokers only showed a 2.13-fold increased risk (adjusted OR = 2.13, 95% CI 1.25 – 3.65). In replication, however, the risks from this variant were comparable between smokers and nonsmokers, although the sample size is small for nonsmokers (adjusted OR = 2.16; 95% CI 0.48 – 9.79 for never-smokers and adjusted OR = 2.07; 95% CI 0.66 – 6.52 for smokers). All the T/T homozygotes of rs56009889 developed lung adenocarcinoma in discovery (P = 0.036). The association exhibited a dose-response relationship between the number of T allele of rs56009889 and lung cancer risk in discovery (P_{trend} = 1.07×10^{-9}). **Conclusion:** rs56009889 highly affected the risk of lung cancer, mainly of lung adenocarcinoma, primarily in women and never smokers. These germline mutations provide important insights for the prevention of lung cancer.

Keywords: lung cancer, germline mutation, ATM gene

MA06.11 DISTINCT ORIGINS OF LYMPHATIC AND BRAIN METASTASIS IN LUNG CANCER

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Background: Generally, distant metastases are seeded by lymph node metastases in most solid tumors. This concept provides a mechanistic basis for the TNM staging system and is the rationale for surgical resection of tumor-draining lymph nodes. However, a recent study found that lymphatic and distant metastases could arise from independent subclones in the primary colorectal cancer. The current study aimed to investigate the origins of lymphatic and brain metastasis in lung cancer. **Method:** 39 samples from twelve patients with primary lung cancer and brain metastases were identified. Three of them had the matched lymph node metastases. All tissues and matched peripheral blood samples were collected before any systemic treatment. Whole-exome (>150×) sequencing were conducted on these samples. **Result:** Compared to the primary lesions, both brain and lymph node metastases had the significantly different patterns of somatic genome alterations. The mutational landscape of brain metastases was also distinctly different from matched lymph node metastases. Primary lesions, matched brain and lymph node metastases showed the similar mutation pattern in terms of transition and transversion, and all of samples displayed a higher percentage of C>T transition. Brain metastases had numerically higher tumor mutational burden (TMB) than primary lesions but it did not reach the statistical significance. Notably, we observed the totally distinct origins of lymphatic and brain metastasis in all three matched cases. **Conclusion:** The current evidence suggested that brain metastases and matched lymph node metastases had different mutational landscape in patients with lung cancer. Brain metastases had higher TMB than their primary lesions. Lymphatic and brain metastasis had distinct origins in lung cancer. These results had profound clinical implications for application of immunotherapy and improvement of prognosis in patients with lung cancer and brain metastases.

Keywords: lung cancer, Brain metastasis

MA07.01 NO LONGER OUTLIERS: UNDERSTANDING THE NEEDS OF LONG-TERM LUNG CANCER SURVIVORS

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MA07.02 LINE OF THERAPY AND PATIENT PREFERENCES TREATING LUNG CANCER: A DISCRETE-CHOICE EXPERIMENT

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Background: Patient preferences now play an important role in cancer research, regulatory science, and value assessment. While there is a growing literature exploring the preference of patients with lung cancer, few studies have explored how preferences vary with patients' treatment experience. We sought to quantify patient preferences for the benefits and risks of therapy and explore how they vary across line of treatment. **Method:** Preferences were estimated using a discrete choice experiment (DCE) developed in partnership with a patient and stakeholder advisory boards. A D-optimal experimental design was used to generate 3 blocks of 9 choice tasks spanning five attributes: progression-free survival (PFS), short-term side effects, long-term side effects, risk of developing late-onset side effects, and mode of administration – each defined across 3 relevant levels. A diverse sample was recruited via email sent to the LUNGevity lung cancer patient database and via social media. A choice mode was estimated use a conditional logistic regression where the dependent variable was the respondents preferred treatment in each profile. The relative attribute importance (conditioned on the chosen attribute levels) was then compared across the respondents' self-reported line of treatment. **Result:** In total we had 350 eligible respondents, of which 279 (80%) completed as least on DCE task of which 3% did not receive a pharmacotherapy, 39% received first line therapy, and 58% had two or more lines of theory. As with previous studies, PFS was the most important attribute for patients and was similarly valued (P=0.406) among first- and later (second lines and more) lines of treatment (33.4% v 33.8%). Patients on first-line treatment placed great emphasis (P<0.001) on long-term side (18.9% v 14.1%) and late onset side effects (15.3% v 10.3%), but less emphasis (P<0.001) on short-term side effects (27.8% v 29.8 %) and mode of administration (4.6% v 12.0%) than those on later lines. **Conclusion:** Population estimate of patient preference remain important, but more effort is needed to understand how patient preference vary across patient with different backgrounds and treatment experiences. We show that line of treatment does not effect how patients value time, but their experience may have an impact on treatment characteristics. Latent class analysis may allow for the identification of groups with similar preferences that could allow for multivariate analyses to explain preference heterogeneity.

Keywords: treatment preference, patient preference

MA07.03 ATTITUDES TO LUNG CANCER IN EUROPE: FINDINGS FROM A GLOBAL CONSUMER SURVEY

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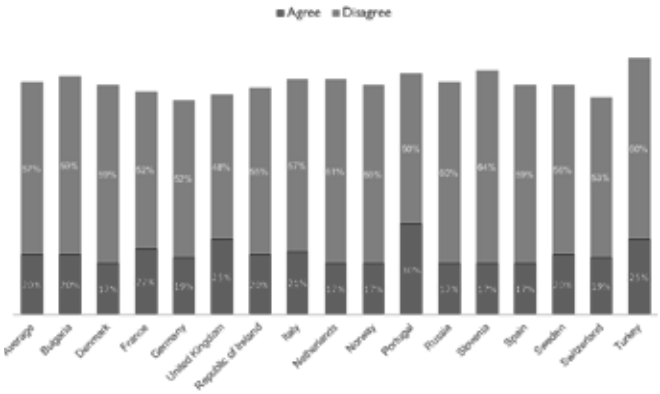
Background: If lung cancer is diagnosed early, patients' chances of successful treatment are increased. Stigma around lung cancer, as a tobacco-related cancer, can discourage patients from talking to their doctor about potential symptoms. In 2017, the GLCC commissioned Populus to undertake an international consumer survey in each of the 25 countries of the GLCC members. **Method:** 1,000 adults, in 16 European countries, participated via an online survey in July 2017. To assess attitudes to lung cancer, they were told that lung cancer is mainly caused by smoking and other tobacco products. They were then asked the extent to which they agreed or disagreed with the statement: "I have less sympathy for people with lung cancer than for people with other cancers." **Result:** One in five (20%) people in Europe agreed that they have less sympathy for people with lung cancer than other forms of cancer (Chart 1). There was variation between countries with 30% of people in Portugal agreeing they have less sympathy in comparison to only 17% agreeing in Denmark, the Netherlands, Norway, Russia, Slovenia and Spain. Men in Europe are generally less sympathetic than women, and those aged over 55 are most sympathetic. In addition, there was a statistically significant correlation between those countries with lower cigarette consumption and people agreeing that they have less sympathy for people with lung cancer. Chart 1: European attitudes to lung cancer



Conclusion: Everyone - no matter what the cause of their cancer - deserves to have high quality treatment and care. The persistent and varied levels of stigma associated with lung cancer across Europe needs to be addressed, so that people experiencing symptoms are not discouraged from seeking early intervention.

Keywords: lung cancer, Attitudes, Europe

MA07.05 PSYCHOSOCIAL NEEDS AND PROGRAMS OF CANCER PATIENTS/SURVIVORS AND THEIR RELATIVES: UNMET NEEDS FROM AN INTERNATIONAL STUDY

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Background: In consideration of the dynamic nature of cancer patients' needs, systematic understanding of their unmet needs from a socio-ecological perspective may be essential as the patients' needs and available services are likely to vary by different healthcare systems in different countries. To investigate the role of geographical influence in cancer patients' unmet needs, this study seeks to compare the unmet needs of and available programs for cancer patients/survivors and their family members by different types of healthcare systems across different countries. **Method:** The IPOS Survivorship Online Survey is distributed to international and regional Psycho-Oncology organization members, which covers countries in six continents. Survey participants' countries where they practice/research will be categorized into four groups by the types of healthcare system: Beveridge Model, Bismarck Model, National Health Insurance Model, and Out-of-Pocket Model. **Result:** With estimated survey to be completed by August 30th, 2018, repeated measures ANOVA will be employed to test differences in patients' unmet needs by the four healthcare system groups, separately for patients' unmet needs and their family caregivers'. Differences by individual countries will also be explored. **Conclusion:** Findings will provide a global overview and a specific knowledge of the geografical differences in the psychosocial unmet needs and psycho-oncological programs for cancer patients/survivors and their family members/caregivers. Findings will also guide how to prioritize areas of cancer care that require improvement in psycho-oncology interventions and practices; and to highlight critical aspects for delivering quality care that vary by healthcare systems.

Keywords: Psychosocial Needs, international study, cancer patients and survivors

MA07.06 TELEPHONIC COMMUNICATION IN PALLIATIVE CARE FOR BETTER MANAGEMENT OF TERMINAL CANCER PATIENTS IN RURAL INDIA - AN NGO BASED APPROACH

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Background: Due to financial incapability and absence of manpower poor families often fail to carry their advanced cancer patients to the nodal centres. This pilot study will explore whether communication by mobile phone can lessen this burden. **Method:** Initially a plan was generated regarding management of an advanced cancer patient in a nodal centre at District Head Quarter. Subsequently every two week a trained social worker attached to nodal centre will follow up and give necessary advice and emotional support to the patients and their families through their registered mobile phone number. Patient's family were also encouraged to communicate with the team by phone in case of fresh complain and urgency in between. **Result:** Since initiation in January 2017, 210 cancer patients were contacted by mobile phone every two weeks to enquire about their difficulties. In 76% of the situation trained social workers could give necessary advice by phone regarding management of their physical symptoms. Moreover patient's family were really overwhelmed by the emotional support offered by the team over phone. Only 24% of cancer patients has to attend the nodal centre for expert advice from Palliative Care specialists. **Conclusion:** This novel approach helped

* In providing regular physical and emotional support to the patients and their families. * In significantly reducing the financial and manpower problems of carrying patients to the nodal units.

* In improve the quality of life of patients by continuous guidance.

More and more team members can take help of this new strategy for better communication and uninterrupted care.

Keywords: terminal cancer, palliative care, rural india

MA07.07 IDENTIFYING THE SEVERITY OF PSYCHOSOCIAL SYMPTOMS AMONG PATIENTS DIAGNOSED WITH LUNG CANCER. DO WE REALLY NEED EMOTIONAL SUPPORT GROUPS?

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Background: Lung cancer is the second most common cancer among men and women. Most of the lung cancers are diagnosed at later stages among those patients who are underprivileged. The diagnosis and treatment of lung cancer is a continuous emotional distress for both patient and their family. We aim to identify the severity of depression, emotional distress, stress and mental fatigue among those patients who are diagnosed with lung cancer . **Method:** A cross sectional study was conducted in Shaukat Khanum Hospital, Lahore from March 2014 to April 2015. Exclusion and Inclusion criteria were made. 150 were enrolled in the study. Socio demographic characteristics were evaluated using Beck Depression Inventory and socio demographic form. Severity of depression was estimated by using Hamilton D (HAM-D). Various variables were analysed including parent's age, level of education, socioeconomic status, gender and number of children. **Result:** 68% of the participants exhibited severe range of depression. 27% showed moderate depression where as 5% participants were showing the mild range of depression. An inverse co relation was found between educational status, occupational status (paid or unpaid), their marital status, socioeconomic family status and depression. Women 71% were found be more depressed than males. **Conclusion:** We concluded that majority of patients from psychosocial symptoms particularly depression and it is mainly associated with some factors. There is need to incorporate patients into the diagnosis and treatment process so that we can over come the effects of depression on the health outcomes of patients diagnosed with lung cancer. This can only be possible through appropriate education and emotional support programmes.

Keywords: lung cancer, emotional support groups, psychosocial symptoms

MA07 TOWARDS SURVIVORSHIP: THE LANDSCAPE, SUPPORTS AND BARRIERS
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MA07.09 WILLINGNESS TO PERFORM MULTIPLE BIOPSIES TO IMPROVE QUALITY OF LUNG CANCER CARE: UNDERSTANDING THE ONCOLOGISTS' PERSPECTIVE

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Background: Biomarker testing of advanced-stage non-small cell lung cancer (NSCLC) at the time of diagnosis is required to determine if a patient will benefit from a targeted therapy or immunotherapy. A patient may, however, need additional biopsies (rebiopsy) if the cancer recurs to determine the next line of therapy or to determine eligibility for a new drug or participation in a clinical trial. A LUNGevity study, conducted with 340 patients, revealed that patients were willing to undergo rebiopsies if that meant access to additional treatment options at the time of recurrence. However, only 36% of patients reported that their doctors recommended repeat biopsies at progression. **Method:** To understand this patient-physician communications gap, we conducted an IRB-approved semi-structured survey-based study of 130 oncologists from academic research centers, community cancer centers, and private practice. **Result:** Of the 130 oncologists surveyed, - Ninety percent of oncologists reported recommending a rebiopsy to their patients. However, when stratified by advanced-stage patient volume, oncologists with higher advanced-stage patient volumes reported higher rebiopsy and testing rates than those with low volumes (95% vs. 78%, $p<0.05$). Only 29% of the oncologists prescribed a rebiopsy in the past one year. - Major barriers to rebiopsy reported by oncologists included cost/reimbursement of a rebiopsy and treatment delay for 2nd- or subsequent lines of therapy - Among the types of biomarker testing performed at the time of progression, oncologists were more likely to prescribe testing for biomarkers with approved treatments (driver mutations – 94%, PD-L1 – 85%) unlike biomarkers for treatments in clinical development (43%) ($p<0.05$). - A forward linear regression analysis revealed that positive predictors of rebiopsy included treatment at a NCI Designated Cancer Center, while treatment at a community cancer center or private practice, presence of driver mutations at the time of diagnosis, and performance status of patient were negative predictors of rebiopsy - When presented with specific treatment scenarios for biomarkers (EGFR and ALK) that have 2nd-line treatment options, oncologists differed in their approach, suggesting a need for oncologist education about rebiopsying and subsequent biomarker testing **Conclusion:** Our study demonstrates that rebiopsy practices vary by practice settings and volume of advanced-stage lung cancer patients. Even when rebiopsies are prescribed, a comprehensive biomarker profile of the tumor may not be obtained, due to variations in tests requested. A major implication is the need for appropriate oncologists' education to ensure practice change for delivery of optimal care to lung cancer patients.

Keywords: biomarker testing, rebiopsy, oncologist

MA07 TOWARDS SURVIVORSHIP: THE LANDSCAPE, SUPPORTS AND BARRIERS
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MA07.10 UTILIZING A PERSONALIZED NAVIGATION PROGRAM TO IDENTIFY BARRIERS AND INCREASE CLINICAL TRIAL PARTICIPATION AMONG LUNG CANCER PATIENTS

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Background: Only about 5% of cancer patients participate in clinical trials. We previously conducted a survey of U.S. lung cancer patients and found that only 22% reported discussing clinical trials with their oncologist at the time of making treatment decisions. We hypothesized that a personalized navigation program could both increase rates of trial discussion and identify barriers to participation among lung cancer patients. **Method:** We asked callers to Lung Cancer Alliance's 1-800 support line if they had considered clinical trial participation and referred willing callers to a navigator for further discussion. Navigators provided basic clinical trial education and a personalized list of trial matches. Patients were encouraged to discuss these trials with their treating oncologist. Navigators then regularly followed up with participants, via email or phone, at two to four-week intervals, to offer further support and collect outcomes information. **Result:** We referred sixty callers to a navigator. Only 43% of callers reported a prior clinical trials conversation with their provider. Patients who had not started treatment or were on first-line treatment reported lower discussion rates (30%) than those on later treatment lines (60%). Among patients with follow up, 13 of 20 patients who had not discussed trials with their provider reported doing so after navigation. Ten of eleven patients that had a previous

trial conversation initiated an additional one. Primary reasons given for not talking discussing after navigation were having stable disease on a current treatment or waiting for a clinical result. Ten patients reported contacting a trial. Primary reasons for not contacting a trial after discussion were disease progression, choosing a standard of care alternative, or waiting for a clinical result. Four patients have enrolled on a trial. Two patients were determined ineligible for a trial they approached for not meeting listed eligibility criteria and two for reasons not appearing in public trial information. **Conclusion:** We identified barriers throughout the clinical trials consideration and enrollment process. One set of barriers was related to care coordination, as exemplified by low rates of trial discussion during early stages of treatment and patient reports of delayed trial consideration when currently receiving treatment or waiting on a clinical result. Communication of trial information was another area presenting barriers, as exemplified by exclusion of patients from trials for reasons not readily apparent from public trial information. Improving integration of trial discussion during care and ensuring availability of accurate, updated trial information may be essential to increase trial participation.

Keywords: patient navigation, clinical trials, lung cancer

MA07 TOWARDS SURVIVORSHIP: THE LANDSCAPE, SUPPORTS AND BARRIERS
MONDAY, SEPTEMBER 24, 2018 - 13:30-15:00

MA07.11 DRUG PRICE COMPARISON IN ADVANCED LUNG CANCER – HIGH COST PRICES IS ACCOMPANIED BY PATIENT BENEFITS?

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Scmed/ Anvisa, Brasilia/BR

Background: In our recent decade we are seen new drugs coming up with high speed development to attend personalized conditions in lung cancer treatment. After the first TKI for EGFR mutation, many other target drugs such as TKI for ALK/ROS1 alteration, third-generation EGFR TKI, anti-PD-1/PD-L1 immunotherapies bring together an improvement in survival with better quality of life than chemotherapies. But this new specialty drugs are also testing the affordability of the market with new launched ceiling prices. Frequently, their prices have been settled down in a context of an unmet condition appeal rather than the truly health benefits. In pricing it is a common practice to use the external reference price between countries to align the prices based on international market. But if the first price is launched (frequently in USA) in countries that don't use metrics based on evidence or clinical benefits, the price plateau could be replicated even without necessarily deserving this price. The objective of this presentation is to show the price comparison of drugs included in TKI class and immunotherapy class between high and middle-income countries. Then to compare the cost-treatment of therapies commonly used in advanced lung cancer and their magnitude of clinical benefit. **Method:** All local currencies were converted to US dollars using PPP factor. The magnitude of effect was evaluated based on the ESMO Magnitude of Clinical Benefit Score. **Result:** USA has the highest drug price followed by Brazil, especially in recent launched drugs. Costs of advanced lung cancer treatment significantly increase 5 times more when compared first-generated TKI and new generation TKI. Immunotherapy for second line costs 6 times more than first line with EGFR TKI and could cost more than 7 to 130 times the chemotherapy with docetaxel. Clinical benefits do not reach the same scale. **Conclusion:** The market of anticancer drug increasing 10% annually, but clinical benefits don't advance in the same compass. Specialized drugs come into the market with pricing warrant of unmeet conditions, but if we think in precision medicine all new drug-target biomarker could be priced higher because it will cover a rare or unmet condition. In the context of precision medicine, is it fear a patient pays more because he has a different biomarker for the same clinical condition? If countries do not start to evaluate and pricing drugs based on value, market strategists will continue to test the ceiling price that health systems can(not) afford.

Keywords: price, clinical benefit, value-based price

MA08 CLINICAL TRIALS IN BRAIN METASTASES
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MA08.01 PHASE 3 TRIAL OF WHOLE BRAIN RADIOTHERAPY WITH CONCURRENT ERLOTINIB VERSUS WBRT ALONE FOR NSCLC WITH BRAIN METASTASES (ENTER)

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Background: Brain metastasis (BM) is a leading cause of death for non-small cell lung cancer (NSCLC). Whole Brain Radiotherapy (WBRT) is a standard-of-care treatment for NSCLC patients with multiple brain metastases. Elevated EGFR expression and activity are important causes of tumor resistance to radiotherapy. This phase 3 trial sought to determine if concurrent erlotinib with WBRT will benefit patients with multiple BM compared with WBRT alone. **Method:** In this open-label, randomised, multicenter phase 3 study in China (NCT01887795), we enrolled NSCLC patients with at least two metastatic brain lesions who were naive to brain radiation and free from any EGFR-TKI for at least 4 weeks. Participants were randomly assigned (1:1) to receive either WBRT (2.0 Gy per day, 5 days per week, to 40 Gy) or WBRT plus concurrent oral erlotinib 150 mg daily (Erlotinib was given for 6 days then concurrently with WBRT). Subsequent treatments were maintenance therapy of erlotinib for *EGFR*-positive patients or standard chemotherapy for *EGFR*-negative patients until unacceptable adverse events or disease progression. The primary endpoint was intracranial progression-free survival (iPFS), defined as time from randomisation to either intracranial disease progression or death for any cause. **Result:** Between August 7, 2013 and November 25, 2016, in total 222 patients from 11 centers across China were randomized to treatments: 115 with WBRT alone and 107 with WBRT and concurrent erlotinib. Median follow-up was 11.2 months (IQR 4.6-18.2). Median iPFS was 11.2 months (95% CI: 7.2-13.7) with WBRT and concurrent erlotinib versus 9.2 months (95% CI: 6.7-10.9) with WBRT alone (HR 0.926; 95% CI: 0.695-1.234; P=0.601). In the subgroup of 109 patients who were positive for the *EGFR* mutation, iPFS was not significantly longer among those who received WBRT with concurrent erlotinib than WBRT with sequential erlotinib (14.6 [95% CI 11.8-17.7] vs 12.8 [7.9-14.9] months; HR 0.743; 95% CI: 0.489-1.129; P=0.164). Median PFS of concurrent erlotinib arm was 5.3 months versus 4.0 of WBRT alone (HR 0.969; 95% CI: 0.735-1.277; P=0.825) and median overall survival (OS) was 12.9 versus 10.0 months (HR 0.913; 95% CI: 0.680-1.226; P=0.545). **Conclusion:** This multi-institutional study demonstrated WBRT with concurrent erlotinib improved neither iPFS significantly than WBRT alone in the intention-to-treat population and the *EGFR*-positive subgroup, nor improved PFS or OS in intention-to-treat population, indicating that erlotinib played limited role when concurrently used with WBRT and for *EGFR*-positive NSCLC patients, WBRT with concurrent erlotinib was not significantly superior to WBRT with sequential erlotinib.

Keywords: EGFR-TKI, Brain metastasis, WBRT

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MA08.02 PROPHYLACTIC CRANIAL IRRADIATION REDUCES THE RISK OF BRAIN METASTASES IN HIGH-RISK LUNG CANCER PATIENTS: EGFR AND ALK MUTATIONS

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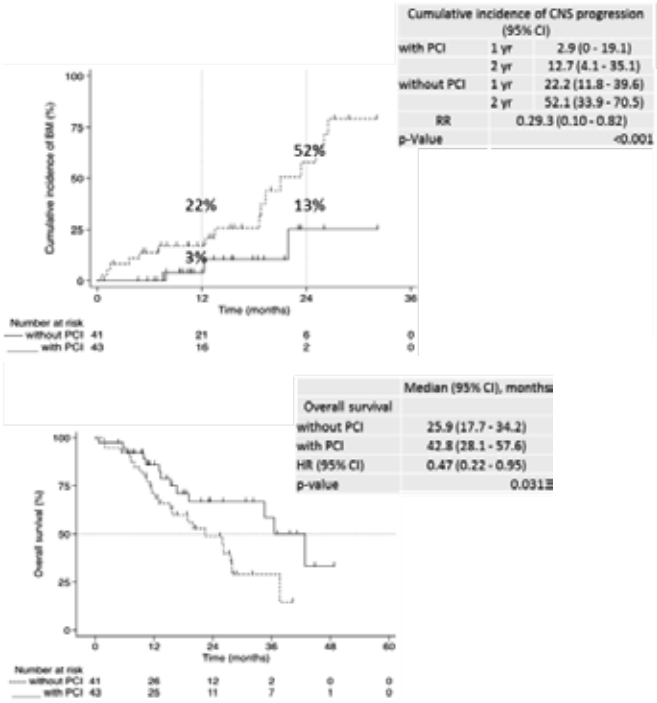
Background: Prophylactic Cranial Irradiation (PCI) is considered standard-of-care for small-cell lung cancer, due to consistent findings of a reduced risk of developing brain metastases (BM) and a survival benefit. The role of PCI for patients with Non-small cell lung cancer (NSCLC) is less well established, since a clear survival benefit has not been identified, although high-risk subgroups have been identified, including patients with driver mutations and with elevated carcinoembryonic antigen (CEA) levels. **Method:** We assessed the use of PCI compared to observation in patients with stage IV NSCLC (NCT01603849). PCI dose was set 25 Gy/10 f. An amendment to the original record was requested so that patients who received PCI after January 2016 had hippocampal sparing. Primary end point was Intracranial Progression-Free survival (IPFS), secondary was overall survival (OS). **Result:** 84 patients were included, 43 were randomized to observation and 41 to PCI. 83.3% had a driver mutation (DM). Baseline characteristics were well balanced among groups. Median IPFS was 21.0 months (95%CI 16.2-25.9). Factors which were independently, positively associated with IPFS included ECOG

(p=0.012) and therapeutic arm (p=0.006). PCI was associated with lower odds of progression to CNS (OR:0.16 (0.04–0.53), p=0.006).Cumulative incidence of BM at 1-yr was higher among patients without PCI (22% vs. 3%, p<0.001). Relative risk for IPFS in patients with DM was 0.29 (0.10-0.82, p=0.01), HR for OS was 0.48 (0.20-1.16, p=0.098). Median OS was higher in the PCI group compared to control [42.8 (95%CI: 28.1–57.6) vs. 25.9 (95%CI: 17.7 – 34.2)] months. Last, PCI was associated with lower hazards of death, 0.47 (0.24–0.95), p=0.035.



Conclusion: PCI significantly increases IPFS and decreases risk of death in patients with advanced NSCLC, without neurocognitive impairment or decreased QoL. This intervention appears to be particularly useful for patients with good performance status and driver mutations. PCI increased IPFS without neurocognitive impairment or decreased QoL.

Keywords: brain metastases, ALK, prophylactic cranial irradiation

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MA08.03 EGFR-TKI PLUS BRAIN RADIOTHERAPY VERSUS EGFR-TKI ALONE IN THE MANAGEMENT OF EGFR MUTATED NSCLC PATIENTS WITH BRAIN METASTASES: A META-ANALYSIS

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Background: It has been confirmed that epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) presented better efficacy than brain radiotherapy (brain RT) in the treatment of brain metastasis (BM) in EGFR mutated NSCLC patients. However, whether the combination of EGFR-TKI and brain RT is better than EGFR-TKI alone remains unclear. We aim to compare the benefit of adding brain RT to EGFR-TKI by a meta-analysis of currently available data. **Method:** A systematic search for relevant articles was conducted in six databases (PubMed, EMBASE, Cochrane database, Medline, Web of Science, Google scholar). The primary outcome was overall survival (OS) between groups, and the secondary outcome was intra-cranial progression-free survival (icPFS), both being measured as hazard ratios (HRs). The data was synthesized by random-effects model using STATA 13.0. **Result:** A total of four retrospective studies involving 507 EGFR mutated patients with BM at the first diagnosis were included, 209 patients received brain RT (predominantly whole brain RT). Combined therapy of EGFR-TKI and brain RT reduced 19% risk of deaths (OS HR=0.81, 95% CI 0.53-1.26; P=0.36) and 16% risk of intracranial progression (icPFS HR=0.84, 95% CI 0.55-1.27; P=0.40) compared with EGFR-TKI alone, however, no statistically significance was observed. Further subgroup analyses suggested that patients with 21 exon L858R mutation were more inclined to have greater icPFS benefit under combination therapy (HR 0.67, 95% CI 0.19-2.40) in contrast to 19 exon deletion patients (HR 1.35, 95% CI 0.88-2.09). In addition, patients older than 65 (HR 0.74, 95% CI 0.37-1.48) might benefit more from combination than those younger than 65 (HR 4.47, 95%CI 0.29-70.13). **Conclusion:** This meta-analysis suggested that the combination of EGFR-TKIs and brain radiotherapy showed similar but potentially better OS and intracrnial control in EGFR-mutated NSCLC patients when compared to EGFR-TKI alone, especially for those with L858R mutations or older than 65. The current results underscore the importance of future randomized control trials and provide information for study design.

Keywords: brain radiotherapy, NSCLC, EGFR-TKI

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MA08.05 BRAIN PENETRATION OF LORLATINIB AND CUMULATIVE INCIDENCE RATES FOR CNS AND NON CNS PROGRESSION FROM A PHASE 1/2 STUDY

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Background: The potent, selective, third-generation ALK/ROS1 tyrosine kinase inhibitor (TKI) lorlatinib was designed to penetrate the blood-brain barrier (BBB). In a phase 1/2 study, lorlatinib showed robust clinical activity in patients with ALK-positive non-small cell lung cancer (NSCLC), most of whom had CNS metastases and failed ≥1 ALK TKI. In preclinical studies, lorlatinib demonstrated high BBB permeability with rapid brain uptake in vivo and significant activity against ALK-positive intracranial tumor models.[1,2] To assess brain penetration of lorlatinib in a clinical setting, we report exploratory analyses from a phase 1/2 study (NCT01970865), evaluating CSF-to-plasma concentration ratios from a small sample of patients and cumulative incidence rates (CIRs) of CNS progression, non-CNS progression and deaths for pretreated patients with ALK-positive NSCLC ± baseline CNS metastases. **Method:** Across the ongoing phase 1/2 study, 5 patients at lorlatinib 100 mg QD starting dose underwent CSF sampling. Patients with ALK-positive NSCLC with ≥1 prior ALK TKI were analysed for progressive disease, categorized as either CNS or non-CNS progression, based on independent central review. CIRs for patients in expansion cohorts EXP2–5 from the phase 2 portion of the phase 1/2 study (N=198) were calculated using competing risks methodology. **Result:** In patients (n=5), mean CSF-to-plasma concentration ratio was 0.73 (SD 0.14). The table shows CIRs at 6 and 12 months.

Months	Cumulative Incidence Probability		
Patients with ≥1 prior ALK TKI[a]	CNS Progression	Non-CNS Progression	Death
All patients (n=198)			
6 mos 12 mos	0.13 0.18	0.25 0.37	0.05 NE
Patients with baseline CNS metastases (n=131)			
6 mos 12 mos	0.14 0.22	0.21 0.31	NE NE
Patients with no baseline CNS metastases (n=67)			
6 mos 12 mos	NE NE	0.32 0.49	0.05 NE

[a]Patients in expansion cohorts EXP2–5 from the phase 2 study NE, not evaluable

Conclusion: Lorlatinib showed high BBB permeability as evidenced by a high mean CSF-to-plasma concentration ratio, in line with preclinical rat studies showing CNS penetration. This translated into high activity against CNS metastases as suggested by the numerically higher probability of the first progression event being extracranial rather than intracranial, including in patients with a history of CNS metastases. **References** 1. Collier, et al. Mol Imaging 2017;16:1–3. 2. Zou, et al. Cancer Cell 2015;28:70–81.

Keywords: lorlatinib, CNS, NSCLC

MA08.06 OUTCOMES AMONG PATIENTS WITH EGFR-MUTANT METASTATIC NSCLC WITH AND WITHOUT BRAIN METASTASES

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Background: Brain metastases (BM) in patients with non-small cell lung cancer (NSCLC) are common, with reported frequencies of up to 44%. The epidermal growth factor receptor-mutant (*EGFR*m) subtype of NSCLC is known to have specific pathologic features that may influence patterns of metastases and outcomes. The prevalence of BM in patients with *EGFR*m NSCLC is unknown; however, incidence is expected to increase as new treatments emerge that prolong survival. Therefore, an understanding of the impact of BM and burden of illness in this population is needed. **Method:** A retrospective observational matched cohort study of adults with *EGFR*m metastatic NSCLC, with BM and without BM (NBM), between January 1, 2014, and July 31, 2016, with follow-up to March 31, 2017. Data were extracted from the iKnowMed™ electronic health record database of patients in the US Oncology Network of community oncology practices, supplemented with chart review. Patients were matched 1:1 by age categories and sex. Patients enrolled in interventional clinical trials or with other cancer diagnoses were excluded. Categorical variables were analyzed using chi-squared tests; time to treatment failure (TTF) and overall survival (OS) were assessed using the Kaplan-Meier method starting from the matched line of therapy for TTF and from NSCLC diagnosis for OS. **Result:** A total of 402 (BM, 201; NBM, 201) patients were included; median age was 70 and 77 years, respectively ($p<.05$). Patients in both cohorts were predominantly female (65%), Caucasian (69%), non-smokers (42%), and had adenocarcinoma (92%). Over 90% of patients were treated in the first-line setting. Median TTF in the BM and NBM cohorts following initial treatment was 10.9 months (95% confidence interval [CI], 9.5-12.0) and 10.4 months (95% CI, 8.9-12.2), respectively. Median OS for the BM and NBM cohorts was 11.9 months (95% CI, 9.7-13.4) and 16.0 months (95% CI, 9.1-20.6), respectively (log-rank $p=.017$). Median OS from onset of BM in the BM cohort was 10.0 months (95% CI, 7.4-11.2). While CNS symptoms were present in both cohorts, they were significantly higher in the BM cohort; patients in the BM cohort had significantly greater use of home healthcare, physical therapy, and social work services ($p<.05$). **Conclusion:** Median TTF was similar in patients with *EGFR*m metastatic NSCLC with BM and NBM; however, OS was significantly worse in the BM cohort. Symptom burden and healthcare resource utilization were also higher in the BM cohort. These findings highlight an unmet treatment need for patients with *EGFR*m NSCLC with BM.

Keywords: NSCLC, brain metastases

MA08.07 REAL WORLD DATA OF OSIMERTINIB IN PATIENTS WITH CENTRAL NERVOUS SYSTEM (CNS) METASTASIS IN ASTRIS KOREAN SUBSET.

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Background: More than 40% of non-small cell lung cancer (NSCLC) patients develop CNS metastasis in their lifetime. Osimertinib is a third-generation EGFR-TKI which selectively inhibits both EGFR-sensitizing and EGFR T790M resistance mutations. Clinical studies have shown superior efficacy of osimertinib in CNS compared to platinum chemotherapy. Treatment efficacy in patients with or without CNS metastasis were observed within the second interim analysis of ASTRIS (NCT02474355). Data cut-off (DCO) was 20 October 2017. **Method:** In ASTRIS, advanced NSCLC patients with a locally confirmed T790M mutation, WHO performance status 0-2, prior EGFR-TKI therapy were enrolled. Patients with stable CNS metastases were allowed. The primary endpoint was overall survival (OS); other endpoints included investigator-assessed response rate (RR), progression-free survival (PFS), time to treatment discontinuation (TTD) and safety. These endpoints were also analyzed according to presence of CNS metastasis. **Result:** A total of 466 patients received at least one dose of osimertinib 80mg from 31 Korean sites. CNS metastasis was evaluated in 310 patients and was present in 211 (68.1%) patients (CNS-met); 181 brain only, 1 leptomeningeal only, 29 both. 99 (31.9%) patients did not have CNS metastasis (CNS-no), and 155 patients were not evaluated (CNS-ne). At DCO, 236 patients (50.6%) were ongoing and median duration of exposure was 11.2 (0–19) months. In patients evaluable for response, defined as at least one dose of osimertinib and one response assessment, RR was 71.0% (320/451; 95% CI, 66.5–75.1): Patients with (N=211), without (N=99), and not-evaluated CNS metastasis (N=155) had RR of 68% (134/197; 95% CI, 61.0-74.5), 79.6% (78/98; 95% CI, 70.3-87.1), and 69.7% (108/155; 95% CI, 61.8-76.8), respectively. Median PFS was 12.4 months (95% CI, 11.1-13.6 months); 10.8 months (95% CI, 9.5-11.5) in CNS-met,11.0 months (95% CI, 9.2-14.5) in CNS-no, and 15.1 months (95% CI, 13.6-18.2) in CNS-ne. Median TTD was 16.5 months (95% CI, 14.1-NC); 11.2 months (95% CI, 9.4-14.8) in CNS-met, 14.7 months (95% CI, 12.2-NC) in CNS-no, and NC (95% CI, 15.5-NC) in CNS-ne. OS was not reached (data maturity: 19.7%). Serious adverse event (AE) regardless of causality were reported in 116 patients (24.9%) and AEs leading to death in 13 patients (2.8%). ILD/pneumonitis-like events were reported in 8 patients (1.7%), and QTc prolongation in 7 patients (1.5%). **Conclusion:** In ASTRIS Korean subset, patients with or without CNS metastasis had comparable efficacy outcome. This data continues to support osimertinib's clinical benefit on EGFRm T790M NSCLC patients with CNS metastasis.

Keywords: osimertinib, T790M, ASTRIS

MA08.09 IMPACT OF BRAIN METASTASES IN IMMUNE CHECKPOINT INHIBITORS (ICI) TREATED ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: Brain metastases (BM) are frequent in NSCLC. Unfortunately, patients with (untreated) BM are often excluded from ICI trials so that their outcome on ICI is largely unknown. **Method:** Retrospective data collection of all consecutive advanced ICI treated NSCLC patients in 6 centers (5 French, 1 Dutch) (nov 2012 – march 2018). Active BM was defined as non-irradiated new and/or growing lesions on brain imaging < 6 weeks before ICI start. Progression free survival (PFS), overall survival (OS) and site of progression on ICI was collected. **Result:** 945 patients included: 63% male, 83% WHO PS 0-1, median age 64 years, 73% non-squamous, 4% targetable driver mutations, 33% known PD-L1 (65% ≥1% expression). ICI treatment was median 2nd line (range 1-12), 94% had monotherapy PD-(L)1 inhibition. 241 patients (26%) had BM, 68% had previous cranial irradiation, 40% had active BM. BM patients were significantly younger than others (61 vs 66 years), had more adenocarcinoma (78 vs 62%), more organs involved (median 3 vs 2), a poorer PS (0-1: 76 vs 85%) and more steroids at baseline (26 vs 9%). Median follow-up: 15 months. Median (95% CI) PFS and OS without and with BM were 2 (2-3) vs 2 (1-2) months and 13 (9-16) vs 9 (7-13) months, respectively. In multivariate analysis, > 2 metastatic sites, PS ≥2 and steroids use were associated with worse PFS and OS, BM were not (table 1). In univariate analysis of BM patients, active BM were not associated with worse outcome compared to stable BM (HR PFS 0.98 (p=0.66), HR OS 0.93 (p=0.92)). Progressing BM patients had more often brain PD and a dissociated response (not specifically brain dissociated) on ICI (40 vs 12% and 13 vs 7%, respectively).

Factor	PFS HR (95% CI)	p-value	OS HR (95% CI)	p-value
Age > 65 vs ≤ 65	1.02 (0.87-1.20)	0.79	1.11 (0.92-1.34)	0.29
Smoking yes vs no	0.53 (0.41-0.69)	<0.001	0.81 (0.59-1.12)	0.20
Histology squa-mous vs adeno	1.07 (0.89-1.28)	0.78	1.24 (0.99-1.55)	0.12
Nr of or-gans with metasta-ses > 2 vs ≤ 2	1.28 (1.09-1.50)	0.003	1.48 (1.22-1.80)	<0.001
Immuno line > 2 vs ≤ 2	1.11 (0.94-1.30)	0.22	1.10 (0.91-1.33)	0.34
WHO PS 0-1 vs ≥2	2.14 (1.75-2.62)	<0.001	3.48 (2.78-4.36)	<0.001
Use of cortico-steroids yes vs no	1.36 (1.10-1.69)	0.005	1.31 (1.03-1.68)	0.03
BM yes vs no	1.05 (0.88-1.26)	0.58	0.96 (0.77-1.19)	0.70

Conclusion: BM, treated or active, do not negatively impact outcome on ICI although BM failure is more common in these patients.

Keywords: Immunotherapy, NSCLC, brain metastases

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MA08.10 REAL-LIFE INTRACEREBRAL EFFICACY OF NIVOLUMAB IN NON-SMALL CELL LUNG CANCER PATIENTS WITH BRAIN METASTASES

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Background: Data regarding intracerebral efficacy of nivolumab in advanced non-small cell lung cancer (NSCLC) are lacking because of routinely exclusion of patients with active brain metastases (BMs) from clinical trials. We aimed at assessing intracranial activity of nivolumab in patients with BMs in a real-life setting and determining the potential role of prior radiotherapy. **Method:** Between 01/09/2015 and 30/09/2016, all consecutive advanced NSCLC patients treated with nivolumab after failure of at least one line of chemotherapy were included. Nivolumab was administered at a dose of 3 mg/kg q2w until progression or unacceptable toxicity. Primary endpoint was intracerebral objective response rate (IORR) assessed by brain magnetic resonance imaging or brain computed-tomography scans. Secondary endpoints were overall response rate (ORR) and median duration of intracerebral response. **Result:** 259 patients were treated with nivolumab in 9 centers. Among them, 77 patients who presented BMs before nivolumab initiation were enrolled: 53 (20.5%) at diagnosis and 24 (9.3%) during the course of treatments. Median age at diagnosis was 57 years [29-78]. Most patients were males (72.7%) with smoking history (90.9%) and had adenocarcinoma (72.7%). 23 patients harbored a KRAS mutation. PD-L1 status was unknown. The median of prior lines was 1 [1-6]. BMs were pretreated in 48 (62.3%) patients: 16 received prior SBRT, 32 WBRT. Median time between prior radiotherapy and nivolumab initiation was 4 months [1-;27]. IORR and ORR were 10.4% and 20.8%, respectively. Among the 8 patients with intracerebral response, 5 (6.5%) had pretreated BMs, 3 (3.9%) had radiotherapy-naïve BMs. Median duration of intracerebral response was 11.5 months. No neurological adverse events occurred during nivolumab treatment. Among 259 patients, 36 (13.8%) developed BMs during nivolumab treatment. **Conclusion:** Nivolumab intracerebral response achieved 10.4% in real-life with a satisfactory neurological safety profile. If prior radiotherapy improves IORR must be determined by further investigations.

Keywords: brain metastases, efficacy, Nivolumab

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MA08.11 EARLY SAFETY DATA OF A PHASE I/II COMBINING NIVOLUMAB AND STEREOTACTIC BRAIN RADIOSURGERY FOR TREATMENT OF BRAIN METASTASES IN PATIENTS WITH NSCLC

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Background: Radiotherapy can stimulate the immune system through various means. Highly cytotoxic stereotactic radiosurgery (SRS) doses (>10Gy per fraction) may synergize with anti-PD1 to reduce intracranial disease progression or recurrence. **Method:** Within a phase I/II trial evaluating the combination of nivolumab with SRS in the treatment of brain metastases from NSCLC and RCC (NCT02978404), 8 patients were enrolled (1 RCC and 7 NSCLC) in the first trial cohort. Herein, only the NSCLC cases are reviewed. Patients were eligible if their KPS ≥70, were minimally symptomatic (RTOG neurological function <2), and had ≤10cc of untreated brain metastases. Prophylactic corticosteroids were not given. Nivolumab (240mg IV q2 weeks) was started 2 weeks prior to SRS, and administered until RECIST progression. SRS (15-20Gy in 1 fraction) was given to each brain metastasis. The aim of the first patient cohort is to estimate the tolerability of the combined treatment strategy. **Result:** The median follow-up of the three male and four female patients was 2 months. Median age was 63 years (55-84 years). Five NSCLC patients completed ≥1 cycle of nivolumab and SRS, and were evaluated for tolerability of the combination. One patient elected to withdraw before the first nivolumab dose and 1 patient died prior to SRS. Median baseline brain edema and total brain metastases volumes were 0.5cc (0-46.97cc) and 1.25 cc (0.1-3.46cc), respectively. To date, the median number of nivolumab cycles administered is 4.5 (1-15). Intracranial adverse effects were limited to apraxia and paresthesias in the patient who had the largest volume of peri-tumoral brain edema at baseline (46.97cc). Nivolumab was held and dexamethasone was given for 74 days at doses >1mg/day until neurological symptoms resolved. Systemic adverse events included one patient with grade 2 arthritis necessitating a 6-week treatment delay and 51 days of prednisone ≥10mg. At last follow-up, three patients had died of extracranial disease progression, including the two patients who did not receive protocol SRS. Among the three patients evaluable for intracranial response, there was one partial response and two stable diseases. All three patients had stable extracranial disease. **Conclusion:** Combining SRS and immunotherapy is safe in regards to acute toxicity with a manageable side effect profile. Close monitoring may be required for patients with significant baseline brain edema. Evaluation for efficacy awaits further follow-up and completion of recruitment in the phase 2 component of the trial.

Keywords: radiosurgery, brain metastasis, nivolumab

MA09 LUNG CANCER SURGICAL AND MOLECULAR PATHOLOGY
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MA09.01 CORRELATION OF PRE-OPERATIVE CANCER IMAGING TECHNIQUES WITH POST-OPERATIVE MACRO AND MICROSCOPIC LUNG PATHOLOGY IMAGES

S. Harrow[1], G. Reines-March[2], C. Dick[3], X. Ju[4], S. Marshall[2]

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Background: This research project aims to investigate the performance of several PET radiotracers in lung cancer by aligning PET-CT and pathology imagery acquired from the same patients at different points in time. The discrimination of tumour substructures is of great importance in therapy planning, as a given treatment may be better adapted depending on the local characteristics of the carcinoma. **Method:** Due to the high deformability of lung tissue, several intermediate steps must be used for merging pathology and pre-operative PET-CT in a coherent manner.

Firstly, the tumour volume is reconstructed from the macroscopic images taken during dissection. For this purpose, an enhanced dissection protocol is used, where the lung specimen is placed in a bespoke slicing rig and embedded in agar to hold it in place. Using a threaded plunger, the specimen is pushed upwards in 5mm steps, sliced and photographed. This procedure allows us to obtain slices of uniform thickness. Secondly, microscopic digital slides of the cancerous tissue are merged with the macroscopic 3D model. Finally, the whole volume is fused with the pre-operative PET-CT scan, using a non-linear deformable model. **Result:** Preliminary results obtained with a synthetic phantom allowed us to analyse the accuracy of the tumour 3D reconstruction algorithm from planar macroscopic slices. Using these findings, we could optimise the interpolation and segmentation routines for building an accurate 3D model of the tumour mass. During our first trial with lung tissue (on-going work), each cross-sectional slice was photographed, the tumour boundary was delineated in each image by a pathologist (CD), and from these contours a high-resolution 3D tumour model was built. Next, the corresponding microscopic digitised slices were merged. To date, ten patients have been identified and consented, therefore allowing us to test our algorithm on different cases and assess its performance. **Conclusion:** We demonstrate a novel set of methods for co-registration of pre-operative PET-CT to macro and microscopically defined lung tumours. This proof of principle now allows interrogation of the raw data from PET-CTs using a range of tracers and the development of algorithms that identify substructure detail within a tumour mass, which could lead to tailored radiotherapy for individual tumours based on tracer patterns and uptake.

Keywords: Pathology, Co-registration, functional imaging

MA09 LUNG CANCER SURGICAL AND MOLECULAR PATHOLOGY
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MA09.02 TUMOR SIZE AND FROZEN SECTION SHOULD BE CONSIDERED JOINTLY TO PREDICT THE FINAL PATHOLOGY FOR LUNG ADENOCARCINOMA

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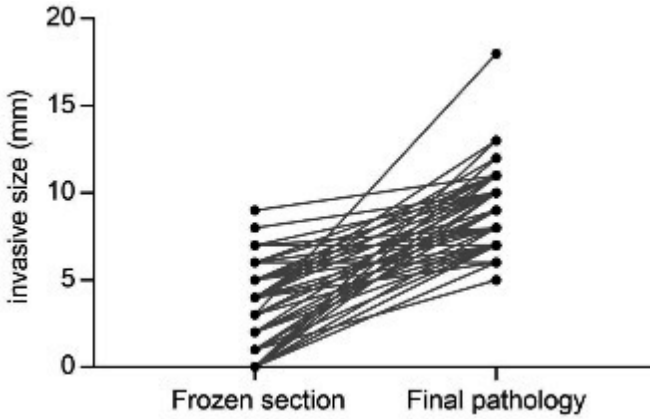
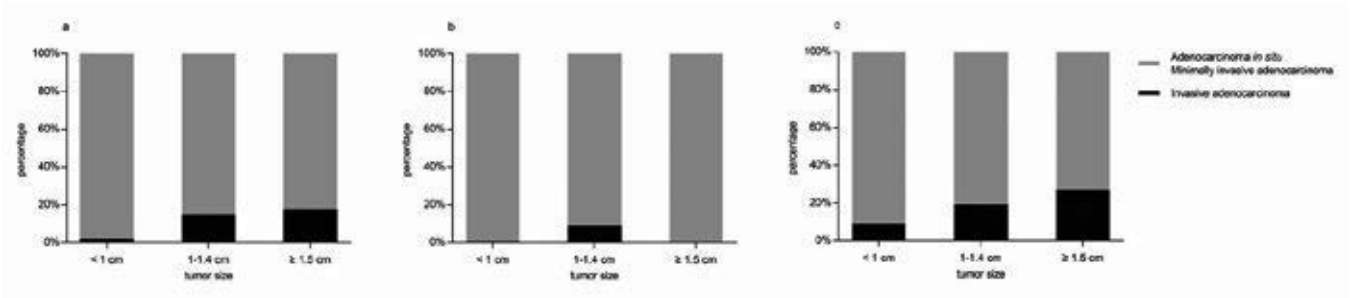
Background: Invasive adenocarcinoma intraoperatively misdiagnosed as adenocarcinoma in situ or minimally invasive adenocarcinoma is more likely to undergo potentially insufficient resection. The purpose of our study was to evaluate the diagnostic accuracy of frozen section. **Method:** We retrospectively reviewed 1,111 lung adenocarcinomas to evaluate the diagnostic performance of frozen section. A derivation cohort consisting of 436 cases of AIS or MIA diagnosed by frozen section in the same period were analyzed to find predictive factors for invasive adenocarcinoma as the final diagnosis. Validation cohorts were included to confirm the results. **Result:** Intraoperatively measured tumor size was the only independent factor for invasive adenocarcinoma as the final diagnosis (P = 0.001) in the derivation cohort, and was confirmed by validation cohorts. Fifty-nine misdiagnosed invasive adenocarcinomas in the three cohorts consisted of 54 lepidic predominant type, 1 papillary and 4 acinar predominant type. There were no positive N1, N2 node, pleural, lymphatic and vascular invasion cases found. Thirty-seven (37/59, 63%) cases of misdiagnosis were attributed to sampling error, which was the main reason.



Conclusion: Adenocarcinoma in situ or minimally invasive adenocarcinoma ≥ 1 cm by frozen section were more likely to be invasive adenocarcinoma because of sampling error.

Keywords: frozen section, Tumor size, lung adenocarcinoma



MA09.03 MULTIPLE PATHOLOGICAL VARIABLES PREDICT EFFICACY OF ADJUVANT CHEMOTHERAPY IN PRIMARY LUNG ADENOCARCINOMA

M. Sereno[1], C. Smith[1], M. Das[2], R. Hastings[1], G. Rake[3], D. Moore[3], J. Le Quesne[1]

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Background: Adjuvant chemotherapy has become established as a vital complement to surgery over the last decade, and improves survival by targeting micrometastatic disease which is clinically inaparrent at the time of surgery. However, in comparison to other common malignancies, the guidelines for the administration of adjuvant chemotherapy in lung cancer are rudimentary, being based solely upon clinical stage II and above at the time of surgery. We set out to discover pathological factors with the potential to better identify patients who are likely to benefit from this vital therapy. **Method:** 662 cases of primary lung adenocarcinoma treated with surgery with curative intent were identified from 2005-2014; 109 received adjuvant chemotherapy. Comprehensive survival/recurrence data, pathological data, and treatment history data were collected. Detailed histopathological data (growth pattern, vascular invasion, pleural stage) were collected by review of scanned histopathological images. Multivariate Cox regression survival models were used to identify interactions between clinicopathological variables and adjuvant chemotherapy. A propensity score matching approasch was used to reduce selection biases in the data. **Result:** The existing stage criteria for the recommendation of adjuvant chemotherapy are stage pN1/2 and size>40mm; only nodal invasion interacts with chemotherapy in an OS model (interaction term HR=0.67 P=0.017). However, signficant interactions are seen with predominant growth pattern (HR=0.47 P=0.001), pleural stage (HR=0.62 P=0.002), and vascular invasion (HR=0.56 P=0.033). We reduced selection bias by balancing treated and untreated groups by propensity matching for all prognostic variables. In the matched dataset, patients with predominantly in situ tumours experience no benefit of chemotherapy (HR=1.81 P=0.18), while higher-grade cases show substantial benefit (HR=0.53 P=0.01). Similar benefits were seen for patients with increasing pleural stage and vascular invasion. In a multivariate model designed to identify which variable(s) had the most ability to predict treatment efficacy, only tumour growth pattern showed a significant interaction with chemotherapy treatment (HR=0.51 P=0.01). **Conclusion:** We find that the existing stage-based criteria for adjuvant chemotherapy can be much improved. Low-grade cases experienced only negative effects of chemotherapy, while higher-grade cases showed a benefit. Pleural stage and vascular invasion were also significantly predictive. We suggest that the current criteria may be leading to substantial over- and under-treatment. A nuanced algorithm for the identification of patients likely to benefit from chemotherapy, which includes these additional pathoogical measures, may significantly improve patient outcomes. This would be especially impactful to the majority of surgical patients for whom no personalised therapy is as yet available.

Keywords: adjuvant chemotherapy, Adenocarcinoma, histopathology

MA09.05 CAN WE PREDICT RADIOSENSITIVITY IN NON-SMALL CELL LUNG CANCER?

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Background: Patients with lung cancer receive different treatments depending on their detailed clinical-pathological context. However, over 70% of patients are treated with radiotherapy, which is of varying efficacy. Rather surprisingly, no biomarkers are currently used to predict tumour response and to aid with radiotherapy dosing or regimen. The aim of this study is to identify histopathological features which may predict tumour radiosensitivity in patients with NSCLC. **Method:** We have identified a set of 67 NSCLC cases with a history of radiotherapy for which pre-treatment archival tissue and CT imaging follow-up is available from the period 2009 to 2014. Digital images of archival diagnostic tissue sections were examined to derive morphological measures with the potential to predict radiosensitivity. Quantitative radiological measures of response up to 6 months after radiotherapy were derived. Since radiographic measurements were taken at variable time-points, we standardised by inferring the fractional maximum diameter of the tumour 100 days after radiotherapy (FRT100) **Result:** The density of multipolar mitoses seen microscopically is related to radiosensitivity (regression against FRT100: R^2 = 0.14, p=0.005*) and a trend toward a negative relationship with neuroendocrine differentiation (R^2 =0.06, p=0.058). The presence of multipolar mitoses was further associated with poor overall survival (Univariate Cox p= 0.02*). Patients with radiological evidence of good response (ie low FRT100) showed a time-dependent survival benefit (p=0.02*), while after 2 years tendency of both groups was similar. Patients showing squamous differentiation had a poor prognosis, with no overall survival after 4 years, while 21.8% of the ACA were still alive after 4 years (p= 0.04*) **Conclusion:** Multipolar mitoses and neuroendocrine differentiation may be predictive histological markers of radiosensitivity in NSCLC. More samples are being gathered, and immhunohistochemical and DNA sequence biomarkers of radiosensitvity are currently being assessed.

Keywords: Radiotherapy, predictive histological markers, NSCLC

MA09.06 THE NEWLY RECOGNIZED FILIGREE PATTERN OF MICROPAPILLARY (MIP) LUNG ADENOCARCINOMA (LADC) IS AS CLINICALLY IMPORTANT AS THE CLASSICAL PATTERN

K. Emoto[1], T. Eguchi[1], R. Vaghjiani[1], Y. Takahashi[1], N. Rekhtman[2], P. Adusumilli[3], W. Travis[2]

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Background: Filigree pattern is a newly recognized addition to the morphological spectrum of the poor prognostic category of micropapillary (MIP) LADC. However, its morphologic features and clinical importance are not well understood. The aim of this study was to investigate the morphologic spectrum and clinical significance of filigree MIP pattern. **Method:** Filigree pattern was defined as tumor cells growing in delicate lace-like narrow stacks of cells (at least 3 piled-up nuclei) without fibrovascular cores, with frequently visible attachments to alveolar walls. This differs from the 2015 WHO description of classical MIP pattern as tumor cells growing in papillary tufts forming florets that lack fibrovascular cores. In order to assess for filigree vs classical MIP, we documented the frequency and extent of both patterns in 1325 Stage I LADC. These were correlated with recurrence free probability (RFP) and lung cancer-specific survival (LCSS) using Kaplan-Meier analysis. **Result:** In addition to 87 MIP predominant ADC previously diagnosed, we identified 57 more cases of MIP predominant LADC due to the new criteria of MIP filigree pattern. Of these 57 cases, 37, 16, and 4 cases were reclassified from papillary, acinar, and solid predominant LADCs, respectively. Survival curves of previously diagnosed MIP and newly diagnosed MIP for RFP showed a similar worse prognosis compared to other LADC histologic subtypes (previously diagnosed MIP vs newly diagnosed MIP, 5-year RFP 66% vs 68% [Figure]) as well as LCSS (previously diagnosed MIP vs newly diagnosed MIP, 5-year LCSS 82% vs 85%). When the MIP cases were divided into filigree or classical predominant MIP, no significant prognostic differences were observed between the two groups.

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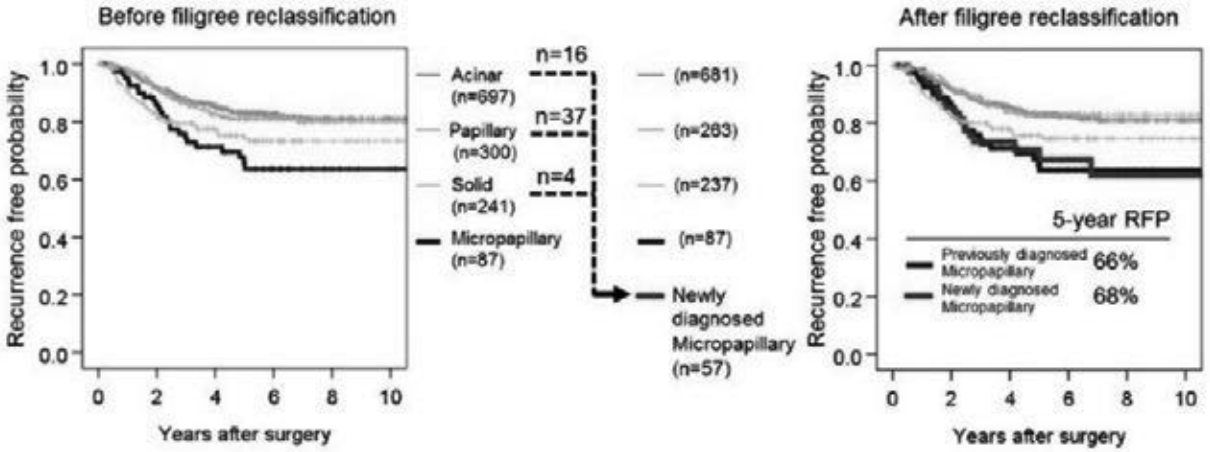

Conclusion: The lack of significant prognostic difference between filigree vs classical predominant MIP LADC supports our proposal that the filigree pattern is an important addition to the morphologic spectrum of the MIP subtype.

Keywords: filigree, lung adenocarcinoma, micropapillary

MA09 LUNG CANCER SURGICAL AND MOLECULAR PATHOLOGY
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MA09.07 DEVELOPING A PATHOLOGICAL GRADING SYSTEM IN PREDICTING PROGNOSIS FOR INVASIVE MUCINOUS ADENOCARCINOMAS

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Background: Invasive mucinous adenocarcinoma (IMA) is a variant of lung adenocarcinoma with a predominance of mucinous type neoplastic epithelial cells, often showing aerogenous spreading and multifocality. The correlation between histopathological features and prognosis has not been well studied due to its relatively rare incidence compared to non-mucinous adenocarcinoma. Our study aims to evaluate the significance of histopathological features in relation to clinical outcome. **Method:** We reviewed a series of 101 cases of IMAs resected between 2000 to 2012, comprised of stage I–IV tumours. Five pathological features were scored for each tumour: predominant histological pattern (lepidic: 1, acinar/papillary: 2, solid/micropapillary/cribriform: 3), nuclear atypia (mild:1, moderate: 2, severe: 3), mitotic activity per $2mm^2$ (<4: 0, ≥4: 1), necrosis (absent: 0, present: 1), lymphovascular invasion (absent: 0, present: 1), and pleural invasion (PL0: 0, PL1: 1, PL2: 2, PL3: 3). Each pathological feature was correlated with disease-free (DFS) and overall survival (OS). Cases were then divided into three grades based on the total pathological score (grade I: 2-4, grade II: 5-7, grade III: 8-11) and correlated with outcome. **Result:** Nuclear atypia, mitotic activity, lymphovascular invasion, and pleural invasion showed significant correlation with OS ($p < 0.05$). Histological pattern and necrosis showed no significant correlation in relation to OS ($p = 0.09$). Pleural invasion and lymphovascular invasion were significantly correlated with DFS ($p < 0.05$), while a trend was noted for nuclear atypia ($p = 0.086$). No correlation with DFS was seen for histological pattern ($p = 0.499$), necrosis ($p = 0.464$), and mitotic activity ($p = 0.931$). There was an inverse correlation between OS and grade, with grade III tumours showing a significantly worse prognosis ($p = 0.001$). There was no significant difference in DFS between the three groups ($p = 0.201$). **Conclusion:** Our pathological scoring system was able to stratify IMAs into three separate groups with statistically significant differences in overall survival between grade III and grades I/II tumours.

Keywords: Mucinous Adenocarcinoma, Prognosis, Pathological Grade

MA09 LUNG CANCER SURGICAL AND MOLECULAR PATHOLOGY
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MA09.09 EBUS-TBNA IN ASSESSING PD-L1 EXPRESSION IN NSCLC

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Background: Pembrolizumab is the only immunotherapy approved as a first line agent for metastatic NSCLC in patients with high programmed death-ligand 1 (PD-L1) expression. The standard samples for PD-L1 testing are considered surgical or core biopsies. In this study, our primary objective is to identify the adequacy of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS TBNA) tumor samples in detecting PD-L1 expression. **Method:** Between July 2016 and April 2017 a total of 1352 consecutive cases of non-small cell lung cancer (NSCLC) were identified. 29 specimens were deemed inadequate (less than 100 viable tumor cells) and were excluded. 1323 specimens analyzed included surgical samples (N=238), small biopsy (N=744) and cytology cell blocks (N=341). Cytology cell blocks were from EBUS-TBNA (N=190), fine needle aspiration (FNA) (N=61) and pleural/pericardial fluid (N=90). PD-L1 expression was examined by staining with Dako PD-L1 IHC 22C3 pharmDx kit. A Tumor Proportion Score (TPS) was categorized as <1%, 1-49% and ≥ 50% tumor cells. **Result:** Most of the 1323 specimens (84%) were non-squamous carcinomas. Overall yield for TPS > 50% was 36%. Rate of PD-L1 positivity was no different in non-squamous (37%) compared to squamous (32%). Diagnostic yield of PD-L1 for different sample types varied substantially (Table 1). The EBUS-TBNA samples had the highest yield for TPS ≥ 50% (p=0.025).

TPS	Surgical resec-tion	Small biopsy	EBUS-TBNA	FNA	Fluid cytol-ogy	Total
Adequacy	100%	99%	98%	96%	92%	98%
≥ 50%	69 (29)	269 (36)	84 (44)	21 (34)	38 (42)	481
1-49%	87 (37)	274 (37)	57 (30)	22 (36)	22 (24)	462
<1%	82 (35)	201 (27)	49 (26)	18 (30)	30 (33)	380
Total	238	744	190	61	90	1323

Conclusion: Our results show that cytology cell blocks could be considered as a valuable resource for PD-L1 testing in advanced NSCLC. Future studies are warranted to explore clinical correlation of PD-L1 on EBUS-TBNA samples and immunotherapy outcome.

Keywords: NSCLC, PD-L1 expression, EBUS-TBNA

MA09 LUNG CANCER SURGICAL AND MOLECULAR PATHOLOGY
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MA09.10 MOLECULAR PROFILING AND PD-L1 STATUS IN 900 CASES OF SURGICALLY RESECTED NON-SMALL CELL LUNG CANCER WITH CLINICAL AND PATHOLOGICAL CORRELATION

Z. Xu[1], M. Castonguay[2], W. Greer[2], A. Alwithenani[2], D. Bethune[3], A. Drucker[4], G. Flowerdew[1], M. Forsythe[2], D. French[3], H. Henteleff[3], M. Johnston[3], M. Macneil[4], W. Morzycki[4], M. Plourde[3], S. Snow[4], A. Surette[1]

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Background: Precision medicine provides efficient treatment options for lung cancer patients as it targets the individual tumor's genetic makeup. Recent development of immune therapy based on immune checkpoint inhibitor also provides hope for patients. Currently lung cancer mutational data available in the literature are mainly from advanced stage non-small cell lung cancer. There is insufficient information from early stage lung cancer patients. PD-L1 status in relation to clinical and pathological characteristics is also unclear. This study tried to address these issues from 900 cases of surgically resected lung cancer. **Method:** Multiplexed molecular profiling in 900 surgically resected lung cancer specimens. A panel of gene including EGFR, KRAS, BRAF, PIK3CA, HER2 and ALK was tested. PD-L1 was also evaluated by immunohistochemistry using pharmDx22C3. Tumor proportional score (TPS) in a 10% increment was measured. Mutational status and PD-L1 TPS in each cancer subtype in relation to cancer pathological characteristics were investigated. Correlations between gene mutation, PD-L1 status and cancer staging were performed. Gene mutation and PD-L1 status with patients' demographic information such as gender, age, smoking history, as well as survival data after surgery were also analysed. **Result:** This cohort includes adenocarcinoma (65%), squamous cell carcinoma (24%), large cell carcinoma (6%), other subtypes (5%). Stage I accounts for 56%, stage II, 26%, stage III, 16%, stage IV, <2% with a mean age of 66 years. In adenocarcinoma, KRAS accounts for 36%, EGFR 10%, BRAF 1%, PIK3CA 1%, ALK 0.2%, no mutations 52%. Only 5% squamous cells carcinoma showed mutations. PD-L1 TPS <1% accounts for (37%), TPS 1-9% (18%), TPS 10-19% (7%), TPS 20-29% (5%), TPS 30-39% (5%), TPS 40-49% (1%), TPS 50-59% (5%), TPS 60-69% (4%), TPS 70-79% (4%), TPS 80-89% (5%), TPS 90-99% (7%) and unsuccessful (2%). EGFR mutations were significantly associated with female (p<0.001) and never smokers (p<0.001), with well differentiated adenocarcinoma (p<0.001), and with absence of vascular invasion (p<0.01). KRAS mutations were more prevalent in younger age group (p=0.003). Poorly differentiated cancer histology was associated with absence of KRAS or EGFR mutations. There was no significant association between PD-L1 expression and age, sex, pathological stage and smoking status. PD-L1 expression was significantly associated with vascular invasion (p=0.035). EGFR mutations were significant associated with absence of PD-L1 expression (p=0.02), but no association between KRAS mutations and PD-L1 expression (p=0.10). **Conclusion:** This study provides comprehensive information enhancing our knowledge in depth about driver gene mutations and immune checkpoint PD-L1 status in non-small cell lung cancer patients.

Keywords: molecular profiling, PD-L1, EGFR, KRAS gene mutations

MA09 LUNG CANCER SURGICAL AND MOLECULAR PATHOLOGY
MONDAY, SEPTEMBER 24, 2018 - 15:15-16:45

MA09.11 GENOMIC LANDSCAPE AND ITS CORRELATION WITH TMB, CD8 TILS AND PD-L1 EXPRESSION IN CHINESE LUNG SQUAMOUS CELL CARCINOMA

T. Jiang[1], J. Shi[2], C. Wu[3], H. Zhang[4], C. Zhou[1]

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Background: The current study aimed to comprehensively depict the genomic landscape of Chinese lung squamous cell carcinoma (LSCC) and investigate its correlation with tumor mutation burden (TMB), CD8 tumor infiltrating lymphocytes (TILs) density and PD-L1 expression. **Method:** Whole-exome sequencing (WES) were performed on tumor tissue collected from 189 patients with surgically resected LSCC. TMB was defined as total number of nonsynonymous single nucleotide and indel variants. High TMB was defined as greater than 75th percentile. CD8+ TILs and PD-L1 expression were assessed by immunohistochemistry. We determined the 5% of CD8+ TIL or PD-L1 expression as the cut-off point for high/low CD8+ TIL or PD-L1 positive/negative expression. **Result:** We found recurrent mutations (>5%) in 8 genes, including *TP53*, *KMT2C*, *NFE2L2*, *KEAP1*, *CDKN2A*, *PTEN* and *FBXW7. FGFR1* and *PIK3CA* amplifications were found in 19% and 11% of samples. 24.9% of patients had high TMB. Except for expected differences by smoking status, baseline clinical variables were similar between those with high and low TMB. Interestingly, *FGFR1*, *PIK3CA* or *SOX2* amplification was independently associated with higher TMB (P=0.020, P=0.017, P=0.029; respectively). Patients with copy number variations had significantly higher TMB than those without (P=0.009). Positive PD-L1 and CD8+ TILs expression were identified in 24.3% and 78.8% of all cases. Baseline features were comparable between those with positive and negative CD8+ TIL or PD-L1 expression. *NFE2L2* mutation and *PIK3CA* amplification were independently associated with significantly higher PD-L1 expression (P=0.003, P=0.014; respectively). *TP53* mutations were associated with higher CD8+ TILs expression (P=0.008), but FGFR1 amplification was correlated with lower CD8+ TILs expression (P=0.042). Of note, there is no association between TMB and PD-L1 expression (r=0.052, P=0.476), or CD8+ TILs expression (r=0.026, P=0.718). None of TMB, PD-L1 and CD8+ TIL expression could individually predict overall survival (OS). However, combination of TMB and PD-L1 could stratify total populations into two groups with distinct prognosis. Patients with negative PD-L1 expression and high TMB had the worst prognosis (P=0.008). Additionally, combination of TMB and CD8+ TIL expression could also divide total populations into two groups with different prognosis (worst prognosis in negative CD8+ TIL expression and high TMB, P=0.022). **Conclusion:** This was the first and most large-scale study to comprehensively portray genomic landscape of Chinese LSCC. The current study provides several meaningful and referential findings for the future design of clinical trials in LSCC, especially immunotherapy based on immune checkpoint inhibitors.

Keywords: Lung Squamous cell carcinoma, PD-L1, Tumor mutation burden

MA10 CONSIDERATIONS IN IMMUNOTHERAPY / REAL WORLD
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA10.01 ANTIBIOTIC USE AND PD-1 INHIBITORS: SHORTER SURVIVAL IN LUNG CANCER, ESPECIALLY WHEN GIVEN INTRAVENOUSLY. TYPE OF INFECTION ALSO MATTERS

X. Mielgo-Rubio[1], L. Chara[2], M. Sotelo-Lezama[3], R. Lopez Castro[4], J. Rubio-Martínez[5], A. Velastegui[6], C. Olier-Garate[1], S. Falagan[7], I. Gómez-Barreda[2], P. Bautista-Sanz[8], J. Silva-Ruiz[1], J. Moreno Rubio[7], C. López[2], A. Cardeña-Gutiérrez[1], E. Pérez-Fernández[9], M. Sereno Moyano[7]

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This abstract is under embargo until September 25 at 10:30 Eastern Time.

MA10 CONSIDERATIONS IN IMMUNOTHERAPY / REAL WORLD
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA10.02 IMPACT OF ANTIBIOTICS ON OUTCOME OF METASTATIC NON SMALL CELL LUNG CANCER PATIENTS TREATED WITH IMMUNOTHERAPY

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Background: Immunotherapy (IO) is effective against metastatic non small cell lung cancer (mNSCLC). Gut microbioma has a strong impact on immune functions and its imbalance due to antibiotics (atbs) may impair the efficacy of IO. Recent works on other malignancies supported this evidence, but data are still lacking. We studied this topic in a case series of mNSCLC patients (pts) treated with IO. **Method:** Data about all consecutive pts with mNSCLC treated with IO at Istituto Nazionale dei Tumori, Milan, Italy, between 04/2013 and 01/2018 were retrospectively collected. Pts were stratified according to atb use between 1 month (mo) before and 3 mos after the beginning of IO, and to atb exposure (AEx) defined as the ratio "days under atb/days under IO". Survival was estimated with Kaplan-Meier method. Log-rank test was used to compare curves. Multivariate analysis was performed with Cox proportional model. **Result:** One hundred fifty-seven pts were analyzed, for a median follow-up of 28.6 mos. IO consisted in an anti-PD1 agent in 62.4% of cases, in an anti-PDL1 agent in 32.5% of cases, in a combination anti-PDL1+anti-CTLA4 in 5.1% of cases. First-line IO was administered in 25 cases, second-line IO in 66 cases, third- or more advanced-line IO in 66 cases. Twenty-seven pts received atbs. The 3 most commonly used atbs were levofloxacin (55.6%), amoxicillin/clavulanate (25.9%), and ceftriaxone (14.8%). No differences in either response rate, progression free survival (PFS) and overall survival (OS) were observed between the subgroups defined by atb use (p .14, .18 and .24, respectively). Median AEx of the treated pts was 5%. The pts with an AEx longer than the median one had significantly worse PFS (2.2 *vs* 7.7 mos, p<.0001) and OS (4.9 vs 16.3 mos, p .0004) than the others. This result maintained significance after correction for IO line (p .0003) and performance status (p .0002), which were the only other variables influencing PFS and OS. **Conclusion:** Though no differences in outcome could be observed in our population according to simple atb use, a significant disadvantage in PFS and OS became evident for pts with a higher AEx. If confirmed, these data may suggest to carefully weigh the prescription of atbs to mNSCLC pts treated with IO.

Keywords: Antibiotics, Immunotherapy, metastatic non small cell lung cancer

MA10 CONSIDERATIONS IN IMMUNOTHERAPY / REAL WORLD
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA10.03 PLASMATIC EVALUATION OF THE INTESTINAL BARRIER AND BLOOD MICROBIOTA, AND ANTIBIOTIC USE IN NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH NIVOLUMAB

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Background: Recent data suggest that gut microbiota and antibiotic use affect the efficacy of immune checkpoint inhibitors. We aimed to evaluate the predictive role of blood microbiota, plasma citrulline (marker of the intestinal barrier), and the impact of early (from 2 months before until 1 month after beginning of nivolumab) and late (after 1 month of nivolumab) antibiotic use on nivolumab efficacy in NSCLC patients. **Method:** We included consecutive patients with advanced NSCLC treated with nivolumab between July 2014 and December 2017. Plasma tests were taken prospectively during treatment. The microbial population present in the plasma samples was determined using sequencing of variable regions of the 16S rRNA bacterial gene at M0. Plasma citrulline concentrations were evaluated by ion exchange chromatography at month (M) 0, M2, M4 and M6 of nivolumab. **Result:** Seventy-two patients were included (male: 62%; smokers: 87%; adenocarcinoma: 63%). Early use of antibiotics (EUA) (n=28/72) was associated with poor overall survival (OS) (median 5.1 months, versus 13.4 months without EUA, p=0.03), whereas later use of antibiotic during treatment had no significant effect. Thirty-six patients (50%) had serial plasma samples available for analyses. The composition of blood microbiota at M0 was associated with tumor response and long-term benefit of nivolumab, with a significant impact of *Paludibacilum*, *Gemmatimonadaceae* and *Nocardioides*. Patients with long-term benefit of nivolumab had significantly higher plasma citrulline concentrations than other patients, at M0, M2 and M4, and maintained high citrulline concentrations at M6. Median progression-free survival (PFS) and OS for patients with citrulline ≥20µM at M0 were 7.9 months and not reached, versus 1.6 months (p<0.0001) and 2.2 months (p<0.0001) for patients with citrulline <20µM, respectively. Patients with EUA had lower median citrulline concentrations at M0 (17µM [IQR 15-30] versus 31µM [IQR 21.3-40.5]; p=0.06). **Conclusion:** This study confirms the negative impact of EUA during nivolumab treatment, and suggests that plasma evaluation of the intestinal barrier and blood microbiota may help to predict the outcome of NSCLC patients treated with nivolumab.

Keywords: microbiota, anti-PD1, non-small cell lung cancer

MA10 CONSIDERATIONS IN IMMUNOTHERAPY / REAL WORLD
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA10.05 EFFECT OF EARLY STEROIDS USE IN ADVANCED NSCLC PATIENTS TREATED WITH IMMUNOTHERAPY

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Background: Immunotherapy (IO) radically improved patients (pts) outcomes in advanced non-small cell lung cancer (NSCLC). Because of their immunosuppressive activity, the use of steroids as supportive care medications or for mild adverse events, even if at anti-inflammatory dosage, is debatable. In this study we assessed the effect of early steroids use on clinical outcomes of pts with advanced NSCLC treated with IO. **Method:** We retrospectively collected demographics, clinical and pathological data of pts with advanced NSCLC treated with IO at our institution with at least one instrumental response assessment. Early use of steroids was defined as the use of a daily prednisone-equivalent dose ≥ 10 mg for at least 1 day within 28 days from the start of IO. Chi-square test or Fisher's exact test were used to analyze the association of early use of steroids with pts' characteristics. The Kaplan-Meier method and the Cox proportional-hazards model were used for survival analyses while the reverse Kaplan-Meier method was used for follow-up quantification. **Result:** We included 151 pts, 35 (23 %) of whom recurred to an early use of steroids. Six pts (4%) received combinatorial PD-L1+CTLA-4 blockade while 145 (96%) received single agent anti PD-1/PD-L1. Early use of steroids was positively associated with ≥2 metastatic sites (OR 3,08, 95% CI 1.33-7.89; *P* = .01) and ECOG PS ≥ 2 (OR 4.57; 95% CI 1.10-20.37; *P* = .03) and negatively associated with disease control (OR 0,32; 95% CI 0.14-0.71, *P* = .006). With a median follow-up of 28.61 months, early use of steroids characterized a poorer median OS (4.86 vs 15.14 months; HR

2.60; 95% CI 1.70-4.10; *P* < .0001). In the multivariable model including the only other covariate significantly associated with survival (ECOG PS), the early use of steroids was confirmed to independently worsen OS (HR 2.38; 95% CI 1.49-3.81; *P* = .0003). Early use of steroids was also associated with a poorer median progression-free survival (PFS) (1.98 vs 3.94 months; HR 1.80; 95% CI 1.20-2.80; *P* = .003). **Conclusion:** In our analysis, the early use of steroids significantly affected disease control, PFS and OS in advanced NSCLC patients treated with IO. If our findings will be further prospectively confirmed, early use of steroids should be avoided in this setting.

Keywords: Immunotherapy, steroids, advanced NSCLC

MA10 CONSIDERATIONS IN IMMUNOTHERAPY / REAL WORLD
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA10.06 IMPACT OF IMMUNE-RELATED ADVERSE EVENTS ON SURVIVAL IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER TREATED WITH NIVOLUMAB

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Background: Anti PD1 and anti PD-L1 monoclonal antibodies represent the standard of care for platinum-pretreated advanced non-small cell lung cancer (NSCLC) patients, having shown to prolong survival compared to chemotherapy in second-line setting in phase III clinical trials. Patients treated with these drugs not infrequently experience immune-related adverse events (irAEs), which we hypothesize might reflect antitumor response. In this study we investigated whether the development of irAEs was associated with nivolumab efficacy in patients with advanced NSCLC. **Method:** We conducted a multicenter retrospective study of patients with advanced NSCLC treated with nivolumab between October 2013 and September 2017. IrAEs were defined as AEs having immunological basis that required intensive monitoring and interventions. We evaluated nivolumab efficacy according to the development of irAEs. **Result:** Among 195 patients (median [range] age, 63 [30-40] years; 128 men [65.6%], 67 women [34.4%]), irAEs were observed in 85 patients (43.6%), including 15 patients (7.6%) with grade 3 or 4 events. Median PFS was 5.7 months in patients with irAEs compared to 2 months of those without irAEs (P < 0.0001). Median OS was 17.8 months compared to 4.04 months of no-irAEs group (P < 0.0001). The survival benefit of irAEs was consistent also in 12- and 6-weeks landmark analysis. Patients who developed ≥ 2 irAEs (n: 37) had a significantly longer median PFS and OS compared to those with one AE (n: 48) or none (n: 110) (PFS: 8.5 months vs. 4.6 vs. 2, P < 0.0001; OS: 26.8 months vs. 11.9 vs. 4, P < 0.0001). Multivariable analysis revealed that irAEs were positively associated with survival outcome, with hazard ratios of 0.48 (95%CI, 0.34-0.77; P < 0.0001) for PFS and 0.38 (95%CI, 0.26-0.56; P < 0.0001) for OS. **Conclusion:** This is the largest study conducted to date aimed to evaluate whether the development of irAEs is predictive of nivolumab efficacy in pre-treated NSCLC patients. In this study we confirmed that the development of irAEs was a strong predictor of survival outcomes in NSCLC patients who had received nivolumab in ≥ 2 line setting. This data was consistent in the 12- and 6-weeks landmark analysis, suggesting that an early onset of irAEs might be predictive of durable clinical benefit in NSCLC patients treated with nivolumab. Moreover, patients who experienced ≥ 2 irAEs had a more pronounced survival benefit compared to those with 1 irAE. Further studies are required to investigate the molecular mechanisms underlying this association.

Keywords: non-small cell lung cancer, immune-related adverse events, immune check-point inhibitors

MA10 CONSIDERATIONS IN IMMUNOTHERAPY / REAL WORLD
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA10.08 CHOICE OF TAXANE AND OUTCOMES IN THE KEYNOTE-407 STUDY OF PEMBROLIZUMAB PLUS CHEMOTHERAPY FOR METASTATIC SQUAMOUS NSCLC

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Background: In the randomized, double-blind, phase 3 KEYNOTE-407 study (NCT02775435), pembrolizumab plus chemotherapy with carboplatin and paclitaxel or nab-paclitaxel significantly prolonged OS (HR 0.64, 95% CI 0.49-0.85, P=0.0008) and PFS (HR 0.56, 95% CI 0.45-0.70, P<0.0001) compared with placebo plus chemotherapy in patients with previously untreated, metastatic squamous NSCLC. The benefit of pembrolizumab plus chemotherapy was observed irrespective of PD-L1 TPS. Pembrolizumab plus chemotherapy also had a manageable safety profile. We performed an exploratory analysis of outcomes by investigator's choice of paclitaxel or nab-paclitaxel, which was a randomization stratification factor. **Method:** 559 eligible patients were randomized 1:1 to pembrolizumab 200 mg or placebo Q3W for up to 35 cycles plus 4 cycles of carboplatin AUC 6 mg/mL/min Q3W and investigator's choice of paclitaxel 200 mg/m^2 Q3W or nab-paclitaxel 100 mg/m^2 QW. Primary end points were OS and PFS; ORR and safety were secondary. **Result:** Paclitaxel was the chosen taxane in 60% of patients. The addition of pembrolizumab to chemotherapy improved OS, PFS, and ORR regardless of choice of carboplatin and paclitaxel or carboplatin and nab-paclitaxel (Table). Incidence of grade 3-5 AEs in the pembrolizumab plus chemotherapy arm vs placebo plus chemotherapy arm was 63.9% vs 59.3% in paclitaxel recipients and 78.9% vs 81.4% in nab-paclitaxel recipients. AEs led to discontinuation of all treatment in 13.6% vs 8.4% of paclitaxel recipients and 12.8% vs 3.5% of nab-paclitaxel recipients and led to discontinuation of any treatment in 19.5% vs 13.2% and 29.4% vs 9.7%, respectively. Immune-mediated AEs occurred in 29.6% vs 9.6% of paclitaxel recipients and 27.5% vs 7.1% of nab-paclitaxel recipients. **Conclusion:** Adding pembrolizumab to chemotherapy with carboplatin and a taxane improved efficacy and was generally tolerable compared with chemotherapy alone as first-line therapy in patients with metastatic squamous NSCLC regardless of whether paclitaxel or nab-paclitaxel was the chosen taxane.

	Carboplatin plus Paclitaxel		Carboplatin plus Nab-Paclitaxel	
	Pembrolizumab + Chemotherapy N = 169	Placebo + Chemotherapy N = 167	Pembrolizumab + Chemotherapy N = 109	Placebo + Chemotherapy N = 114
OS, median (95% CI), mo	14.0 (12.6-16.6)	10.3 (8.2-14.8)	NR (NE-NE)	12.6 (9.6-NE)
HR (95% CI)[a]	0.67 (0.48-0.93)		0.59 (0.36-0.98)	
PFS, median (95% CI), mo	6.4 (6.0-8.3)	4.4 (4.2-5.1)	6.5 (6.2-8.5)	5.9 (4.4-6.9)
HR (95% CI)[a]	0.52 (0.40-0.68)		0.65 (0.45-0.94)	
ORR, % (95% CI)	57.4 (49.6-65.0)	37.7 (30.4-45.5)	58.7 (48.9-68.1)	39.5 (30.4-49.1)

[a]Based on a Cox regression model with treatment as a covariate.

Keywords: Immunotherapy, PD-1, chemotherapy

MA10.09 NECPAL 2: A MULTICENTRE DESCRIPTIVE STUDY OF PRIMARY AND CONTINUOUS ATTENTION IN PALLIATIVE CARE IN ARGENTINA: LUNG CANCER COHORT

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Background: In Argentina Lung cancer is the most deadly neoplasm (9230 annuals death). Early identification of palliative care (PC) needs has proven benefits in terms of quality of life, survival, and decision making in Lung cancer patients. The NECPAL CCOMS-ICO© tool is face and content-validated instrument to identify patients likely in need of PC. **Method:** To implement and evaluate a demonstration multicenter program for early and continuous PC for Lung cancer patients in Buenos Aires using the NECPAL-CCOMS-ICO© tool (multifactorial assessment) in every level of attention. We reported the results of one University Cancer center lung cancer cohort (2016-2018). We categorized patients as surprise question positive (SQ+), (Would you be surprised if this patient were to die in the next 12 month?). If the healthcare professional answered 'NO', the patient was considered SQ+ and they were also considered NECPAL+ when they presented at least one additional parameter from the NECPAL tool. All patients classified as NECPAL+ were considered to be in need of PC. Then using a Cox regression model analyzed predictors for overall survival (OS). **Result:** 82 patients out of 206 were SQ+ and NECPAL +. Median age 64 (35-82). 46 % had stage IVB (8th) ,18 % IVA , 19.5% locally advanced, and 7 ptes early stage. 6 ptes presented SCLC . Male were 59%. 78 ptes were analyzed for overall survival; n=4 were excluded due lost of follow up. 56% had died with a Median OS of 11 months (7.2-14.7). 5/82 ptes did not receive any kind of oncology treatment due ECOG, comorbidities or patients' choice. Median OS was 17 months (10.5-23.4) for men and 10 months (3.7-16.2) for females (p=0.08). In the univariate analyses, only metastasis in vital organs (nervous central system, liver, massive lung) was predicted of survival (17 vs 8 months; p=0.035). The other NECPAL indicators did not met the criteria for significance. The multivariate analysis, did not find a statistically significant combination of predictors for overall survival except metastasis in vital organs. It was noted an small number of low PPS score (11/78), as well as nutritional (14/78) or severe functional deterioration (5/78), in spite of the majority of the cohort had advanced disease. **Conclusion:** This Program adds a prospective direct method of measuring prevalence of PC needs including a Palliative approach. The results presented support consideration of the NECPAL tool as a prognostic tool in our setting.

Keywords: palliative care NSCLC

MA10.10 LUNG CANCER STIGMA: A TEN-YEAR VIEW OF PATIENT, PROVIDER, AND PUBLIC ATTITUDES ABOUT LUNG CANCER.

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Background: The presence of lung cancer stigma is well documented (Chapple, 2004; Chambers, 2012; Marlow, 2015) and impacts the care and treatment of lung cancer survivors (Tod, 2008; Carter-Harris, 2014). In 2008, a large survey of patients, oncologists, and general public revealed that most participants felt lung cancer was principally caused by external factors, was preventable, and lung cancer patients were partly to blame for their illness (Weiss 2014; 2017). We replicated the survey to understand whether perceptions have changed over the last decade. **Method:** 1001 members of the general public, 208 lung cancer patients, and 205 oncologists who treat lung cancer were surveyed with the identical instrument as 2008 plus 3-11 questions at the end including Cataldo Lung Cancer Stigma Scale (Cataldo, 2011) strongest-loaded items for the patient survey. The survey was administered by phone and online during summer 2018. **Result:** General lung cancer awareness has significantly improved in a decade with 94% of the public reporting familiarity with lung cancer, every segment reporting increased media visibility (65%, 78%, 85% for public, patients, and oncologists, respectively), and patients reporting significantly increased use of advocacy organizations (39% vs 18%, p<.05). Additionally, significantly more oncologists reported having adequate treatment options to prolong patients' lives (52% vs 31%, p<.05) and most patients reported satisfaction with medical care (87%) and treatment options (71%). Despite these advances, stigma remains a critical problem. In 2018, significantly more of the public believed lung cancer patients are viewed/treated differently than other cancer patients (37% vs 31%, p<.05) and a similar proportion (56%) felt patients are partly to blame for their illness. Oncologists continue to believe there is stigma associated with lung cancer (68%) although more felt stigma was lower for never-smokers. More oncologists indicated patients blame themselves (67% vs 57%). Patients reported significant increases (p<.05) in presence of stigma associated with lung cancer (70% vs. 54%), lung cancer patients being treated differently by society (63% vs. 45%), having personally been treated different by society (43% vs 25%), and loved ones would be more supportive if they had a different type of cancer (25% vs. 11%). **Conclusion:** After a decade of lung cancer research progress, results indicate considerably elevated awareness. Unfortunately, disease stigma remains. Interestingly, stigma is reported more frequently by lung cancer patients and may be felt more acutely, perhaps due to increased awareness and empowerment. This work underscores the need to address stigma with proactive multilevel approaches (Hamann, 2018).

Keywords: stigma, survivorship, quality of life

MA11.01 COMPARATIVE EFFICACY OF T-CELL INTRINSIC VERSUS EXTRINSIC PD-1 BLOCKADE TO OVERCOME PD-L1+ TUMOR-MEDIATED EXHAUSTION

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Background: Anti-PD-1 agents are effective in overcoming PD-L1+ mediated T-cell exhaustion. Effective therapeutic regimens include multiple, long-term administration. We hypothesized that a single dose of T-cell intrinsic PD-1 blockade by expression of a dominant negative receptor (PD1-DNR) can be equally effective as multiple doses of anti-PD-1 agent administration in the treatment of PD-L1 overexpressing thoracic cancers. **Method:** Human T cells engineered to target the cancer-antigen mesothelin (MSLN) by expression of a chimeric antigen receptor (CAR) with or without co-transduction with a PD1-DNR underwent repeated antigen stress with cancer cells with constitutive overexpression of PD-L1. For comparative efficacy evaluation, anti-PD-1 antibody was co-administered with CAR T cells (CARs). *In vitro* efficacy was evaluated by cytotoxicity (chromium-51 release assay). *In vivo,* mice with established pleural tumor were treated with either a single dose of MSLN CARs (with and without anti-PD-1 agent) or MSLN PD1-DNR CARs. Tumor burden regression by bioluminescence imaging and median survival were evaluated. **Result:** *In vitro,* constitutive PD-L1 overexpression (Fig. A) inhibits MSLN CAR effector function as evidenced by a decrease in cytotoxicity following repeated stimulation with MSLN+PD-L1^{hi} tumor cells (Fig B). MSLN PD1-DNR CARs had increased cytotoxicity when compared to MSLN CARs with or without high frequency anti-PD-1 antibody supplementation. *In vivo,* mice treated with MSLN CAR (with or without anti-PD-1 antibody) or MSLN PD1-DNR CARs demonstrated enhanced tumor regression (Fig C) and prolonged median survival (Fig D) compared to MSLN CARs alone. Furthermore, a single low dose of MSLN PD1-DNR CARs shows equal anti-tumor efficacy compared to MSLN CARs with multiple doses of anti-PD-1 antibody.

(See next page)

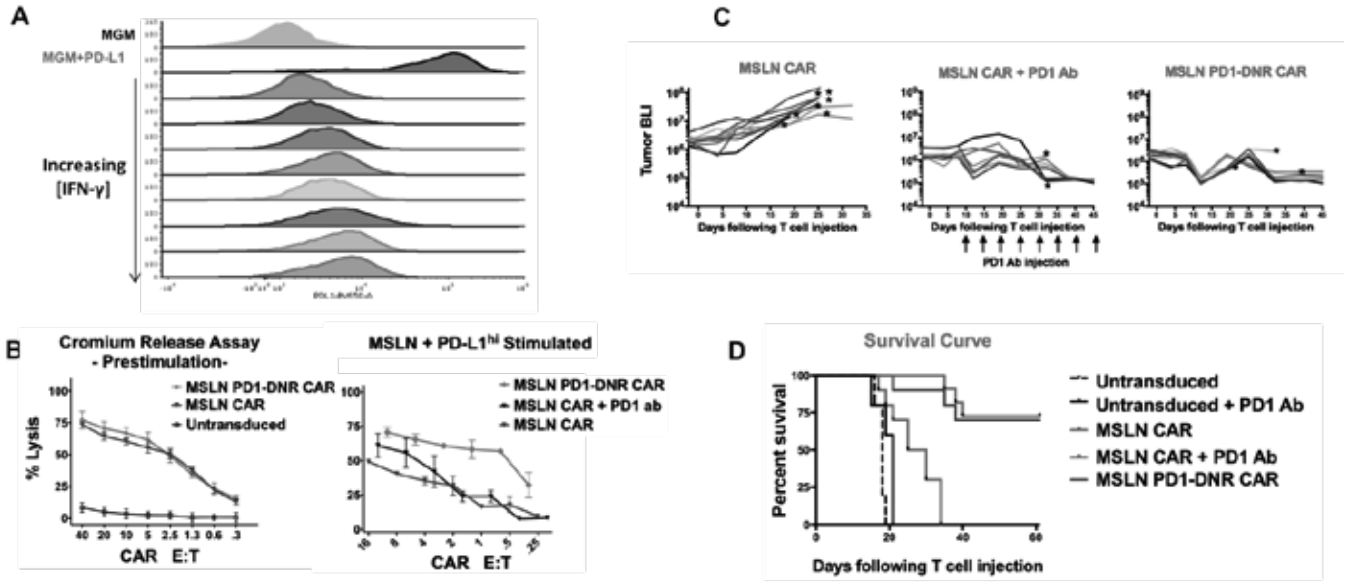

Figure 1: Tumor cell line with constitutive overexpression of PD-L1 **(A)**. *In vitro*, prior to antigen stimulation MSLN and MSLN PD1-DNR CARs have equal cytotoxicity. However, following repeated antigen stimulation with MSLN+ PD-L1^{hi} tumor cells, MSLN PD1-DNR overcomes PD-L1 mediated inhibition when compared to MSLN CARs with or without anti-PD-1antibody (**B**). Mice with established tumor burden who receive a single low dose of MSLN PD1-DNR have enhanced tumor regression **(C)** and median survival **(D)**. A single low dose of M28z DNR performed equally to combined MSLN CAR + anti-PD-1 antibody

Conclusion: Our results demonstrate that CAR T cells engineered to express a cell-intrinsic PD-1 dominant negative receptor overcome PD-L1 mediated T-cell inhibition equally compared to multiple doses of anti-PD-1 antibody administration. A clinical trial with MSLN CAR PD1-DNR CAR T cells is being initiated.

Keywords: Checkpoint blockade, Cell-intrinsic PD1-DNR, thoracic cancer

MA11 BIOMARKERS OF IO RESPONSE
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MA11.02 INCREASED CD3+ TIL INFILTRATION AND LOW FOXP3+/CD8+ TIL RATIO CAN PREDICT ANTI-PD-1 THERAPEUTIC RESPONSE IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: To determine whether distinct tumor microenvironments differentially affect the clinical response to anti-PD-1 therapy in non-small cell lung cancer (NSCLC), we investigated the expression level of PD-L1 and tumor infiltrating lymphocytes (TILs) and elucidate their predictive role. **Method:** Forty pretreated specimens (including 21 resected and 19 biopsied tissues) from 36 advanced, treatment-refractory NSCLC patients who underwent PD-1 blockade therapy were analyzed. PD-L1 expression by tumor cells and the distribution of CD3, CD8, CD4, FOXP3 and PD-1 positive TILs were immunohistochemically assessed. The mean number of cells positive for each marker in covered total fields was expressed in density per mm^2 using digital image analyzer. In addition, CD8+/CD3+, CD8+/CD4+, FOXP3+/CD8+, and PD-1+/CD8+ ratios were calculated for each specimen using the mean number of total fields. **Result:** CD3+ and CD8+ TILs were distributed more in PD-L1 positive group compared to PD-L1 negative group. Inversely, *EGFR* mutant group showed fewer CD3+ TILs than *EGFR*-naïve group. The patients in the clinical benefit group with PD-1 blockade showed a higher number of CD3+, CD8+ TILs and a higher CD8+/CD3+ TIL ratio (p=0.003, p=0.001, and p =0.042) and a lower FOXP3+/CD8+ TIL ratio compared to non-responders (p=0.001). We analyzed the effects of TIL, PD-L1 and clinicopathologic factors in PD-1 blockade therapeutic response using logistic regression. In multivariate analysis, increased CD3+ TIL infiltration and low FOXP3+/CD8+ TIL ratio were found to be independent predictors of clinical benefit with PD-1 blockade. (p=0.014 and p=0.03, respectively). Using receiver operating characteristic curves, levels of CD3+ TIL and FOXP3+/CD8+ TIL ratio that provide the best distinguishing point between responder versus non-responder to PD-1 blockade were 617.5/mm^2 and 25%, respectively (p=0.007 and p=0.003). Considering that 1 mm^2 is about 5 high power fields (HPF), a good response to the PD-1 blockade can be expected when CD3 + TIL is observed in 120 per 1 HPF and CD8 + TIL : FOXP3 + TIL are greater than 4 : 1. In addition, there were no difference between sample acquisition method (resection vs. biopsy) and duration (3, 6, and 12 months before PD-1 blockade treatment), and TIL expression. **Conclusion:** Based on our results, TIL is an independent predictive factor of response to PD-1 blockade and we suggested a cutoff value of TIL to predict responder group. In addition, properly sampled small biopsy tissue and well preserved archival specimens are feasible to evaluate TIL status.

Keywords: Predictive, Tumor infiltrating lymphocytes, PD-1 blockade

MA11 BIOMARKERS OF IO RESPONSE
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA11.03 INTERACTION OF TUMOR INFILTRATING LYMPHOCYTES AND CANCER NUCLEI PREDICTS RESPONSE TO NIVOLUMAB IN NON-SMALL CELL LUNG CANCER (NSCLC)

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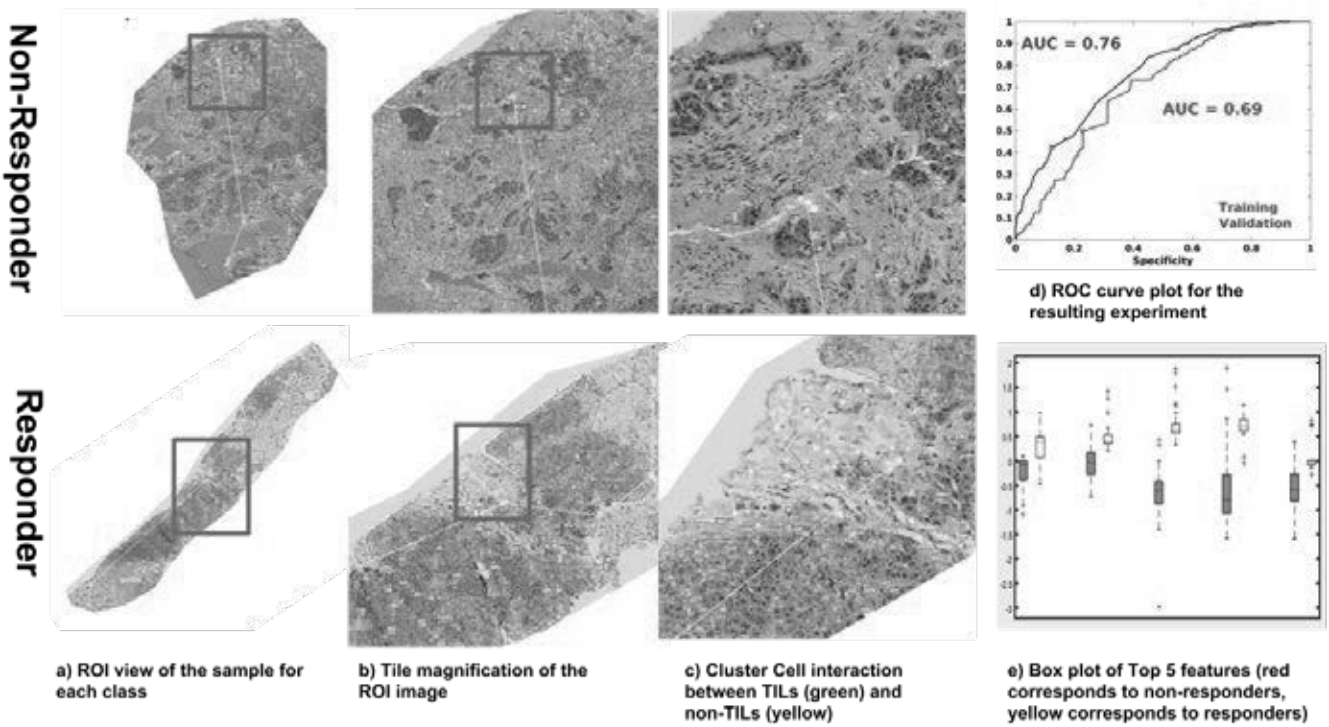
Background: Immune checkpoint inhibitors, particularly drugs targeting the Programmed death-1 (PD-1) pathway, are promising agents in NSCLC. These drugs however are effective in only a small subset of patients. Programmed death Ligand-1 (PDL1) expression in the tumor predicts response to these agents but is not an optimal biomarker because of spatial and temporal heterogeneity associated with PDL1. PD-L1 is upregulated in response to inflammation in the tumor and strongly correlates with Tumor-infiltrating lymphocytes (TILs). In this work, we evaluated whether quantitative measurements relating to the spatial interplay and arrangement of TILs and cancer nuclei from diagnostic biopsy tissue slide images (H&E) was predictive of response to Nivolumab. **Method:** Tumor biopsies of total 82 NSCLC patients previously treated

with Nivolumab from two different institutions were employed in this study. The RECIST criteria was used to define response. [vv1] The 492 features characterizing the global interaction of TILs and cancer cells through graph interplay metrics are extracted from tumor regions delineated by two expert pathologists to interrogate the difference of phenotypes. Top 5 features were learnt on learning set by random forest classifier from one institution (n=32) and independently validated on patients from a second site (n=50). **Result:** The most predictive features comprised of difference of characteristic path length between lymphocyte graph and cancer nuclei graph and cosine similarity between lymphocyte node and cancer nuclei node based on their node centrality index. The random forest classifier yielded an area under the receiver operating characteristic curve (AUC) of 0.76 on the training cohort and 0.68 on the validation set (Figure 1).



a) ROI view of the sample for each class

b) Tile magnification of the ROI image

c) Cluster Cell interaction between TILs (green) and non-TILs (yellow)

d) ROC curve plot for the resulting experiment

e) Box plot of Top 5 features (red corresponds to non-responders, yellow corresponds to responders)

Conclusion: Our results showed that quantitative measurements relating to the spatial interplay and arrangement of lymphocyte and cancer nuclei from H&E slide images were predictive of response to Nivolumab in NSCLC. Additional independent multi-site validation of these features is needed.

Keywords: Prediction response to Nivolumab, Quantitative image analysis, Interaction of TILs and cancer cells

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MA11.05 INDOLEAMINE 2,3-DIOXYGENASE EXPRESSION IN NON-SMALL-CELL LUNG CANCER: ANALYSES OF PREVALENCE, CLINICAL CORRELATIONS AND PROGNOSTIC IMPACT

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Background: Indoleamine 2,3-dioxygenase-1 (IDO-1) is a cytosolic enzyme involved in the catabolism of tryptophan; IDO-1-related immune suppression is due to decreased tryptophan availability and to the generation of tryptophan metabolites, culminating in substantial suppression of T-lymphocytes. Here we investigate IDO-1 expression in a cohort of non-small-cell lung cancer (NSCLC) specimens, both in tumor cells and in immune infiltrate, with correlation of IDO-1 to PD-L1 expression, clinical patient demographics and outcomes. **Method:** A cohort of 1.200 NSCLC samples were obtained from 437 patients who underwent surgical lung resections at Austin Health, Melbourne, Australia. IDO-1 expression was evaluated by immunohistochemistry. Correlations were assessed using Spearman and Kendall tests. A Cox proportional hazards (PH) model was used to assess if overall survival (OS) was associated with IDO-1 positivity in univariate and multivariable settings. **Result:** Samples from 437 patients were analyzed for IDO-1 expression, with 111 (25.4%) determined as positive (H-Score ≥ 1) and 326 patients (74.6%) as negative (H-Score: 0). IDO-1 expression was determined to be greater in tumor immune infiltrate, with 406 patients (93.8%) determined as positive, while just 27 (6.2%) were IDO-1 negative. There was a significant positive correlation between IDO-1 positive tumor cells and immune cells (0.2167, $p < 0.001$). Both continuous and binary versions of tumor H-Score showed a significant positive correlation with the amount of tumor immune infiltrate (0.1806 and 0.1698, $p < 0.0001$, respectively). None of the analyzed variables (age, sex, histology, stage, EGFR, KRAS and PD-L1 status) were found to display a significant correlation with IDO-1 positivity in tumor and immune cells. IDO-1 positivity in tumor cells was found to be significantly associated with OS in the univariate setting and in the multivariable model where variables age, sex, histology, stage, EGFR, KRAS and PD-L1 status were included [P-value = 0.009 and 0.021, respectively; HR: 0.72 (95% CI: 0.55-0.95)]. IDO-1 positivity in immune cells was found to be significantly associated

with OS in the univariate setting and was borderline significant in the multivariable model [P-value = 0.006 and 0.053, respectively; HR: 0.798 (95% CI: 0.635-1.003)]. **Conclusion:** To our knowledge, this is the most extensive analysis of IDO-1 expression in NSCLC patients reported in the literature. Our results suggest the possible prognostic role of IDO-1 expression in tumor and immune cells, highlighting the relevance of IDO-1 detection in tumor tissue. Since new compounds targeting IDO-1 are actually under investigation, the identification of potential prognostic and predictive biomarkers will be needed.

Keywords: NSCLC, Immunotherapy, IDO-1

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MA11.06 PROGNOSTIC VALUE OF COMPLEMENT SYSTEM IN NSCLC AND ITS ASSOCIATION WITH PD-1 AND PD-L1 EXPRESSION

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Background: Recent research has unveiled novel molecular mechanisms linking imbalanced complement activation and cancer progression. In this context, complement inhibition has emerged as a treatment option for maximizing the clinical efficacy of current immunotherapies that target the PD-1/PD-L1 immune checkpoint. **Method:** Lung cancer tissues were obtained from 140 patients treated by surgery at the Clinica Universidad de Navarra. Inclusion criteria were: NSCLC histology, complete resection of the primary tumor, absence of cancer within the five years previous to the lung cancer surgery, and no treatment with chemo- or radiotherapy prior to surgery. Resected primary lung tumors were fixed in formalin and embedded in paraffin. After antigen retrieval samples were incubated with anti-human C4d, C5aR1, C1q, PD-1 and anti-PD-L1 followed by detection with the Envision system (Dako). Peroxidase activity was visualized with 3,3'-diaminobenzidine. Sections were slightly counterstained with hematoxylin. Two independent and blinded observers calculated an H -score based on intensity and extension of the staining. Survival curves were generated using the Kaplan–Meier method, and statistically significant differences were analyzed with the log rank test. **Result:** Immunohistochemistry of complement proteins in NSCLC was performed for C1q, the target recognition of the complement pathway in NSCLC, C4d, a split product of complement activation, and C5aR1, the complement C5a anaphylatoxin receptor. Immunohistochemical analysis showed positive staining for all these proteins, indicating complement activation in primary lung tumor cells. Importantly, high levels of C1q, C4d, and C5aR1 predict poor disease-free survival (P=0.004; P=0.044; and P=0.02; respectively) and poor overall survival (P=0.031; P=0.022; and P=0.048; respectively) in NSCLC patients. A significant association between PD-1 expression levels in immune cells and disease-free survival was found (P=0.002) but this association was not significant for overall survival. PD-L1 expression levels in both immune cells and tumor cells were not associated with prognosis in NSCLC patients. Interestingly, those patients with high levels of C4d presented a significant decrease of PD-L1 expression in tumor cells (P<0.001) suggesting a link between complement activation and the immune homeostasis of the tumor microenvironment. **Conclusion:** Complement activity in primary NSCLC tumors predicts poor prognosis. C4d, a marker of complement activation, is associated with low levels of PD-L1 expression in tumor cells. Harnessing complement system as therapeutic target may enhance PD-1/PD-L1 immune checkpoint-based immunotherapies.

Keywords: PD-L1, Prognosis, Complement system

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MA11.07 EXPRESSION OF LAG-3 AND NY-ESO-1IN TUMOR CELLS IS PROMISING BIOMARKER PREDICTING DURABLE CLINICAL BENEFIT OF PD-1 BLOCKADE IN ADVANCED NSCLC

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Background: Anti-PD-1 antibodies are currently used in treating advanced non-small cell lung cancer (NSCLC). PD-L1 expression in tumor cell or immune cell is the only available predictive biomarker in the clinic. Lymphocyte activation gene-3 (LAG-3) is an inhibitory checkpoint in immune cells and NY-ESO-1 is an antigen expressed in tumor cells. We investigated LAG-3 and NY-ESO-1 protein expression and its relationship to response to anti-PD-1 therapy in NSCLC. **Method:** We retrospectively reviewed the medical records of 38 patients with advanced NSCLC who were enrolled in prospective clinical trials of nivolumab or pembrolizumab monotherapy (NCT01295827, NCT01905657, and NCT02175017) between October 2013 and April 2016 at Seoul National University Hospital and Seoul National University Bundang Hospital. Immunohistochemial staining (IHC) of NY-ESO-1(E978, Invitrogen), and PD-L1 (22C3, Dako) in tumor cell and LAG-3(EPR4392, Abcam) in immune cell was performed to determine protein expression. **Result:** LAG-3 and NY-ESO-1 protein expression were assessed in 38 patients. LAG-3, NY-ESO-1 and PD-L1 were expressed in 76.3% (29/38), 50% (19/38) and 18.5% (7/36, 50% cut-off value), respectively. Sixteen patients with durable clinical benefit (DCB, anti-PD-1 therapy more than 6-month) were grouped as responder. NY-ESO-1 expression (DCB 11/19 vs 5/19, p= .05) and LAG-3 expression (DCB 16/29 vs 0/9, p= .003) were significantly correlated with the DCB to Anti-PD-1 therapy, while PD-L1 expression was identified in 5 patients with DCB (5/7 vs 11/29, p= .12). Patients with both NY-ESO-1 and LAG-3 expression had high rate of DCB (73.3%, 11/15 pts). With the results of the interaction with DCB, the calculation of positive predictive value and negative predictive value about durable clinical benefit is assessed and the significance of each measurement was proven by Fisher's exact test. As a result, NPV of LAG-3 expression in tumor cell was 100% and PPV of each protein expression was LAG-3 (55.17%), NY-ESO-1(57.89%) and PD-L1 (71.43%) respectively. In survival analysis, LAG-3 expression was a significant predictor for PFS (HR 0.170; CI 0.066-0.437; p< .0001) and OS (HR 0.250; CI 0.140-0.599; p= .002). **Conclusion:** NY-ESO-1 expression on tumor tissue and LAG-3 expression on tumor microenvironment may be useful for identifying advanced NSCLC patients for the treatment of anti-PD-1 therapy. These protein markers seem quite promising and warrant further investigation in large sample size.

Keywords: non small cell lung cancer, immune checkpoint inhibitor, Predictive biomarker

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MA11.09 SINGLE-CELL CHARACTERIZATION OF THE IMMUNOLOGIC MICROENVIRONMENT IN ADVANCED-STAGE, ONCOGENE-DRIVEN NSCLC

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Background: The immunologic microenvironment in oncogene-driven non-small cell lung cancer (NSCLC) is poorly understood. Despite high initial response rates to tyrosine kinase inhibitors (TKIs) in patients with oncogene-driven NSCLC, responses are incomplete and transient. Furthermore, response rates to subsequent checkpoint inhibitor immunotherapies are very low. Understanding the immunologic microenvironment may facilitate understanding treatment resistance in this population. **Method:** From October 2016 to March 2018 we performed single-cell sequencing on 35 tissue samples from 28 patients with NSCLC. Fresh tissue samples were obtained at time of standard of care biopsies and as research sample collections. Single-cell level whole transcriptome RNA sequencing was performed using SmartSeq2. Cells were clustered into distinct cell states on a multi-dimensional gene expression space and visualized using t-distributed stochastic neighbor embedding (t-SNE) for further dimensionality reduction. Cellular identities for each cluster were established by examining the enrichment of known cell-type specific genes across all distinct clusters. **Result:** Tumor samples were obtained from predominantly stage IV lung adenocarcinoma (90.6%) harboring an oncogenic driver (EGFR-mutant 50%, ALK-rearranged 21.9%, BRAF V600E 9.4%, ROS1-rearranged 9.4%, MET exon 14 skipping 6.3%, and KRAS-mutant 3.1%). Samples were collected prior to treatment (21.9%), during treatment (46.9%), and at disease progression on therapy (31.3%). All patients with a targetable oncogenic driver received a standard of care TKI and the KRAS-mutant patient received pembrolizumab monotherapy. A total of 6048 cells were isolated, including 3457 immune cells, with an average of one million reads and 2500 genes per cell. The immunologic microenvironment (average 108 immune cells/sample) included macrophages/monocytes (33% of cells), T cells (31.9%), and B cells (11.6%), as well as a smaller fraction (<10%) of dendritic cells, Langerhans cells, mast cells,

neutrophils, and NK cells. Unbiased gene expression-based subclustering of T cells identified 7 distinct T cell populations, including naïve (22.6%), cytotoxic and/or memory T cells (44.1%), and T regulatory cells (5.6%), as well as 6 tumor-associated macrophage populations with distinct gene expression patterns. **Conclusion:** Single-cell RNA sequencing to identify immune cell populations is feasible in advanced-stage NSCLC biopsy specimens across multiple time points during treatment. Here, we describe the heterogeneity of infiltrating immune cell phenotypes including T cell and macrophage subtypes. An improved understanding of the immunologic microenvironment in oncogene-driven NSCLC may facilitate patient selection for immunotherapy treatment and aid in the rational design of alternative or combination immunotherapy strategies for a patient population rarely responsive to current immunotherapeutic agents.

Keywords: Immunology, Single-cell, Targeted therapy

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MA11.10 IDENTIFICATION OF MISMATCH REPAIR DEFICIENT LUNG ADENOCARCINOMAS USING TARGETED NEXT-GENERATION SEQUENCING

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Background: Mismatch repair (MMR) deficiency/microsatellite instability (MSI) results from the inactivation of DNA mismatch repair proteins. Due to the defect in DNA repair, MMR-deficient (D) tumors display an elevated tumor mutation burden (TMB) and a characteristic increase in small insertions/deletions within homopolymer tracts ("homopolymer indels"), a signature that can be detected using next generation sequencing methods. MMR-D/MSI predicts response to immune oncology (IO) agents (Le et al., 2017) and is an approved biomarker for pembrolizumab therapy in the relapse setting irrespective of histologic diagnosis. In this study, we retrospectively analyzed a large cohort of non-small cell lung carcinomas using targeted next generation sequencing to examine the prevalence and clinicopathologic associations of MMR-D in this tumor type. **Method:** TMB and MSI status was derived from a 309-447 gene targeted next generation sequencing panel (OncoPanel) using an internally validated method (Nowak et al., 2017), that relies on an empirically defined homopolymer indel cutoff of >=1.52/Mb to identify candidate MMR-D tumors. MMR/MSI status was confirmed using MSI PCR (5 marker panel) and/or immunohistochemistry (IHC) for MLH1, PMS2, MSH2, and MSH6. When indicated, MLH1 promoter methylation status was evaluated by methylation-specific PCR. **Result:** 2242 lung tumors, including 1835 non-squamous non-small cell lung carcinomas (NSCLC), were interrogated. A total of three lung tumors (all adenocarcinoma) with confirmed MSI/MMR-D by orthogonal methods were identified, for a prevalence of 0.1% of all lung tumors and 0.2% of non-squamous NSCLC. The TMB of these tumors averaged 42.5 mutations/Mb with 7-10 homopolymer indels / Mb. All three tumors showed loss of MLH1 and PMS2 staining by IHC; two cases had somatic loss-of-function MLH1 variants and one showed MLH1 promoter methylation. All were from female patients whose mean age was 68 years (range: 53-83). All showed a poorly-differentiated histology with moderate to brisk lymphoid infiltrates. One patient was a never-smoker; her tumor had a concomitant EML4-ALK rearrangement. The other two patients had moderate/heavy smoking histories (12.5-80 pack-years) both showed RASA1 and NF1 inactivating mutations. One tumor evolved in the context of usual interstitial pneumonia. **Conclusion:** MMR-D is very rare in lung tumors, where it appears to arise as somatic event and is enriched in adenocarcinoma. MMR-D may coexist with other relatively uncommon driver alterations, including those not traditionally associated with IO response. Additional investigation is needed to determine if MMR-D confers sensitivity to IO in lung carcinomas.

Keywords: MMR deficiency, lung adencarcinoma, next generation sequencing

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MA11.11 DISCREPANCY OF TUMOR NEOANTIGEN BURDEN BETWEEN PRIMARY LESIONS AND MATCHED METASTASES IN LUNG CANCER

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Background: Personalized vaccine based on tumor neoantigens showed the striking antitumor effect on several solid tumors, suggesting its significant and potential role in curing cancer. However, whether tumor neoantigens identified from primary lesions were similar to their matched metastases remain unknown. Here, we aimed to compare the tumor neoantigen burden (TNB) between primary lesions and matched metastases in lung cancer. **Method:** Primary lung cancers, matched metastatic sites and peripheral blood (10 mL, EDTA) were collected before any systemic therapy as part of the standard clinical care. Genomic DNA was extracted from all included samples. The matched peripheral blood leukocytes were used as the source for germline DNA control. DNA libraries were subjected to whole-exome capture and then sequenced on an Illumina HiSeq X-TEN platform. The criteria for tumor neoantigen identification were tumor specific mutations (missense, frameshift, inframe insertion or deletions), fold change > 10, high predicted affinity (IC_{50} < 500 nM) and predicted peptide of 9-10 amino acids in length. **Result:** Totally, 14 cases with matched lung primary lesions and metastases were enrolled, including 10 patients with liver metastases and 4 with brain metastases. A wide range of TNB were identified in both primary lesions (median 157, range 21-1156) and metastases (median 135, range 35-1902). We observed a large discrepancy of TNB between primary lesions and matched metastases, with a median unique percentage of 82.20% (74.03%-95.24%) in primary lesions and 84.50% (77.45%-97.14%) in metastases. In patients with brain metastases, primary lesions had a percentage of 90.98% (79.57%-95.24%) unique tumor neoantigens, while metastases had 86.03% (77.45%-97.14%). For those with liver metastases, the median unique percentage of tumor neoantigens was 80.58% (74.03%-88.66%) in primary lesions and 83.35% (78.49%-91.14%) in metastases. Smoking history and histological types had no impact on the discrepancy of TNB (P > 0.05, P > 0.05; respectively). TNB of primary lesions was similar to matched metastases (P = 0.733). However, primary lesions of brain metastases had a significantly higher percentage of unique tumor neoantigen than that of liver metastases (P = 0.025). **Conclusion:** There is a large percentage of different tumor neoantigens between primary lesions and matched metastases in lung cancer. Whether this discrepancy could affect the efficacy of following personalized vaccine on primary lesions or matched metastases need further investigation.

Keywords: non-small cell lung cancer, metastasis, neoantigen

MA12 MESOTHELIOMA SURGERY AND NOVEL TARGETS FOR PROGNOSIS AND THERAPY
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MA12.01 THE INFORMATION PATHWAY TO RANDOMISATION: PATIENTS EXPERIENCE OF THE MESOTHELIOMA AND RADICAL SURGERY (MARS2) FEASIBILITY TRIAL

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Background: The Mesothelioma and Radical Surgery 2 (MARS 2) trial was established in the UK to evaluate the role of radical surgery, (Pleurectomy decortication), for the treatment of malignant pleural mesothelioma (MPM). It compares chemotherapy and surgery to chemotherapy alone. The feasibility trial included a nested qualitative sub-study. The sub study aimed to 1) understand the patient experience of MARS2 trial process and interventions and 2) Identify any information and support needs required by patients. We present here the results related to MARS2 participant's information experiences and needs at the point of randomisation. Implications for information provision to enhance patient experience and overcome recruitment barriers[1] within MPM trials are considered. **Method:** 41 in-depth longitudinal qualitative methods were used with 15 participants following randomisation. 9 participants received chemotherapy and surgery and 6 received chemotherapy alone. Interviews were conducted following randomisation, and at 6 and 12 months after the initial interviews. Participants randomised to surgery also had an interview after post-operative discharge. Data was collected between August 2015 and March 2017 and analysed using Framework

analysis[2] **Result:** The findings provide insight into the challenging context within which potential participants have to assimilate knowledge about a trial such as MARS2. Prior to hearing about the trial participants had encountered a diverse range of new and concerning experiences. These included worrying symptoms, diagnostic tests, investigations and the drainage of litres of fluid from the lung. They had to absorb an array of life-changing facts in a short time including that they had a rare incurable cancer with a poor prognosis; their illness was an occupational disease with legal and financial implications due to asbestos exposure. Participants attended their trial consultation soon after this challenging diagnostic information provision. The study reveals variations in understanding of the trial procedures, specifically decision-making regarding treatments, equipoise and the process of randomisation. Motivations for participating in the trial were identified along with preferences for information formats. **Conclusion:** This study provides unique insight into the information pathway of MPM trail participants, from diagnosis to randomisation. Results suggest that improvements in presentation of trial information and the development of formats that can be tailored to individual needs and preferred ways of learning, many enhance experience of and recruitment to MPM trials. Working with patients to co-produce information that communicates challenging concepts effectively, (such as randomisation and equipoise), may be a useful approach to meeting this challenge.

Keywords: Longitudinal qualitative research, Mesothelioma, patient experience

MA12 MESOTHELIOMA SURGERY AND NOVEL TARGETS FOR PROGNOSIS AND THERAPY
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MA12.02 QUALITY OF LIFE FOLLOWING PLEURECTOMY DECORTICATION AND EXTRAPLEURAL PNEUMONECTOMY FOR PLEURAL MALIGNANT MESOTHELIOMA

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Background: Few studies have focused on quality of life (QoL) after treatment of malignant pleural mesothelioma (MPM). Questions remain as to which surgical procedure, extrapleural pneumonectomy (EPP) or pleurectomy (P/D), is most effective and results in better outcomes for survival and involves fewer complications. A comprehensive review was conducted on MPM patients to assess differences in QoL following P/D and EPP. **Method:** Original research studies on QoL after mesothelioma surgery were identified through May 2018: 17 articles, 14 datasets encompassing 659 patients, were retrieved. Measures of lung function (FEV, FVC) and EORTC QLQ-C30 were compared 6 months following surgery with preoperative values. **Result:** QoL data was available for 102 EPP patients and 432 P/D patients. Two studies directly compared QoL between the two techniques. While QoL was still compromised 6 months following surgery, P/D patients fared better than EPP patients across all QoL measures. Physical function, social function, global health and dyspnea were higher at follow-up for PD than for EPP, while other indicators such as pain and cough were similar. FEV and FVC were higher at follow-up for P/D compared to EPP, although only one study reported FEV and FVC following EPP. **Conclusion:** QoL is better for patients undergoing P/D compared to EPP for an extended period following surgery. Given the need for multimodality therapy and the aggressive nature of MPM, QoL outcomes should be strongly considered when choosing type of surgery for MPM.

Keywords: surgical approach, Mesothelioma, quality of life

MA12 MESOTHELIOMA SURGERY AND NOVEL TARGETS FOR PROGNOSIS AND THERAPY
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MA12.03 THE IMPACT OF MALIGNANT PLEURAL MESOTHELIOMA HISTOLOGY ON THE USE OF SURGERY AND SURVIVAL IN A POPULATION-BASED ANALYSIS

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Background: Histologic subtype for malignant pleural mesothelioma (MPM) is known to be an important determinant of both treatment and survival. This study aimed to quantify the impact of MPM histology on the use of surgery and survival in a population-based analysis. **Method:** Overall survival (OS) of patients with stage I-III epithelioid, sarcomatoid, and biphasic MPM in the National Cancer Database from 2004 to 2015 was evaluated using Kaplan-Meier survival analysis and multivariable Cox proportional hazard models. **Result:** Of the 3,346 patients who met inclusion criteria, the histologic subtype was epithelioid in 2,326 patients (70%), biphasic in 482 patients (14%), and sarcomatoid in 538 patients (16%). Median survival was 16.2 [95% CI: 15.3 – 17.2] months in the epithelioid group, 10.9 [95% CI: 9.8 – 11.9] months in the biphasic group, and 5.3 [95% CI: 4.7 – 6.0] months in the sarcomatoid group (p<0.001). Cancer-directed surgery was utilized more often in epithelioid (31%, n=718) and biphasic patients (38%, n=181) compared to sarcomatoid patients (17%, n=91) (p<0.001). Among patients who underwent surgery, median survival was significantly better for epithelioid (22.6 [95% CI: 21.2 – 24.8] months) and biphasic (14.7 [95% CI: 12.6 – 17.3] months) histologies compared to sarcomatoid histology (7.7 [95% CI: 6.4 – 8.6] months) (p<0.001). Surgery was associated with better survival in multivariable analysis for epithelioid (HR 0.81; [95% CI: 0.72 – 0.93], p=0.002) and biphasic histologies (HR 0.69; [95% CI: 0.53 – 0.89], p=0.004), but not for sarcomatoid type mesothelioma (HR 0.87; [95% CI: 0.65 – 1.16, p=0.34). Further, the absolute difference in median survival between surgical and non-surgical therapy was more clinically significant for the epithelioid (22.6 vs 15.8 months; p <0.001 and biphasic (14.7 vs 10.4 months; p=0.001) patients compared to the sarcomatoid (7.7 vs 7.2 months; p=0.13). **Conclusion:** In this U.S. national analysis of patients with malignant pleural mesothelioma, surgery was most commonly used for epithelioid and biphasic histologies and was associated with a median survival of nearly 2 years and over 1 year, respectively. However, surgery was also used in almost 1 in 5 patients with sarcomatoid mesothelioma but was associated with a median survival of less than 8 months. These results suggest that the specific mesothelioma histology should be firmly established before surgery, and it is reasonable to aggressively treat select patients with epitheloid and biphasic mesothelioma with surgery, but that surgery should not be performed for most patients with sarcomatoid mesothelioma.

Keywords: Mesothelioma, sarcomatoid, Epithelioid

MA12 MESOTHELIOMA SURGERY AND NOVEL TARGETS FOR PROGNOSIS AND THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA12.05 PHASE 1 STUDY OF HSP90 INHIBITOR GANETESPIB WITH PEMETREXED AND CISPLATIN/CARBOPLATIN CHEMOTHERAPY FOR PLEURAL MESOTHELIOMA

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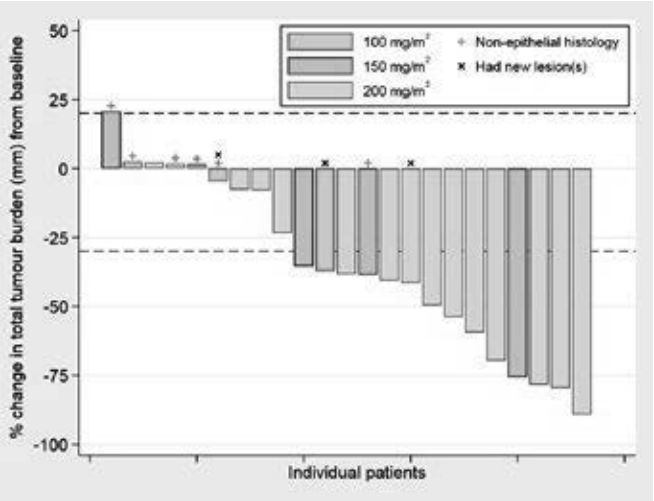
Background: There have been no new licenced therapies for mesothelioma in over a decade. Ganetespib is a small-molecule heat-shock protein 90 (Hsp90) inhibitor, with significant activity for down-regulating Hsp90 client protein levels. Prior evidence indicates efficacy for ganetespib in mesothelioma through critical survival pathways and synergies with antifolates and platinum chemotherapy. **Method:** We conducted a dose-escalation study of ganetespib in patients with pleural malignant mesothelioma and ECOG 0-1. Ganetespib was combined with standard pemetrexed/platinum therapy, using either cisplatin (GCisP), or carboplatin (GCarbP). Three ganetespib cohorts were: 100, 150 & 200mg/m^2 given days 1 and 15, every 21 days. GCisP was evaluated using a 3+3 design. GCarbP followed an accelerated titration run-in using single patients, switching to a 3+3 design after one dose limiting toxicity (DLT). DLT was assessed during cycles 1-2 for GCisP and cycle 1 for GCarbP. Genomic instability was inferred by array-based analysis of somatic copy number. **Result:** 27 patients were treated (GCisP, *n*=16; GCarbP, *n*=11). Median age 66 (range 37-76), 6 PS-0/21 PS-1, and 25 male. Only 3 patients experienced DLTs, all at 200mg/m^2: grade 3 nausea (GCisP, *n*=1; GCarbP, *n*=1); grade 2 infusion-related reaction (GCarbP, *n*=1). This dose was the maximum tolerated dose. Partial tumour response rate was 61% (14/23 evaluable patients); 7 patients had tumour burden reduction of >50% (Figure). PFS was better using 200mg/m^2 versus 100mg/m^2 (hazard ratio 0.32, 95%CI 0.11-0.95, p=0.04). One patient remains progression-

free even after 37 months. Total loss of heterozygosity (LOH) was correlated with increased tumour burden (*n*=7, correlation=0.7, p=0.078). Figure. Best tumour response (% change in tumour burden from baseline)



Conclusion: Ganetespib plus pemetrexed and platinum chemotherapy was well-tolerated in patients with pleural mesothelioma, with evidence of activity, particularly at the recommended dose of 200mg/m². LOH correlated with poorer response to this triplet combination.

Keywords: HSP90 inhibition, Dose-escalation, Pleural mesothelioma

MA12 MESOTHELIOMA SURGERY AND NOVEL TARGETS FOR PROGNOSIS AND THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA12.06 STELLAR – FINAL RESULTS OF A PHASE 2 TRIAL OF TTFIELDS WITH CHEMOTHERAPY FOR FIRST-LINE TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA

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Background: Tumor Treating Fields (TTFields) are an anti-mitotic, regional treatment modality, utilizing low intensity alternating electric fields delivered non-invasively to the tumor using a portable, medical device. In-vitro, human mesothelioma cells were highly susceptible to TTFields. TTFields have been shown to significantly extend survival of patients with glioblastoma when added to chemotherapy. **Method:** The trial accrued 80 patients with unresectable, previously untreated mesothelioma. Patients were treated with continuous 150 kHz TTFields (>18h/day) in combination with pemetrexed and cisplatin or carboplatin (at standard dosing). Inclusion criteria included ECOG PS of 0-1, pathologically proven mesothelioma and at least one measurable lesion according to modified RECIST criteria. Patients were followed q3w (CT scan q6w) until disease progression. The primary endpoint was overall survival (OS) and secondary endpoints were response rate, progression free survival (PFS) and toxicity. This prospective, single arm study assumed an historical control with a median survival of 12.1 months (Vogelzang et al. 2003). The sample size provides 80% power with a two-sided alpha of 0.05 to detect an increase in median OS of 5.5 months. **Result:** All 80 patients were enrolled between 2016 and 2017, with a minimum follow up of 12 months. Median age was 67 (range 27-78), 84% were male and 56% smokers. 16% (13 patients) had metastatic disease and 44% (35 patients) had an ECOG PS of 1. 66% (53 patients) had epithelioid histology. Compliance with TTFields was 68% (16.3 hours/day) during the first 3 months of therapy and 63% (50 patients) received carboplatin. Median OS was 18.2 months (95% CI 12.1-25.8) compared to 12.1 months in the historical control. Median PFS was 7.6 months (95% CI 6.7-8.6) compared to 5.7 months in the historical control. Partial responses were seen in 40.3% of patients and clinical benefit (PR+SD) was seen in 97.2% of patients. No device-related serious adverse events (AEs) were reported. Expected TTFields-related dermatitis was reported in 46% (37 patients). Only 4 patients (5%) had grade 3 dermatitis. The following grade 3-4 systemic AEs were reported in >3% of patients: hematological AEs (15%) and fatigue (4%). **Conclusion:** The study met its primary endpoint of significant extension of survival for previously untreated mesothelioma patients. Secondary efficacy endpoints were also improved compared to historical control. The study demonstrated no safety concerns for the combination of TTFields to the thorax together with standard chemotherapy. These results support the addition of TTFields to standard chemotherapy in the treatment of first-line malignant pleural mesothelioma.

Keywords: TTFields, Tumor Treating Fields, malignant pleural mesothelioma

MA12 MESOTHELIOMA SURGERY AND NOVEL TARGETS FOR PROGNOSIS AND THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA12.07 GC1QR EXPRESSION IS INDEPENDENTLY PROGNOSTIC FOR SURVIVAL BENEFIT FOLLOWING CHEMOTHERAPY IN MESOTHELIOMA

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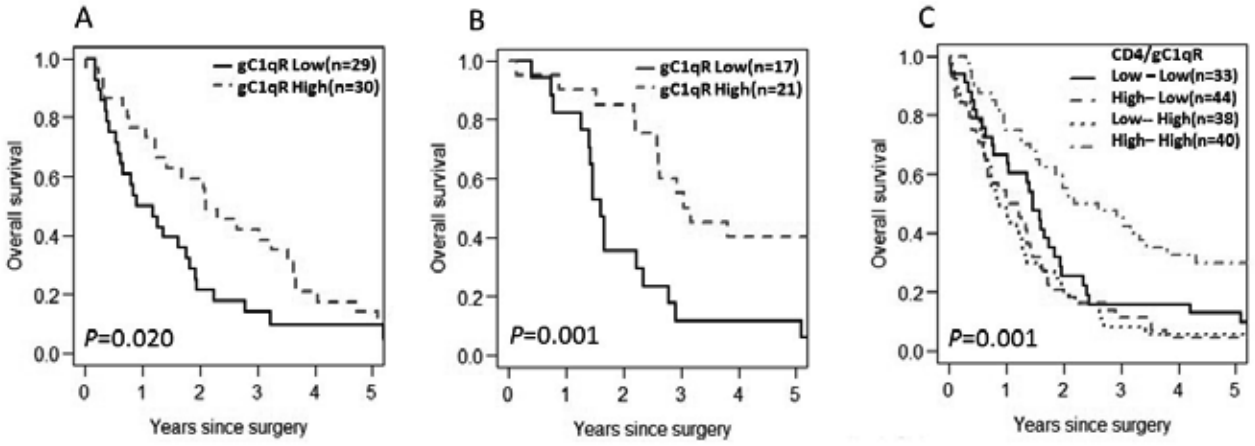
Background: Overexpression of gC1qR, a multicompartmental and multifunctional cellular protein, has been shown to promote chemotherapy-induced apoptosis in cancer cells, but compromise CD4 T-cell proliferation in viral infections. The goal of this study was to investigate the overexpression of gC1qR, and its prognostic association with chemotherapy and CD4 T-cell infiltration in malignant pleural mesothelioma (MPM). **Method:** Tissue microarrays comprising 6 tumoral and 3 stromal cores from 265 patients with MPM (216 epitheloid, 26 biphasic, and 23sarcomatoid, 1989-2010) were investigated by immunohistochemistry for gC1qR expression (intensity and distribution by H-score, range 0-300), and CD4 T-cell infiltration. Overall survival (OS) was analyzed by the Kaplan-Meier method (high versus low gC1qR expression delineated by median score). Multi-variable analysis included clinical, pathological factors and stage (T, N). **Result:** In comparison to benign and reactive mesothelial cells (median H-score 30), gC1qR is overexpressed (median H-score 155) in all histological types of MPMs (263/265, 99.2%). In epithelioid MPM patients – 1) among patients who received neoadjuvant chemotherapy (NAC), high gC1qR was associated with better median OS (25 vs.11 months, Fig1A), 2) among patients without NAC, high gC1qR was associated with better survival, survival benefit is pronounced in patients who received postoperative chemotherapy (median OS 38 vs.19 months, Fig1B), and 3) in multivariate analysis, high gC1qR was an independent factor for better OS. gC1qR expression did not correlate with CD4 T cell infiltration. However, among patients without NAC, high CD4+ T cell infiltration-high gC1qR expression was associated with better OS (26 vs 18,12, and11 months, Fig1C).

(See next page)

Figure1. High gC1qR expression is associated with improved survival following neoadjuvant (A) and postoperative chemotherapy(B). Among patients who did not receive neoadjuvant chemotherapy, high CD4-gC1qR showed improved survival (C) .



Conclusion: gC1qR is overexpressed on MPM cells. MPM patients with high gC1qR expression have a significant survival benefit particularly following chemotherapy; or in the presence of high CD4 T-cell infiltration.

Keywords: malignant pleural mesothelioma, gC1qR, Prognostic

MA12 MESOTHELIOMA SURGERY AND NOVEL TARGETS FOR PROGNOSIS AND THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA12.09 PRECLINICAL INVESTIGATIONS OF FOLATE RECEPTOR TARGETED NANOPARTICLES FOR PHOTODYNAMIC THERAPY OF MALIGNANT PLEURAL MESOTHELIOMA

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Background: Photodynamic therapy (PDT) following lung-sparing extended pleurectomy (EPD) for malignant pleural mesothelioma (MPM) has been investigated as a potential means to kill residual microscopic cells. High expression of folate receptor 1 (FOLR1) has been reported in MPM, and targeting the FOLR1 has been considered as a new potential strategy. We have developed FOLR1-targeting porphyrin-lipid nanoparticles (folate-porphysomes; FP) for PDT. The inhibition of survival pathways of activated epidermal growth factor (EGFR) also enhance the PDT efficacy. Here, we have combined these approaches by using FP based PDT together with an EGFR-tyrosine kinase inhibitor (EGFR-TKI). **Method:** The frequency of FOLR1 and EGFR expression in MPM was analyzed using tissue microarrays. Confocal microscopy and a cell viability assay were performed to confirm the specificity of FOLR1-targeting cellular uptake and photocytotoxicity *in vitro*. In vivo fluorescence activation and the therapeutic efficacy were then examined. The effect of EGFR-TKI was assessed *in vitro*. The *in vivo* combined anti-tumor effect of EGFR-TKI and FP-PDT was then evaluated. **Result:** FOLR1 and EGFR were expressed in 79 % and 89 % of the MPM samples, respectively. The intracellular uptake of FP corresponded well with FOLR1 expression. When MPM cells were incubated in FP and then irradiated at 671 nm, there was significant *in vitro* cell kill, which was inhibited in the presence of free folic acid, suggesting the specificity of FPs. FOLR1 targeting resulted in disassembly of the porphysomes and subsequent fluorescence activation in intrathoracic disseminated MPM tumors, as demonstrated by *ex vivo* tissue imaging. FP-PDT resulted in significant cellular damage and apoptosis *in vivo*. Furthermore, the combination of pre-treatment with EGFR-TKI plus FP-PDT showed further marked improvement of treatment responses. **Conclusion:** Folate-porphysome based PDT shows selective destruction of MPM cells based on FOLR1 targeting, and pre-treatment with EGFR-TKI further enhances the therapeutic response.

Keywords: folate receptor 1 (FOLR1), Mesothelioma, photodynamic therapy (PDT)

MA12 MESOTHELIOMA SURGERY AND NOVEL TARGETS FOR PROGNOSIS AND THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA12.10 LONG-TERM IMPACT OF RADIOTHERAPY BEFORE SURGERY FOR MESOTHELIOMA ON THE DISTRIBUTION OF MEMORY T CELL SUBSETS

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Background: Postoperative recurrence remains one of the critical issues in treatments for mesothelioma. We previously reported that non-ablative, hypo-fractionated radiation before surgery generated an antigen-specific activation of the immune system and could provide an in situ vaccination with long-term protection against mesothelioma in our murine model. An effective immunological protection depends on memory T cell subset diversification. However, limited work has been done to address the distribution of memory T cell subsets and its effects on the immune system after radiotherapy followed by surgery for mesothelioma. **Method:** C57BL/6 mice bearing AE17-OVA tumor were treated with local radiotherapy (LRT). LRT 5Gy was delivered on days 10, 11 and 12. We performed radical tumor resection 7 days after LRT. The mice were re-challenged under the skin or into thoracic cavity with AE17-OVA 28 days after surgery and defined as immunological protective memory model if the tumors were completely rejected. Memory model received subcutaneous tumor inoculation once again (second rechallenge), samples were harvested on day 0, 3, 10. We investigated memory T cell subsets using flow cytometry. In addition, the harvested total splenocytes (effector) were co-cultured with CFSE-labeled AE17-OVA (target) for three days. Each of their cytotoxic potential was analyzed by evaluating a number of AE17-OVA and its early or late apoptosis. **Result:** 8 out of 10 mice completely rejected the subcutaneous tumor in mice treated with LRT and surgery after re-challenged. We observed significantly better survival in the memory model re-challenged into the thoracic cavity compared with no treatment mice. After subcutaneous

tumor inoculation, central memory T cells (CD44[+]CD62L[+]KLRG1[-]) on day 0, effector memory T cells (CD44[+]CD62L[-]KLRG1[-]) and terminal effector T cells (CD44[+]CD62L[-]KLRG1[+]) on day 0, 3, 10 increased significantly in CD8[+] splenocytes of memory model compared with no treatment mice. This observation was also seen in draining and non-draining lymph nodes. The MFI of CFSE reflecting a number of AE17-OVA cells decreased, whereas the proportion of early (Annexin V[+]FVD[low]) or late (Annexin V[+]FVD[high]) apoptotic cells in CFSE[+] cells increased, depending on time passage and effector/target ratio after tumor inoculation in both memory model and naïve mice. However, during time passage, memory model always had a stronger cytotoxicity (even at Day 0) as compared to naïve mice. **Conclusion:** Our data raise an important possibility that non-ablative, hypo-fractionated radiotherapy followed by surgery for mesothelioma contributes to the development and long-term maintenance of memory T cell subsets, which could remain poised to rapidly recall effector functions upon antigen re-exposure.

Keywords: immunological effect, Radiotherapy followed by surgery, Mesothelioma

MA12 MESOTHELIOMA SURGERY AND NOVEL TARGETS FOR PROGNOSIS AND THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA12.11 ANALYSIS OF ANGIOGENIC AND STROMAL BIOMARKERS IN A LARGE MALIGNANT MESOTHELIOMA COHORT

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Background: Malignant mesothelioma (MM) is an aggressive malignancy of the pleura and other mesothelium membranes. Agents targeting vascular endothelial growth factor (VEGF) receptor such as bevacizumab; and multi-kinase inhibitors like nintedanib [angiokinase inhibitor of VEGF, platelet-derived growth factor (PDGF) receptor and fibroblast growth factor receptor (FGFR)] have recently demonstrated efficacy in MM. In the setting of these new therapies, it is important to evaluate angiogenic and stromal markers in MM to assess their associated prognostic implications. **Method:** Tissue microarrays (TMAs) were created from formalin-fixed, paraffin-embedded tissue samples obtained from 326 patients who underwent surgical resection or biopsy for MM between 1988 and 2014. PDGF-CC, FGFR-1, VEGF and CD31 expression were analysed by immunohistochemical (IHC) staining. The H-score method assigned a score of 0–300 to each sample, based on the percentage of cells stained at different intensities. The discriminatory threshold was set for each IHC stain (usually the median score) and samples were classified as low (below median) or high expression (above median). CD31 was evaluated via Chalkley's method to evaluate microvessel density. We evaluated the association between expression of the biomarkers, clinicopathological factors and outcomes, in patients with MM. **Result:** The histological subtypes comprised of 203/325 (62.5%) epithelioid; 72/325 (22.2%) biphasic; 42/325 (12.9%) sarcomatoid, or indeterminate. The median age was 67 (range 24-88) with Male: Female ratio of 266: 53. CD31 high (≥5) was seen in only 31/302 (10.3%) irrespective of histology (13/31 (42%) epithelioid; 10/31 (32%) sarcomatoid; 7/31 (23%) biphasic; 1/31 indeterminate). PDGF-CC high (≥150) was seen in 203/310 (65%) of all samples but was higher in epithelioid subtype [129/203 (64%)]. VEGF high (≥80) was seen in 219/322 (68%) of all MM with 143/209 (68%) of epithelioid histology. FGFR-1 high (≥40) was seen in 127/310 (41%) of all MM and 73/127 (57.5%) are of epithelioid histology. There was no association of VEGF and FGFR-1 IHC with survival nor differences between histological subtypes. There was a non-significant trend towards poorer survival in epithelioid tumours with increased PDGF-CC expression (OS 18.5 vs 13.2 months; HR 0.7928; 95%CI 0.5958 to 1.055, P=0.1110). High CD31 score was associated with significantly poorer survival (OS 12 vs 8.6 months; HR 0.48; 95%CI 0.2873 to 0.7941, P=0.0044). Of the 31 patients with high CD31 scores; 23/31 (74%) were also high for PDGF-CC and 20/31 (64%) with high VEGF scores. **Conclusion:** High PDGF-CC expression and CD31 scores are associated with poor survival in MM. Abrogating these pathways may have prognostic implications.

Keywords: angiogenic biomarkers, Mesothelioma, stromal biomarkers

MA13 INTERVENTIONAL PULMONOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA13.01 CT-GUIDED TRANSTHORACIC NEEDLE BIOPSY FOR EVALUATION OF PD-L1 EXPRESSION: COMPARISON OF 22C3 AND SP263 ASSAYS

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Background: Although there are a few studies about concordance of different assays testing PD-L1 expression using surgical specimens, there hasn't been any such concordance study using real-world biopsy specimens. However, many of the patients requiring immunotherapy and thus PD-L1 testing have unresectable lung cancer and have to rely on small biopsy results. Although phase 2 of Blueprint phase 2 does include core biopsy specimens, they are mixed with bronchial biopsy specimens and the absolute number is very small (n=20). We sought to evaluate the concordance of 22C3 and SP263 assays in a larger number CT-guided transthoracic needle biopsy (TNB) specimens. The purpose of this study was to assess the concordance of two commercially available diagnostic assays (22C3 and SP263) in evaluating programmed cell death ligand-1 (PD-L1) expression using specimens from CT-guided TNB in a routine clinical setting. **Method:** This retrospective analysis reviewed 202 non-small cell lung cancer (NSCLC) patients who underwent CT-guided TNB at our institution from April 2017 to February 2018. Among these, biopsy specimens tested with both 22C3 and SP263 assays were included for review. Concordance of PD-L1 expression levels determined by the two assays was assessed using intraclass correlation coefficient, and the agreement of dichotomized values at various cut-offs (1%, 25%, and 50%) were assessed using Cohen's κ coefficient of agreement. Clinical characteristics and biopsy-related factors were also assessed for the association of concordance of PD-L1 expression detected by different assays **Result:** In total, 80 patients (M:F =47:33, mean age: 68.0 years) were included in the study. Concordance of PD-L1 expression levels was high (intraclass coefficient: 0.892) between 22C3 and SP263 assays. Agreements at cut-off levels of 1%, 25%, and 50% were also good, with κ values of 0.878, 0.698, and 0.790 respectively. Positive percent agreement was 93.2%, 100.0%, and 95.2% for agreements at 1%, 25%, and 50%. At multivariate analysis, the presence of emphysema was significantly related to discordant PD-L1 results (odds ratio: 0.059, p= 0.005). **Conclusion:** There is a high concordance of PD-L1 expression evaluated with 22C3 and SP263 assays using CT-guided TNB specimens.

Keywords: CT-guided biopsy, PD-L1 assay

MA13 INTERVENTIONAL PULMONOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA13.02 PD-L1 EXPRESSION IN EBUS-GUIDED CYTOLOGY SPECIMENS OF NON-SMALL CELL LUNG CANCER IS NOT AFFECTED BY TYPE OF FIXATION: A STUDY OF MATCHED PAIRS

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Background: No previous trials of immune modulators (IMs) to treat non-small cell lung cancer (NSCLC) have included 'cytology' specimens, dispersed cells aspirated from a tumour deposit or body cavity, for immunochemical assessment of PD-L1, a useful complementary or compulsory companion diagnostic test. This has led to the widely-held view that, in the absence of such 'validation', cytology specimens cannot be used to assess it. In many centres, endobronchial ultrasound (EBUS)-guided aspiration of the tumour or intra-thoracic lymph nodes is the preferred means of diagnosis and staging of NSCLC and such specimens account for the majority received for analysis. Failure to asses them has serious implications for appropriate management and might deny patients effective therapy. Much of this reluctance centres on the alleged effect of fixation in alcohol-based fixatives, the preferred method of cytopathologists, rather than formalin, the standard fixation medium for tissue specimens, on the expression of PD-L1 on the cell surface. **Method:** We compared expression of PD-L1 in 50 paired specimens of NSCLC, one fixed in an alcohol-based fixative and one in neutral-buffered formalin, taken from the same tumour deposit or lymph node during the same procedure. All were spun down and formed into a cell block before assessment for PD-L1 expression, which was by two appropriately-

trained pathologists with extensive experience in its interpretation. **Result:** In none of the 50 pairs studied was there any significant difference, qualitative or quantitative, in the pattern or extent of PD-L1 expression and, in the great majority, it was identical irrespective of fixation. **Conclusion:** There is no evidence from this study that the use of alcohol-based fixatives has any effect on the expression of PD-L1 or its interpretation. Notwithstanding the general challenges in accurately assessing such expression, which are common to specimens of tissue as well as dispersed cells, pathologists should feel able to interpret cytology specimens with confidence and clinicians able to rely on the results.

Keywords: EBUS-cytology, Fixation, PD-L1

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MA13.03 HETEROGENEITY ANALYSIS OF EBUS-TBNA-DERIVED SPECIMENS FOR EVALUATION OF PD-L1 EXPRESSION AND COPY NUMBER ALTERATIONS IN PATIENTS WITH NSCLC

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Background: Most patients with non-small cell lung cancer (NSCLC) are diagnosed at advanced stages and only small biopsy specimens are available for diagnosis in the majority of the patients. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a useful diagnostic modality and is becoming more relevant and essential procedure in the real-world clinical setting. However, it is poorly elucidated whether EBUS-TBNA-derived small specimens are suitable for evaluation of biomarkers such as PD-L1 alterations, because heterogeneity of PD-L1 expression limits the power as a guide to select patients who are likely to benefit from the PD-1/PD-L1 blockade therapy. In addition, *PD-L1* copy number alterations (CNAs) have been proposed to potentially complement the predictive performance of PD-L1 expression. We here evaluated the utility of EBUS-TBNA-derived specimens in the assessment of PD-L1 protein and CNAs focusing on the heterogeneity with other biopsy/resected samples. **Method:** PD-L1 protein expression and CNAs in 71 EBUS-TBNA specimens of NSCLC were assessed. Corresponding 68 transbronchial biopsy (TBB) specimens, 13 resected primary tumors, and 6 resected metastases were comparatively analyzed. PD-L1 expression on tumor cells was assessed by immunohistochemistry (E1L3N). Positivity of ≥1% was used as the cut-off. *PD-L1* CNAs were assessed with fluorescent *in situ* hybridization, and were classified into three categories: amplification, polysomy, and disomy. Concordance between EBUS-TBNA and other specimens were calculated. **Result:** The median age was 68 years (38-90 years). The cohort comprised 48 men (67.6%), 15 never-smokers (21.1%), and 39 adenocarcinomas (54.9%). The concordance of PD-L1 positivity between EBUS and the other specimens was moderate; κ=0.63 for EBUS vs TBB, κ=0.68 for EBUS vs the resected primary tumors, and κ=1.00 for EBUS vs the resected metastases. The concordance of *PD-L1* CNA statuses was comparable with that of PD-L1 expression: κ=0.60 for EBUS vs TBB, and κ=0.74 for EBUS vs the resected primary tumors. When the *PD-L1* copy number was assessed as a continuous variable, the correlation was also good/moderate: ρ=0.60 for EBUS vs TBB specimens, ρ=0.56 for EBUS vs the resected primary tumors, and ρ=0.80 for EBUS vs the resected metastases. Intratumorally, PD-L1 expression was significantly heterogeneous in whole sections of resected tumors, but *PD-L1* CNAs was less heterogeneous than protein expression. **Conclusion:** EBUS-TBNA-derived specimens can be used for the assessment of PD-L1 alterations including CNAs. The concordance of PD-L1 CNAs between EBUS-TBNA and TBB/resected specimens were comparable with that of PD-L1 expression. However, spatial heterogeneity should be taken into account to interpret both PD-L1 protein expression and CNAs.

Keywords: PD-L1, EBUS-TBNA, copy number alteration

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MA13.05 THE CANADA LYMPH NODE SONOGRAPHIC SCORE: NATIONAL VALIDATION OF A SONOGRAPHIC SCORE TO DETERMINE MEDIASTINAL LYMPH NODE MALIGNANCY

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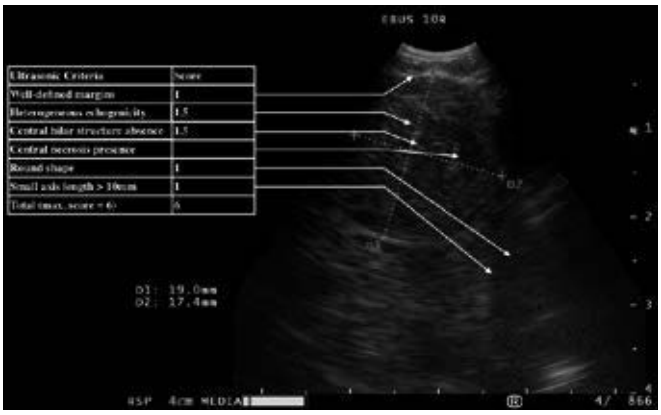
Background: At the time of endobronchial ultrasound (EBUS) staging for Non-Small Cell Lung Cancer (NSCLC), 6 ultrasonic criteria (Fig. 1) are used to assign a Lymph Node Sonographic Score (LNSS) that is predictive of malignancy. The LNSS has not gained widespread use due to lack of research demonstrating its validity and reliability among endoscopists. We hypothesized that LNSS correlates well with the probability of malignancy, potentially guiding decisions for lymph node (LN) biopsy.



Method: We conducted a prospective study to assess the validity and reliability of the LNSS. The validation cohort comprised LN that were video-recorded from patients with NSCLC, and assigned a LNSS by an experienced endoscopist. Videos were then circulated to thoracic surgeons and interventional respirologists across Canada, who were asked to assign a score to each LN. All raters had demonstrated proficiency using our online education module, were blinded to staging information, and to each other. Each LN was scored by at least 3 independent raters. Pathological specimens were used as the gold standard for determination of malignancy. Regression, receiver operator curve (ROC), and Gwet's AC1 analyses were used to test LNSS score performance, discriminatory capacity, and inter-rater reliability. **Result:** A total of 300 LNs (18% malignant) from 140 patients were analyzed by 11 endoscopists across 7 Canadian centres. LNSS=0 was strongly predictive of benign LN (NPV= 95.69%, OR=49.2, p=0.001). LNSS ≤2.5 (OR=44, p=0.001) was determined as the cutoff for malignancy based on ROC analysis (c= 0.7757, 95%CI: 0.70281-0.84853). Inter-rater reliability for LNSS=0 was 0.8553 (95%CI:0.8158-0.8947, p=0.0001) and 0.46 for LNSS ≤2.5 (95%CI=0.3521-0.5012, p=0.0001). **Conclusion:** The Canada LNSS shows excellent performance in identifying benign LN at the time of EBUS. A cutoff ≤2.5 has the potential to inform decision-making regarding biopsy or repeat biopsy/mediastinoscopy if the initial results are inconclusive. Further teaching and education are required to improve inter-rater reliability.

Keywords: Enodobronchial ultrasound, Sonographic features

MA13.06 ENDOSONOGRAPHY WITH LYMPH NODES SAMPLING FOR RESTAGING THE MEDIASTINUM IN LUNG CANCER: A SYSTEMATIC REVIEW AND POOLED-DATA ANALYSIS

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Background: Mediastinal restaging after induction treatment is still a difficult and controversial issue. We aimed to investigate the diagnostic accuracy of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for restaging the mediastinum after induction treatment in patients with lung cancer. **Method:** Embase and PubMed databases were searched from conception to July 2017. Data from relevant studies were analyzed to assess sensitivity and specificity of EBUS-TBNA and EUS-FNA, and to fit the Hierarchical Summary Receiver-Operating Characteristic curves. **Result:** A total of nine studies consisting of 542 patients fulfilled the inclusion criteria. All patients were restaged by EBUS-TBNA, EUS-FNA or both. Negative results were confirmed by subsequent surgical approaches. There were no complications reported during any endosonography approaches reviewed. The pooled sensitivities of EBUS-TBNA and EUS-FNA were 66%(95% CI, 60%-72%) and 73%(95% CI, 52%-87%), respectively; and specificities were 100%(95% CI, 98%-100%) and 99%(95% CI, 90%-100%), respectively. The area under the HSROC curves(AUC) were 0.84(95% CI, 0.81-0.87) for EBUS-TBNA and 0.99(95% CI, 0.98-1) for EUS-FNA. Moreover, for patients who received chemotherapy alone, the pooled sensitivity of endosonography with lymph node sampling for restaging was 69% (95% CI, 63%-75%), and specificity was 100% (95% CI, 97%-100%); and for patients who received chemoradiotherapy, the results seemed similar with sensitivity of 65% (95% CI, 50%-78%) and specificity of 100% (95% CI, 96%-100%).

Variables	No. of patients	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Negative Likelihood Ratio	AUC
In all mediastinal stations					
Overall	543	0.70 (0.65-0.75)	1.00 (0.98-1.00)	0.30 (0.21-0.43)	0.93 (0.91-0.95)
EBUS-TBNA	424	0.66 (0.60-0.72)	1.00 (0.98-1.00)	0.38 (0.26-0.54)	0.84 (0.81-0.87)
EUS-FNA	226	0.73 (0.52-0.87)	0.99 (0.90-1.00)	0.27 (0.14-0.53)	0.99 (0.90-1.00)
Combine	106	0.67 (0.53–0.79)	0.96 (0.86–0.99)	N/A	0.81 (0.73–0.87)
Subgroup analysis					
Chemo alone	365	0.69 (0.63-0.75)	1.00 (0.97-1.00)	0.35 (0.26-0.48)	0.90 (0.88-0.94)
Chemo radio-therapy	130	0.65 (0.50-0.78)	1.00 (0.96-1.00)	0.25 (0.06-1.02)	0.97 (0.95-0.98)

If negative Likelihood Ratio(LR-) is smaller: essentially a definite diagnosis when negative result. **Conclusion:** Endosonography with lymph node sampling is an accurate and safe technique for mediastinal restaging of lung cancer. For nondiagnostic results, a further more invasive approach should be thoroughly considered.

Keywords: EUS, Mediastinal restaging, EBUS

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MA13.07 DIAGNOSTIC YIELD OF N3 HILAR STAGING BY ENDOBRONCHIAL ULTRASONOGRAPHY (EBUS) IN LUNG CANCER

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Background: Systematic lung cancer staging with EBUS has proven to be equivalent to cervical mediastinoscopy. Nevertheless, in the daily practice it is common to explore and sample negative PET-CT hilar N3 lymph nodes (LN). This study aims to explore if there is enough evidence to support this clinical practice. **Method:** Retrospective study from our database including 1,013 explorations over the last 5 years. Including criteria were patients with lung cancer staged by PET-CT and EBUS-TBNA. Mediastinal and hilar N3 LN with a short axis ≥ 5 mm were sampled with a 21G needle and assessed by rapid on site evaluation (ROSE). A single nuclear medicine expert reviewed blindly all PET-CT scans and determined the SUVmax of every LN. Those that were ≥ 5 SUVmax by PET-CT and/or ≥ 10mm in short axis by EBUS were considered abnormal. **Result:** 87 patients were included, of which 87% were male with a mean age of 66 years (SD 12.6). The final histopathology diagnoses were adenocarcinoma (46%), squamous cell carcinoma (39%) and other histology (14%). EBUS-TBNA was performed 30 days (SD 16.9) after PET-CT. None of the 61 normal hilar and normal mediastinum N3 LN, and none of the 7 normal N3 hilar LN with abnormal mediastinal LN (3 by PET-CT, 3 by EBUS and 1 for both) resulted positive for lung cancer. Of the 19 patients with abnormal N3 hilar LN (6 by PET-CT, 8 by EBUS and 6 for both) malignancy was found in 16.7% , 25% and 60% for both techniques, respectively.

Mediastinum		Hiliar		Positive N3 hiliar	Sample	%
EBUS	PET-CT	EBUS	PET-CT			
-	-	-	-	0	61	0
>10mm	-	-	-	0	3	0
-	>5 SUVmax	-	-	0	3	0
>10mm	>5 SUVmax	-	-	0	1	0
+/-	+/-	>5 SUVmax	-	1	6	16,7
+/-	+/-	----------	>10mm	2	8	25
+/-	+/-	>10mm	>5 SUVmax	3	5	60

Conclusion: In absence of abnormal N3 hilar LN (PET: SUVmax<5; EBUS<10mm in short axis) it seems there is not enough evidence to sample them, regardless of N3 mediastinal status.

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MA13.09 ELECTROMAGNETIC NAVIGATION BRONCHOSCOPY AS AN INTEGRATED APPROACH TO AID IN DIAGNOSIS AND TREATMENT OF PULMONARY LESIONS

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Background: Electromagnetic navigation bronchoscopy (ENB) is an image-guided localization approach to guide endoscopic tools to lung targets. In a single procedure, ENB aids in localizing lung lesions for biopsy or molecular profiling, fiducial placement for stereotactic body radiation therapy (SBRT), or dye marking for surgical resection. The

multidisciplinary utility of ENB in a large, prospective, multicenter study is unknown. **Method:** NAVIGATE (clinicaltrials.gov, NCT02410837) is a prospective, multicenter, observational cohort study of ENB using the superDimension™ navigation system. From April 2015 to August 2016, 1,215 consecutive subjects were enrolled at 29 United States sites. Two-year follow-up is ongoing. A prespecified 1-year interim analysis is presented. **Result:** ENB was used to aid in lung lesion biopsy (n=1157 subjects), fiducial placement (n=258), pleural dye marking (n=23), and/or lymph node biopsy (n=30). EBUS-guided lymph node staging was conducted in the same procedure in 448 subjects. The median lesion-to-pleura distance was 9mm. The median lesion size was 20mm; most were in the middle (30%) and peripheral (67%) thirds of the lung. Pathology results were malignant in 44.3% (484/1092) (54.1% Stage I, 11.1% Stage II, 17.0% Stage III, 17.7% Stage IV). Molecular testing was attempted in 30.7% (80/261) of adenocarcinoma or NSCLC-not-otherwise-specified cases overall and 57.9% (33/57) of Stage IIIB/IV cases. Tissue was adequate in 87.5% (70/80) of cases. EGFR mutations (14.7%) and ALK translocations (4%) were the most frequently observed genetic alterations. The ENB procedure was well-tolerated; 2.9% of subjects had procedure-related pneumothorax requiring hospitalization or intervention, lower than published rates for CT-guided core biopsy (25%) and CT-guided fine needle aspiration (19%). Subject-reported impact of ENB on daily activities was 0.9 out of 10 (0 = no impact). **Conclusion:** In the largest prospective, multicenter study to date, ENB aided in lesion biopsy in the middle and periphery of the lung and tissue collection for molecular testing, with a very low morbidity. ENB facilitates a multidimensional approach to lung biopsy and mediastinal/hilar staging, offering the opportunity for multiple sites/tissues to be safely sampled in one anesthetic event.

Keywords: fiducial and pleural dye marking, Electromagnetic Navigation Bronchoscopy, molecular profiling

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MA13.10 COMPARISON OF PULMONARY NODULE LOCATION BETWEEN PREPROCEDURAL CT AND INTRA-PROCEDURAL CONE-BEAM CT DURING GUIDED BRONCHOSCOPY

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Background: Electromagnetic navigation bronchoscopy relies on pre-procedural CT scans to create a virtual airway reconstruction that is used as a roadmap during bronchoscopy. These systems assume similarity between the position of the nodule during bronchoscopy and the pre-procedure CT scan. However, there are multiple factors that suggest that such assumption maybe inaccurate. These include differences in positioning, breathing motion, and the presence of atelectasis. In this study, we evaluated the lung nodule position between pre-procedural CT to interprocedural cone-beam CT (CBCT). In addition, we assessed the ability of a novel augmented endobronchial fluoroscopic guidance system (LungVision, Body Vision Medical Ltd, Israel) to overcome those differences in real-time. **Method:** This was a prospective study of 21 patients with 23 peripheral pulmonary nodules. CT scans were imported into the planning software and the physician identified the nodule and navigation pathway. CBCT (Philips Allura Xper FD20) was used to scan the patient during the procedure. LungVision was used for real-time navigation and guidance during biopsy. The divergence in nodule location between the pre-procedural CT and the interprocedural CBCT was measured. **Result:** The average patient age was 69 ± 8.6, median nodule size was 18mm with 74% of the nodules in the upper lobes. The average divergence of the nodule was 14.11 ± 9.9mm. Successful navigation was verified by CBCT in 91% of cases. Malignancy was diagnosed in 20 of 23 nodules for a diagnostic yield of 87%. No adverse events were reported. **Conclusion:** This study demonstrates a significant divergence in lesion location between pre-procedural CT and intra-procedural CBCT during guided bronchoscopy. This finding indicates that the change in nodule position between the CT and bronchoscopy could have a great impact on the diagnostic success of the procedure. This movement, sometimes greater than the size of the nodule itself, can lead to an inaccurate localization when relying solely on virtual bronchoscopic or electromagnetic navigation. CT to patient divergence does not appear to influence the accuracy of this novel navigation platform. The system is capable of tracking the nodules dynamically and can compensate for changes in patient positioning and respiratory motion during both navigation and biopsy which leads to a high diagnostic yield.

Keywords: CT-to-body divergance, augmented fluoroscopy, navigation bronchoscopy

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MA13.11 PHOTODYNAMIC THERAPY FOR PERIPHERAL-TYPE LUNG CANCER IN A MULTI-CENTER CLINICAL TRIAL

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Background: Photodynanic therapy (PDT), is a treatment modality for many cancers, and uses a tumor-specific photosensitizer and laser irradiation. Recently, we have developed a new minimally invasive laser device using a 1.0 mm in diameter composite-type optical fiberscope (COF), which could transmit laser energy and images for observation in parallel.In this study, we aimed to develop a new endobronchial treatment for peripheral cancer using PDT and a COF, and we evaluated the feasibility of PDT using COF for peripheral lung cancer. **Method:** This phase I study enrolled 3 patients with peripheral lung cancers (primary tumor< 20 mm, stage IA), which were definitively diagnosed by bronchoscopic modalities such as EBUS-GS and brocnhoscopic navigation system. We conducted irradiation using a diode laser (664 nm) and a COF 4 hours after the administration of NPe6 40 mg/m^2. We evaluated the tumor lesions using EBUS, and then we introduced the COF into the peripheral lung cancer, and irradiated of red light 664 nm (120 mW, 50 J/cm^2 or 100J/cm2). **Result:** We performed PDT for 3 patients with c-stage IA peripheral lung cancer, using a laser dose (120mW, 50J/cm2), and confirmed the feasibility of the dose. We escalated the laser dose and performed 4 patients using a laser dose (120mW, 100J/cm2). Seven patients met our criteria, and 5 cases were adenocarcinoma and 2 case squamous cell carcinoma. We were able to observe the cancer lesions at the peripheral lung by the COF, and feasibly irradiated. Two weeks and 3 months after NPe6-PDT, complications such as pneumonia and pneumothorax were not found, but one mildly found light skin-photosensitivity. Six months later, we found CR in 3 cases and SD in 4 cases. **Conclusion:** The 1.0 mm COF was a very useful device of NPe6-PDT for peripheral lung cancers, and PDT was a feasible and non-invasive treatment for a peripheral type early lung cancer. In the future, for non-invasive adenocarcinoma such as AIS, NPe6-PDT will become a treatment modality.

Keywords: photodynamic therapy, lung cancer

MA14 SURVIVORSHIP, SOCIOECONOMIC AND END-OF-LIFE CONSIDERATIONS
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MA14.01 LIFE SUSTAINING PROCEDURES, PALLIATIVE CARE AND HOSPITAL COST TRENDS IN DYING LUNG CANCER PATIENTS IN U.S. HOSPITALS: 2005-2014

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Background: Little is known about the extent to which dying patients with lung cancer receive life-sustaining treatments and palliative care services at the end-of-life in U.S. hospitals. We examine hospital cost trends and the impact of palliative care utilization on the use of life-sustaining procedures in this population. **Method:** Retrospective nationwide cohort analysiswas performed using National Inpatient Sample (NIS) data from 2005 and 2014. We examined the receipt of both palliative care and life-sustaining procedures, defined as systemic procedures, local procedures, or surgeries using the International Classification of Diseases, 9th revision (ICD-9-CM). **Result:** Figure 1. We used compound annual growth rates (CAGR) to determine temporal trends and multilevel multivariate regressions to identify factors associated with hospital cost. Among 77,394,755 hospitalizations, 120,144 patients were examined. During 10 years, the CAGR of hospital cost was 7.05% (p<.0001). In contrast, the CAGR of hospital lengths of stay was -3.77% (p<.0001). The CAGRs of palliative care was over ten percentage (13.30 %, p<.0001). However, the CAGRs of systemic procedures, local procedures, and surgeries were less than around one percentage (-1.13%, -1.07% and 1.42%, each p<.0001). Systemic procedures, local procedures and surgeries were associated with increased hospital cost and lengths of stay by 50.6%, 74.4%, 68.5%, and 7.4%, 50.6%, 4.6% respectively (each p<.001). Palliative care was associated with decreased hospital cost and length of stay by 28.6% and 4.6% (each, p<.001).

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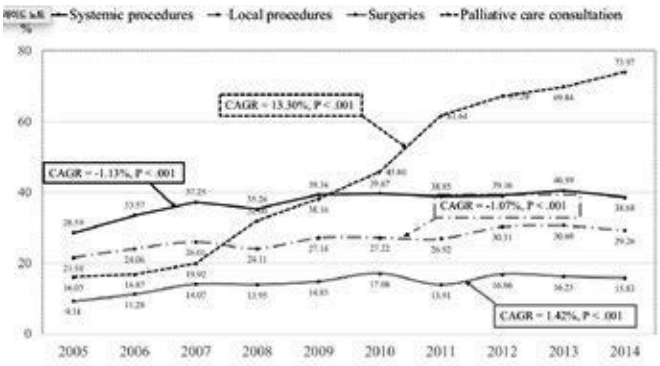

Conclusion: The volume of life-sustaining treatments is the biggest driver of cost increase although there is a cost-saving effect from greater palliative care utilization at the end-of-life in dying lung cancer patients.

Keywords: lung cancer, hospital cost, palliative care

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MA14.02 USE AND IMPACT OF A SYSTEMATIC ADVANCED CARE PLANNING IN HOSPITALIZED LUNG CANCER PATIENTS: A PROSPECTIVE STUDY.

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Background: End-of-life communication is crucial, particularly for cancer patients. In usual practice, advanced care planning discussions with the patients are uncommon and rarely documented. The aim of this study was to investigate the impact of advanced care planning on intensity of care in cases of organ failure in lung cancer patients. **Method:** This prospective study was performed at the Grenoble University Hospital in France. Consecutive patients hospitalized in thoracic oncology unit between 01/28/2014 and 03/31/2016 were included and followed up to 12/31/2016. At each hospital admission, lung cancer patients benefited from advanced care planning. We defined 3 intensities of care: intensive care, maximal medical care and exclusive palliative care. The propositions of care could be modified during the hospitalization. Patients' wishes should be received. **Result:** Data of 715 hospitalizations corresponding to 473 patients were studied. Hundred fifty nine patients had a second hospitalization and 69 a third. At first admission, 247 (52%) patients had a performance status of 0 to 2, 186 (39%) were not yet treated for the cancer and 165 (35%) in progression. Main reasons of admission were an acute disease (n=208, 44%) and supportive care of cancer symptoms (n=167, 35%). During the three first admissions, 173 (25%) patients developed an organ failure. Among them, 56 (32%) had intensive care proposition, 104 (61%) maximal medical care, and 13 (7%) exclusive palliative care. Median time between admission and organ failure was 9 days [IQR 25%-75%, 3-13]. All patients benefited from intensity of care equal or lower than the proposed intensity of care. Among patients planed for intensive care, 17 (30%) patients received intensive care, 22 (39%) maximal medical care and 17 (30%) exclusive palliative care. Thirteen of the 39 patients not admitted in ICU despite organ failure and previous proposition of intensive care were considered too well by the oncologist. Patients' wishes were recorded for 158 (91%) patients, and a discussion about end of life conditions was led with 116 (73%) patients or families. **Conclusion:** In case of organ failure, an advanced care planning appears helpful to provide reasonable intensity of care. The proposition of care seems to be adapted to the patient's general condition and cancer characteristics. 3/4 of the patients with an organ failure benefited from a discussion about end of life conditions. ClinicalTrials.gov Identifier: NCT02852629 Funding from the publicly funded nonprofit organization *Cancéropole Lyon Auvergne Rhône-Alpes* (CLARA).

Keywords: advanced care planning, end of life conditions, lung cancer

MA14 SURVIVORSHIP, SOCIOECONOMIC AND END-OF-LIFE CONSIDERATIONS
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MA14.03 AGGRESSIVENESS OF CARES ON THE MONTH BEFORE DEATH OF PATIENTS WITH LUNG CANCER: A FRENCH NATIONAL DATABASE SURVEY

O. Bylicki[1], C. Tournier[2], F. Canoui-Poitrine[3], C. Blein[2], C. Chouaid[4]

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Background: Prior studies have demonstrated that high-intensity end of life (EOL) cares improves neither survival nor quality of life for cancer patients. The National Quality Forum endorses markers of poor EOL care for cancer patients but there is little data's concerning lung cancer patients (1). The aim of this study was to assess, the quality of management during the last month of life of lung cancer patients managed in France and factors associated EOL aggressiveness. **Method:** Using a French hospital discharge database (PMSI, Programme de Médicalisation des Systèmes d'Information), all patients with lung cancer who died between January 1, 2010 and December 31, 2011 (cohort 1) and between January 1, 2015 and December 31, 2016 (cohort 2) were identified through the International Classification of Diseases 10th version (ICD-10). Aggressiveness of EOL cares was assessed by the following criteria's 1) chemotherapy administrated within last 14 days of life (DOL); 2) > 1 hospitalization within 30 DOL; 3) ICU admission within 30 DOL; and 4) Palliative care < 3 days before death. Multivariate analysis was performed to identify individual determinants EOL aggressiveness. **Result:** A total of 90,827 incident adult patients were identified (cohort 1: 43,862, cohort 2: 46,965): men: 74%, median age: 67 years], metastatic at diagnosis: 70%; 57% have at least one marker of aggressiveness of EOL cares (repeated hospitalizations: 49%, ICU admissions: 12%, chemotherapy within 14 DOL: 9%, palliative care < 3 days before death: 5%). A significant increase was observed between 2010/2011 and 2015/2016 for repeated hospitalizations (48% vs 51%, p<.001) and ICU admissions (11% vs 13%, p<.001); the two other markers have remained stable. In multivariate analysis of cohort 2, the risk of aggressiveness of care in EOL was increased by the presence of COPD (OR: 1.08, 95%CI: 1.02-1.14) and a management in an anti-cancer center (OR: 2.32,95%CI 2.05-2.61) while advanced age (OR: 0.51, 95%CI 0.47-0.55), female sex (OR: 0.86 95%CI: 0.82-0.90), malnutrition (OR: 0.72, 95%CI:0.68-0.76) were protective factors for EOL aggressiveness of cares. **Conclusion:** Despite growing focus on providing appropriate EOL cares, in this analysis 57% of deceased lung cancer patients in France received aggressive EOL cares. Research must be undertaken to better identify patients at risk of aggressive EOL cares and to improve the quality of cares of last days of life these patients. 1.McNiff KK, . Measuring supportive care in medical oncology practice: lessons learned from the quality oncology practice initiative. JCO 2008;

Keywords: Non-Small-Cell-Lung-Cancer, Aggressiveness of End-of-Life, Population Based-Study

MA14 SURVIVORSHIP, SOCIOECONOMIC AND END-OF-LIFE CONSIDERATIONS
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MA14.05 SOCIAL ISOLATION INCREASES PSYCHOLOGICAL DISTRESS IN PATIENTS WITH NSCLC

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Background: The Psychosocial Screen for Cancer (PSSCAN-R) questionnaire is a validated screening tool used to identify the psychosocial needs of patients with cancer. The questionnaire assesses patients' perceived social supports and identifies patients at risk for developing psychological distress. The study goal was to examine patients with NSCLC who reported risk factors for social isolation and their risk for developing psychological distress. **Method:** All patients with NSCLC referred to BC Cancer from 2011-2015 who completed a prospective PSSCAN-R questionnaire at the time of first visit were included in the study. Perceived social support questions include: if patients live alone, lost a life partner recently, have no help with IADLs, have no regular contact with friends and family or have no emotional support from others. Demographics were collected retrospectively. Chi-squared test and logistical regression were used to compare patient groups based on age, gender and perceived social support factors. **Result:** The study cohort was comprised of 4428 patients who completed the PSSCAN-R questionnaire. Female 50%, patients ≥65 years 69%, live alone 29%, lost life partner 13%, no help with IADLs 9%, no regular contact 3% and no emotional support 5%.

	MODERATE TO SEVERE ANXIETY				MODERATE TO SEVERE DEPRESSION			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
<65 years vs. ≥65 years	1.74 (1.52-1.98)	<0.01	1.69 (1.47-1.95)	<0.01	1.57 (1.37-1.81)	<0.01	1.57 (1.36-1.81)	<0.01
Female vs. Male	1.52 (1.34-1.72)	<0.01	1.57 (1.38-1.79)	<0.01	1.45 (1.28-1.66)	<0.01	1.38 (1.20-1.58)	<0.01
Live Alone vs. Live With Someone	0.85 (0.74-0.97)	0.02	0.76 (0.65-0.89)	<0.01	1.19 (1.03-1.37)	0.02	0.98 (0.83-1.16)	0.81
Lost Life Partner vs. Have Life Partner	0.95 (0.80-1.15)	0.62	1.10 (0.89-1.34)	0.38	1.30 (1.08-1.57)	0.01	1.37 (1.11-1.69)	<0.01
No Help vs. Receives Help With IADLs	1.23 (1.0-1.51)	0.05	1.24 (0.97-1.58)	0.09	1.69 (1.37-2.08)	<0.01	1.43 (1.12-1.69)	<0.01
No Emotional Support vs. Have Emotional Support	1.30 (0.97-1.73)	0.08	1.09 (0.78-1.53)	0.62	1.86 (1.40-2.49)	<0.01	1.31 (0.93-1.84)	0.13
No Regular Contact vs. Have Regular Contact With Friends or Family	1.53 (1.09-2.14)	0.01	1.22 (0.83-1.79)	0.32	2.27 (1.63-3.16)	<0.01	1.60 (1.09-2.35)	0.02

Conclusion: Female patients and patients younger than 65 are more at risk for developing moderate to severe anxiety and depression. Lack of perceived social support also contributes to the risk of developing psychological distress. In addition to developing gender and age-based resources for patients addressing their psychosocial needs, greater efforts in assessing patients' perceived social supports and allocating community and institutional resources to isolated patients should also become an important part of the patients' comprehensive and holistic care.

Keywords: distress, Social Isolation, NSCLC

MA14 SURVIVORSHIP, SOCIOECONOMIC AND END-OF-LIFE CONSIDERATIONS
TUESDAY, SEPTEMBER 25, 2018 - 10:30-12:00

MA14.06 PREDICTORS OF FINANCIAL TOXICITY, AN UNDER-RECOGNIZED PATIENT-REPORTED OUTCOME

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Background: In contemporary cancer care, financial distress has been established as a clinically relevant patient-reported outcome (PRO) associated with worse mortality and quality of life, but remains under-recognized by health care providers. Our goal was to define predictors of patient financial toxicity (FT) in a public healthcare system. **Method:** Patients with advanced lung cancer were recruited from outpatient clinics at the Princess Margaret Cancer Centre (Toronto, Canada). FT was measured with the validated Comprehensive Score for Financial Toxicity (COST) instrument, an 11-item survey scored from 0-44 with lower scores reflecting worse financial well-being. Data on patient and treatment characteristics, total out-of-pocket costs (OOP) and extended insurance coverage (EIC) were collected. Associations between variables and COST score were evaluated using multivariable regression analyses. **Result:** Of 249 patients approached, 200 (80%) participated. Median age of the cohort was 65 years; 44% were male, 36% immigrants, 67% employed or on pension, with median OOP between $1000-5000 CAD. Median COST score was 21 (range 0-44). FT was associated with age, with patients <65 years reporting greater FT than older patients (COST 18 vs. 25; P<0.0001). Employed patients or those receiving pension income reported less FT than unemployed patients (22 vs. 19; P=0.01). Less FT occurred in patients with EIC compared to those without (23 vs. 19; P=0.03). Patients with higher OOP reported more FT (P<0.0001). Patients on clinical trials reported less FT than others (25 vs. 20; P=0.04). In multivariable linear regression, younger age was a predictor of higher FT, when adjusting for income, employment status, OOP and EIC (P<0.0001). **Conclusion:** Age is a predictor of FT in the Canadian (Ontario) public healthcare system, with younger lung cancer patients reporting greater financial distress. This study highlights priority patient populations where FT should be routinely assessed and appropriate resources for support offered.

Keywords: patient-reported outcome, financial toxicity

MA14 SURVIVORSHIP, SOCIOECONOMIC AND END-OF-LIFE CONSIDERATIONS
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MA14.07 THE IMPACT OF SOCIOECONOMIC STATUS AND GEOGRAPHIC LOCATION ON PALLIATIVE CHEMOTHERAPY UPTAKE IN PATIENTS WITH METASTATIC NSCLC

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Background: Socioeconomic status (SES) and geographic factors may impact patient treatment choices. Canada has a publically funded health care system and in BC, there are 35 community oncology network sites that delivery treatment in patients' local communities. We studied the impact between SES and geographic location upon delivery of chemotherapy/survival in metastatic NSCLC. **Method:** All patients with metastatic NSCLC referred to BC Cancer centres from 2011-2015, who completed a prospective Canadian Problem Checklist questionnaire at the time of their first visit and for which chemotherapy data was available were included in the study. The CPC assesses patient distress in 6 domains including practical aspects of cancer care. The Postal Code Conversion File Plus uses data from Statistics Canada 2011 census to determine population size and income quintiles. Baseline characteristics and chemotherapy treatments were collected retrospectively. Univariate analysis using the Chi-squared test and Fisher's exact test were used for analysis. **Result:** 1113 patients were included with median age of 69 years, 54% female and 77% were former/current smoker and 47% received palliative chemotherapy. Uptake of chemotherapy did not differ between lowest + mid-lowest 44%, middle 51% /mid-highest + highest 49% income quintiles (p=0.18). Chemotherapy use was also similar between patients reporting financial concerns 50% versus none 47% (p=0.51). Uptake of chemotherapy was lower in patients who lived in rural communities population<10 37% (P 0.00), 10K-1.5M 41%, >1.5 million 53% (p<0.001). Chemotherapy use was lower for patients with concerns about getting to appointments (39% vs 49%, p=0.008) or accommodations (33% vs 48%, p=0.012). **Conclusion:** This dataset provide evidence that patients from rural communities were less likely to receive palliative chemotherapy treatment for metastatic NSCLC in BC despite the availability of multiple local community oncology services. SES did not appear to impact the proportion of patients treated, congruent with a government funded health care system. An in depth assessment of distances to local cancer services and treatment delivery is warranted to investigate these differences and their effect on mortality.

Keywords: socioeconomic, geographic, non-small cell lung cancer

MA14.09 MORTALITY OF LUNG CANCER AS A SECOND PRIMARY MALIGNANCY AMONG CANCER SURVIVORS: A STUDY OF SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS DATABASE

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Background: Cancer survivors are at increased risk of developing a second primary malignancy, including lung cancer. However, the prognosis of lung cancer as a second primary malignancy (lung-2) remains largely unknown. **Method:** Primary lung cancer patients diagnosed from 1988 to 2014 in the SEER program were included. Lung-2 was ascertained by a previous diagnosis of primary malignancy in SEER. Hazard ratios (HRs) of overall and lung cancer specific mortality were estimated among patients with lung-2 compared to lung-1. **Result:** 679,541(88.8%) and 85,758 (11.2%) patients were identified as lung-1 and lung-2, respectively. The median time from first primary malignancy to lung-2 diagnosis was 4.8 years. Compared to lung-1, patients with lung-2 were more likely to be diagnosed at localized stage, with smaller primary tumor, and treated with surgery. Lung-2 patients were at lower risk of lung cancer specific mortality in the first five years (HR 0.77, 95% CI 0.76 - 0.78 at < 1 year; HR 0.87, 95% CI 0.86 - 0.89 from 1 to < 5 years) but at higher risk thereafter. Patients with lung-2 were associated with reduced risk of overall mortality during the first year after diagnosis (HR 0.91, 95% CI 0.91 - 0.92), but with significantly increased risks thereafter.

Table Hazard ratios (HRs) of overall and lung cancer specific mortality among patients with lung-2

	N (%) of patients	From 0 to <1 year after diagnosis		From 1 year to < 5 years after diagnosis		From 5 years to 10 years of follow-up after diagnosis	
		N (IR)	HR (95% CI) *	N (IR)	HR (95% CI)*	N (IR)	HR (95% CI)*
Overall mortality							
First primary lung cancer	**679,541**	**383,208 (99.9)**	**1.00**	**135,513 (29.3)**	**1.00**	**16,821 (9.8)**	**1.00**
Second primary lung cancer	**85,758**	**44,288 (84.1)**	**0.91 (0.91-0.92)**	**20,073 (29.4)**	**1.10 (1.08-1.12)**	**3,133 (14.6)**	**1.32 (1.27-1.37)**
Lung cancer specific mortality							
First primary lung cancer	**679,541**	**325,633 (84.9)**	**1.00**	**111,348 (24.1)**	**1.00**	**8,147 (4.7)**	**1.00**
Second primary lung cancer	**85,758**	**31,247 (59.3)**	**0.77 (0.76-0.78)**	**12,485 (18.3)**	**0.87 (0.86-0.89)**	**1,158 (5.4)**	**1.10 (1.03-1.17)**

N, number of deaths; IR, incidence rate per 100 person-years * HR was adjusted for age and calendar period at diagnosis, sex, race, cohabitation status, percentile of cost of living and high-school education in county of residence, tumor stage, histology, tumor grade, surgery, radiation therapy, and chemotherapy. **Conclusion:** Lung-2 is associated with favorable lung cancer specific and overall survival within early period of diagnosis. Inferior overall survival afterwards cannot be attributed to aggressiveness of lung-2, highlighting the importance of managing first malignancy and comorbidities.

Keywords: mortality, Lung cancer as a second primary malignancy

MA14.10 QTC INTERVAL-PROLONGING MEDICATIONS IN LUNG CANCER: IMPLICATIONS FOR CLINICAL TRIAL ELIGIBILITY AND ROUTINE CLINICAL CARE

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Background: Concomitant medication use, including agents that prolong the QTc interval, may exclude cancer patients from clinical trials. To estimate potential impact on accrual, we determined the prevalence of QTc-prolonging medication prescriptions in a national patient cohort. **Method:** We identified adult patients in the United States Veterans' Affairs system diagnosed with lung cancer 2003-2016. QTc-interval prolonging medications and risk category were obtained from CredibleMeds®. We calculated prevalence of prescriptions for QTc-prolonging medications with known or possible risk of torsades de pointes (the most common criteria employed as trial exclusion criteria) in the 3 months up to and including date of cancer diagnosis. Rates across patient groups and time periods were compared using Chi-square test. **Result:** 280,068 patients were included in the study. Mean age was 70 years, 98% were male, and 72% were white. Overall, 29.7% were prescribed a QTc-prolonging medication. Patients receiving QTc-prolonging medications were marginally younger (mean age 68.9 years versus 70.9 years; $P<0.001$) and more likely to be black (14.1% versus 11%; $P<0.001$). The most commonly prescribed QTc-prolonging medications were antimicrobials (14.0%), psychiatric agents (10.2%), antiemetics (2.6%), and cardiovascular medications (1.7%). Seven percent of patients were prescribed two or more QTc-prolonging medications. Over the period of study, the rate of QTc-prolonging medication use increased 20% (25% in 2004 versus 31% in 2016; $P<0.001$). **Conclusion:** A substantial and growing proportion of individuals with lung cancer are prescribed QTc-prolonging medications. These prescriptions may limit eligibility for clinical trials and complicate the administration of standard cancer therapies. Given the prevalence of chronic and/or multiple QTc-prolonging medication prescriptions, it may be challenging to address this obstacle to trial enrollment simply through prescription substitution or discontinuation. Further research into the actual clinical risks and optimal management of QTc-prolonging medications in cancer populations is warranted.

Keywords: eligibility criteria, medications, clinical trials

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MA14.11 FACTORS ASSOCIATED WITH EARLY MORTALITY IN NON-SMALL CELL LUNG CANCER PATIENTS FOLLOWING SYSTEMIC ANTI-CANCER TREATMENT

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Background: To determine a 30-day mortality rate benchmark and assess factors associated with early mortality of non-small cell lung cancer (NSCLC) patients following receipt of systemic anti-cancer therapies (SACT). **Method:** In a 10-year population-based analysis, NSCLC patients receiving SACT in 2005-2014, with or without other treatments, and captured in the Glans-Look Lung Cancer Database, which contains demographic, clinical, pathological, treatment and outcome data were reviewed. 30-day mortality after most recent SACT cycle was calculated, and end-of life (EOL) regimen changes in the last 14 days of life were identified. Univariate analysis and multivariable logistic regression were used to identify demographic, tumor or treatment-related factors that correlated with mortality risk. **Result:** 1044 eligible NSCLC patients receiving at least one cycle of SACT in 2005-2014 were identified. 51% were female, 62% adenocarcinoma, 79% current/former smokers, 83% advanced stage at diagnosis, and 77% receiving palliative-intent treatment. 233 (22.3%) deaths occurred ≤ 30 days following SACT receipt, and 32 (13.7%) EOL regimen changes identified. Risk of early mortality decreased for never-smokers and those receiving SACT between 2010-2014, and increased in association with male gender, advanced disease at diagnosis, palliative-intent treatment, and use of EGFR-targeting agents. No factors were associated with a decreased risk of EOL regimen change. (Table 1). The predominant SACT-modality among those experiencing 30-day mortality was EGFR-targeting agents (54%).

	Early Mortality			EOL Regimen Change		
	Odds Ratio	95% Confidence Interval	p-value	Odds Ratio	95% Confidence Interval	p-value
Male	1.48	1.12-1.95	0.006*	1.84	1.16-2.92	0.010*
Advanced Disease at Diagnosis	1.85	1.19-2.88	0.006*	3.40	1.21-9.60	0.021*
Use of EGFR-targeting Agent	4.50	3.27-6.18	<0.001*	1.81	1.10-2.98	0.020*
Palliative-intent Treatment	6.75	3.88-11.77	<0.001*	4.43	1.67-11.74	0.003*
Never Smoker	0.62	0.41-0.95	0.028*	0.77	0.36-1.63	0.495
SACT Receipt in 2010-2014	0.65	0.49-0.96	0.002*	0.97	0.61-1.53	0.893
* denotes significance at $\alpha = 0.05$						

Conclusion: Our findings from a real-world population identify several factors which affect the risk of early mortality in NSCLC patients following SACT, and establish a 30-day mortality benchmark for Canadian NSCLC populations. Evolving SACT modalities may facilitate an increased use of SACT at EOL and associated early mortality; however, in this cohort, decreased early mortality risk in the 2010-2014 timeframe suggests concomitant evolution of decisions regarding EOL SACT and/or palliative and EOL care may be underway at our centre, but represents an area for ongoing investigation.

Keywords: Systemic anti-cancer therapy, 30-day mortality benchmark, early mortality risk

MA15.01 STRONG PD-L1 EXPRESSION PREDICTS POOR RESPONSE AND DE NOVO RESISTANCE TO EGFR TKIS AMONG NON-SMALL CELL LUNG CANCER PATIENTS WITH EGFR MUTATION

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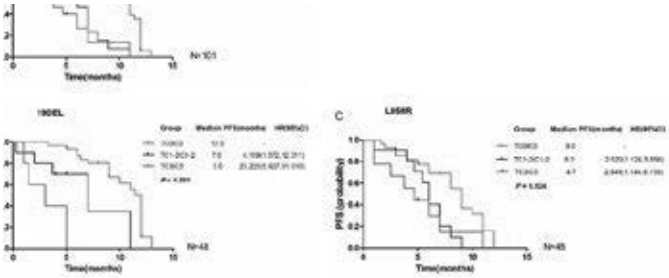
Background: This study evaluated whether tumor expression of programmed death-ligand 1 (PD-L1) predicted the response of EGFR-mutated non-small cell lung cancer (NSCLC) to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). **Method:** We retrospectively evaluated patients who received EGFR-TKIs for advanced NSCLC between April 2016 and September 2017 at the Guangdong Lung Cancer Institute. None of them were enrolled in clinical studies, and their *EGFR* and PD-L1 statuses were simultaneously evaluated. **Result:** Among the 101 eligible patients, strong PD-L1 expression significantly decreased the objective response rate (ORR) compared with those with weak or negative PD-L1 expression (35.7% *vs* 63.2% *vs* 67.3%, *P*=0.002) as well as shortened progression-free survival (PFS, 3.8months *vs* 6.0months *vs* 9.5months, *P*<0.001), regardless of *EGFR* mutation types (19del or L858R). Furthermore, positive PD-L1 expression was predominantly observed among patients with *de novo* resistance rather than acquired resistance to EGFR-TKIs (66.7% vs 30.2%, P=0.009). Notably, patients with *de novo* resistance had a high proportion of dual positive for PD-L1 and CD8 (46.7%, 7/15). Finally, one patient with *de novo* resistance to EGFR-TKIs and dual positivity for PD-L1 and CD8 experienced a favorable response to anti-PD-1 therapy.



1. Kaplan Meier survival curves of associations between PD-L1 expression and progression survival in non-small cell lung cancer patients with (A). overall population ; (B). 19 tion and (C). L858R mutation. The PD-L1 expression was divided into three groups: /IC3, TC1-2/IC1-2, and TC0/IC0.

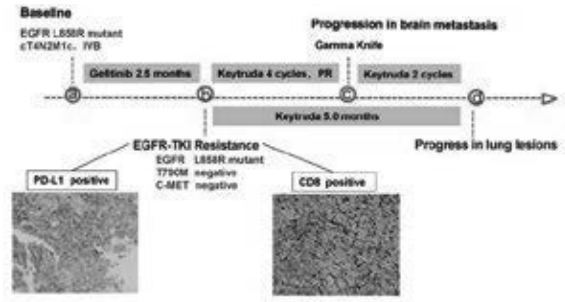


Figure 2. Case presentation.

Conclusion: This study uncovered the adverse impact of PD-L1 expression on the efficacy of EGFR- TKIs, especially in those with *de novo* resistance NSCLC, which inclined to reshape an inflamed immune phenotype of dual positive for PD-L1 and CD8 and showed potential therapeutic sensitivity to PD-1 blockade.

Keywords: de novo resistance, EGFR, PD-L1

MA15 COLLIDING APPROACHES - EGFR AND IMMUNOTHERAPY
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MA15.02 LONG-TERM SAFETY AND CLINICAL ACTIVITY RESULTS FROM A PHASE IB STUDY OF ERLOTINIB PLUS ATEZOLIZUMAB IN ADVANCED NSCLC

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Background: Patients with *EGFR* mutation–positive non-small cell lung cancer (NSCLC) achieve favorable outcomes with EGFR tyrosine kinase inhibitors (TKIs); however, the long-term efficacy of these agents is limited by development of acquired resistance. Atezolizumab (anti–PD-L1 mAb) monotherapy has shown tolerability and durable clinical activity in NSCLC. By selectively targeting PD-L1 to block its interaction with receptors PD-1 and B7.1, atezolizumab can reinvigorate anti-cancer T-cell activity. Thus, combining atezolizumab and erlotinib could result in improved anti-tumor immunity and durable anti-tumor effects. Safety and preliminary clinical activity from a Phase Ib study of erlotinib plus atezolizumab in locally advanced or metastatic NSCLC have been previously reported (Rudin, et al. WCLC 2016). Here we describe updated findings from this study (NCT02013219). **Method:** EGFR TKI-naive patients with NSCLC were enrolled into a safety-evaluation stage (Stage 1) regardless of *EGFR* status, and an expansion stage (Stage 2) enrolled patients with *EGFR*-mutant NSCLC who were previously untreated or treated with 1 prior non–EGFR TKI therapy. A 7-day run-in period with erlotinib 150 mg PO QD was followed by addition of atezolizumab 1200 mg IV q3w. The primary endpoint was safety/tolerability of the combination; secondary endpoints included clinical activity per RECIST v1.1. **Result:** At data cutoff (August 18, 2017), 28 patients (Stage 1, n = 8; Stage 2, n = 20) were evaluable for safety, and the median survival follow-up was 26.0 months (range, 7.8-32.9; Stage 2). The median age was 61 years (range, 47-84), and the most common *EGFR* mutation was exon 19 deletion (44%). Grade 3 treatment-related AEs (TRAEs) were reported in 43% of patients; no Grade 4 or 5 TRAEs occurred. The most common TRAEs were increased ALT, pyrexia, rash and diarrhea (2 patients each). Serious AEs occurred in 54% of patients; treatment-emergent AEs led to atezolizumab discontinuation in 18% and erlotinib discontinuation in 11%. Clinical activity was evaluated in Stage 2 patients. ORR was 75% (95% CI: 50.9, 91.3), with a median DOR of 16.7 months (range, 4.2-26.0+). Median PFS was 15.4 months (95% CI: 8.4, not estimable [NE]), and median OS was 32.7 months (95% CI: 32.7, NE). **Conclusion:** Atezolizumab plus erlotinib demonstrated a tolerable safety profile and compared favorably with prior reports of efficacy with erlotinib monotherapy. OS data are expected to mature and improve with longer follow-up; updated clinical and biomarker data will be presented. Further investigation of the combination is warranted to assess its full potential.

Keywords: atezolizumab, Erlotinib, NSCLC

MA15 COLLIDING APPROACHES - EGFR AND IMMUNOTHERAPY
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MA15.03 PD-L1 EXPRESSION IN UNTREATED EGFRM ADVANCED NSCLC AND RESPONSE TO OSIMERTINIB AND SOC EGFR-TKIS IN THE FLAURA TRIAL

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Background: In the Phase III FLAURA trial (NCT02296125), osimertinib significantly improved PFS relative to SoC EGFR-TKIs (gefitinib/erlotinib) in patients with untreated Ex19del/L858R positive (EGFRm) NSCLC. EGFRm NSCLC tumors can exhibit high PD-L1 expression, an important biomarker for immunotherapy treatment decisions. The frequency and clinical relevance of exhibiting both biomarkers prior to treatment are unclear. We report PD-L1 expression in patients with EGFRm advanced NSCLC and association with clinical outcomes following EGFR-TKI treatment. **Method:** Tissue samples from 994 patients with advanced NSCLC were screened for EGFR Ex19del/L858R mutations for enrolment in FLAURA; 556 were randomized to treatment. 197 tissue-blocks from the screened population (including EGFR mutation-positive and -negative samples) were tested for PD-L1 using the SP263 (Ventana) immunohistochemical assay; positive tumour cell (TC) staining PD-L1 TC≥25% and TC≥1% thresholds were applied. PFS was investigator-assessed, per RECIST 1.1, according to PD-L1-expressers (TC≥1%) or -negatives (TC<1%) in randomized patients. **Result:** 193/197 blocks had sufficient tumor tissue for staining. 65/193 patients were EGFR mutation-negative. 128/193 patients were EGFR mutation-positive: 106/128 were randomized to treatment (osimertinib: 54; SoC: 52). The table presents PD-L1 expression according to EGFR mutation status. For PD-L1-expressers (TC≥1%), median PFS was 18.4 months for osimertinib and 6.9 months for SoC (HR 0.30 [95% CI 0.15, 0.60]). For PD-L1-negative patients (TC<1%), median PFS was 18.9 months for osimertinib and 10.9 months for SoC (HR 0.37 [95% CI 0.17, 0.74]).

	PD-L1 TC≥1%, n (%)	PD-L1 TC≥25%, n (%)
EGFR mutation-negative (n=65)		
Screened population (n=65)	**44 (68)**	**23 (35)**
EGFR mutation-positive (n=128)		
Screened population (n=128)	**65 (51)**	**10 (8)**
Randomized to treatment (n=106)	**52 (49)**	**8 (8)**
Randomized to osimertinib (n=54)	**28 (52)**	**3 (6)**
Randomized to SoC EGFR-TKI (n=52)	**24 (46)**	**5 (10)**

Conclusion: There was PFS benefit with osimertinib versus SoC regardless of whether tumors were PD-L1-expressers (TC≥1%) or -negatives (TC<1%). Using the TC≥25% threshold, PD-L1 prevalence was lower in EGFR mutation-positive than mutation-negative samples; there were insufficient patients with TC≥25% tumors for PFS assessment. These results support the efficacy of EGFR-TKIs, including osimertinib, as first-line treatment of EGFRm advanced NSCLC, irrespective of PD-L1 expression.

MA15 COLLIDING APPROACHES - EGFR AND IMMUNOTHERAPY
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MA15.05 THE MUTATIONAL PROFILES OF EGFR 19 EXON DELETION AND 21 EXON L858R MUTATION AND THEIR ASSOCIATION WITH PRIMARY RESPONSE TO EGFR-TKIS

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Background: In addition to the known resistant genetic alterations, such as de novo T790M and TP53 mutations, some recent studies suggested that other concomitant mutations might also compromise the efficacy of EGFR-TKIs. Meanwhile, it has been widely observed that EGFR 19 exon deletion (19del) was associated with better outcomes in treatments with EGFR-TKIs than L858R mutation (L858R). It is of interest to explore whether the respective mutational profiles of 19del and L858R may explain their different sensitivity to EGFR-TKIs. **Method:** We obtained individual patient data from 7 studies (including 1 from our center) using next generation sequencing to comprehensively determine the mutational profile of EGFR mutated patients. As different panels were used by different studies, we analyzed T790M, TP53 and the loci that were reported by at least 4 studies (half of the included ones). **Result:** A total of 250 19del and 279 L858R patients were included. We found similar prevalence of all co-mutations (19del 65.2% vs. L858R 64.2%), TP53 (19del 36.8% vs. L858R 40.9%), APC, BRAF, PIK3CA, STK11, PDGFRA, PTEN, AKT1 and KIT between the two types, except for de novo T790M (19del 34.4% vs. L858R 50%, P=0.07), CDKN2A (19del 10.5% vs. L858R 3.4%, P=0.03) and KRAS (19del 0.5% vs. L858R 4.0%, P=0.01). In addition, the number of co-mutations was equivalent between the two types (19del 0.95±0.95 vs. L858R 0.93±0.90, P=1.00). Through multivariate logistic regression, we found that EGFR mutation type, de novo T790M, TP53 and other co-mutations, all had independent adverse effects on primary response rate. Consistently, we found that in those without co-mutations, 19del still showed better outcomes compared with L858R (pure EGFR mutations: 19del 88.0% vs. L858R 68.4%), and that the response rates in both mutation types decreased in the same extent when contaminated with other mutations (EGFR mutations with co-mutations: 19del 53.1% vs. L858R 30.0%). **Conclusion:** Our study demonstrated that the presence of T790M, TP53 and other concomitant mutations indicated poor response to EGFR-TKIs, but most of them showed similar prevalence between 19del and L858R. Patients with L858R showed significantly less response than those with 19del regardless of the co-mutation status, indicating that some intrinsic factors and potentially de novo T790M, rather than other co-mutations, might underlie the different sensitivity of 19del and L858R to EGFR-TKIs.

Keywords: EGFR 19 Exon Deletion, EGFR 21 Exon L858R Mutation, Concomitant Mutations

MA15 COLLIDING APPROACHES - EGFR AND IMMUNOTHERAPY
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MA15.06 CIRCULATING TUMOR DNA PORTRAYS THE RESISTANCE LANDSCAPE TO A NOVEL THIRD GENERATION EGFR INHIBITOR, AC0010

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Background: In a Phase I/II dose-escalation and expansion study conducted at Guangdong Lung Cancer Institute, AC0010 demonstrated promising efficacy and good tolerability in advanced NSCLC patients with EGFR *T790M*-mediated resistance to previous EGFR TKIs, (NCT02330367). As disease progression (PD) with EGFR *T790M*-directed therapy also emerges over time, we investigated the resistance mechanisms to AC0010 in this study. **Method:** Serial ctDNA samples obtained from patients who developed PD with AC0010 were analyzed using ultra-deep sequencing capturing 295 cancer-related genes. Alterations that were absent before treatment and acquired at PD or that increased in abundance during treatment were identified as putative resistance mechanisms. **Result:** Longitudinal plasma samples were obtained from 23 patients who progressed on AC0010 (data cut-off October 14, 2016; figure1). Putative resistance mechanisms to AC0010 were identified in 19/23 patients (>1 putative resistance mechanism was detected in some patients). *EGFR* amplification was the predominant resistance mechanism (21.1% [4/19 patients]), followed by *TP53* loss of heterozygosity (15.8% [3/19]). *EGFR C797S* mutation, *Met* amplification and mutations in the PI3KCA pathway each occurred in 10.5% of patients (2/19). SCLC transformation, *ERBB2* amplification, *CD79A*_A32G mutation, *CDKN2A*_R80 mutation, *CRLF2* amplification, *MLH1* amplification, *Rb1* loss, and concurrent rise in the allelic fraction of tumor suppressor gene *TP53* and *Rb1* were each detected in 5.3% of patients (1/19). In a patient with PD following single-agent AC0010 and *EGFR* amplification as the putative resistance mechanism to AC0010, subsequent treatment with AC0010 plus nimotuzumab (EGFR monoclonal antibody) successfully overcame resistance, resulting in a response that lasted for 7.7 months.

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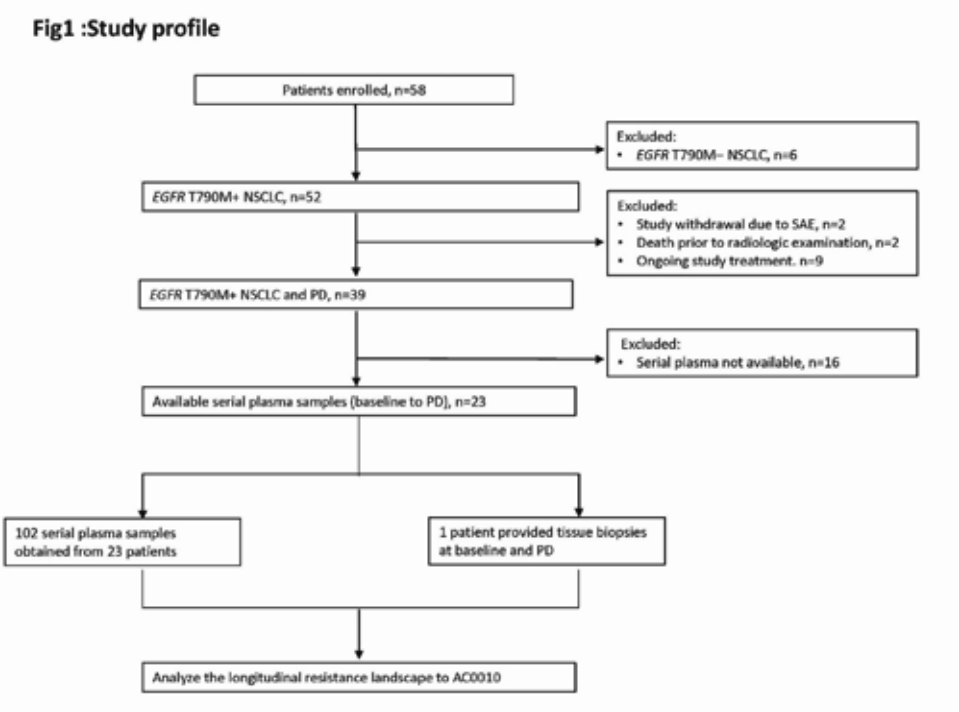

Conclusion: The resistance landscape to AC0010 appears to differ from that described previously with osimertinib. In this cohort of patients in China, *EGFR* amplification was the predominant resistance mechanism to AC0010 and could be potentially overcome by EGFR dual inhibition.

Keywords: Resistance, Circulating Tumor DNA, third generation EGFR inhibitor

MA15 COLLIDING APPROACHES - EGFR AND IMMUNOTHERAPY
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MA15.07 DIFFERENT RESPONSES TO OSIMERTINIB IN PRIMARY AND ACQUIRED EGFR T790M-MUTANT NSCLC PATIENTS

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Background: Primary EGFR T790M could be occasionally identified by routine molecular testing in tyrosine kinase inhibitor TKI-naive non-small cell lung cancer (NSCLC) patients. This study was aimed to compare clinical characteristics of primary and acquired T790M mutations and their responses to Osimertinib in NSCLC patients. **Method:** We collected clinical characteristics of patients diagnosed with epidermal growth factor receptor (EGFR) mutation from 2012 to 2017 in Shanghai Chest Hospital. For patients with primary and acquired T790M mutations, the responses to Osimertinib were analyzed. **Result:** Primary T790M was identified in 1.03% (61/5900) of TKI-naive patients. Acquired T790M was detected in 45.50% (96/211) of TKI-treated patients. T790M always coexisted with sensitizing EGFR mutations. Primary T790M was always coexisted with 21L858R (45/61) whereas acquired T790M was coexisted with 19del (61/96). Among them, 18 patients with primary T790M mutation acquired Osimertinib and 75 patients with acquired T790M mutation received Osimertinib. The median progression-free survival (mPFS) of Osimertinib in primary T790M group was greatly longer than that in acquired T790M group (18.0 months:95% CI:15.0-21.0 VS 10.0months:95% CI:8.3-11.7, P=0.016). The DCR of both groups were 89.3% and 100%. In primary T790M group, the mPFS of concomitant occurrence of 20 T790M and 21 L858R or 19del were 15.7m and 24.0 m, respectively. In acquired T790M group, the mPFS of concomitant occurrence of 20 T790M and 21 L858R or 19del were 11.0m and 10.0m, respectively. **Conclusion:** Primary and acquired T790M-mutation patients showed different molecular characteristics. Both of them may respond to Osimertinib. However, primary T790M patients showed greater survival benefits from Osimertinib than acquired T790M patients.

Keywords: EGFR T790M, osimertinib, NSCLC

MA15 COLLIDING APPROACHES - EGFR AND IMMUNOTHERAPY
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MA15.09 DYNAMIC MONITORING AND PREDICTIVE VALUE OF CIRCULATING TUMOR CELLS IN EGFR MUTANT ADVANCED NSCLC PATIENTS TREATED WITH FIRST-LINE EGFR-TKIS

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Background: We proposed a non-invasive, folate receptor (FR)-based circulating tumor cell (CTC) assay counts to predict and dynamically monitor the therapeutic response to first-line EGFR-TKIs in patients with EGFR-mutant non-small cell lung cancer (NSCLC). **Method:** Eligible patients were enrolled and three milliliter (mL) of blood were obtained prior to initial treatment, after one month, and follow-up every two months hereafter. CTCs were isolated based on negative enrichment by immunomagnetic beads and detected by a ligand-targeted polymerase chain reaction (LT-PCR) method. **Result:** 232 patients with EGFR mutations treated with first-line EGFR-TKIs were included. The objective response rate (ORR) of patients with low baseline CTC level (<20.5 FU/3 mL) were significantly higher than those with high baseline CTC level (≥20.5 FU/3 mL) (55.8% vs 38.5%, $P = 0.030$). Moreover, patients with low baseline CTC level had a markedly longer progression-free survival (PFS) than those with high baseline CTC level (HR = 0.50, $P < 0.001$). This difference remained significant after multivariate analysis ($P = 0.003$). Dynamic change of CTC value was significantly associated with partial response (PR) ($P = 0.042$) and stable disease (SD)/progression disease (PD) ($P = 0.032$). Of note, dynamic monitoring of CTC provided evidence of resistance to EGFR-TKIs before CT scanning, median: 113 days; range: 45 to 169 days.

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Table 1. Clinical and molecular characteristics of included patients.					
	CTC ≤ 20.5 (n = 165)	%	CTC > 20.5 (n = 52)	%	P value
Age, years					
Median	61		63		
Range	27-85		40-83		
Sex					
Male	79	47.88	28	53.85	0.453
Female	86	52.12	24	46.15	
Smoking status					
Never-smoker	122	73.94	35	67.31	0.351
Current/ever Smoker	43	26.06	17	32.69	
Pathological type					
ADC	150	90.91	47	90.38	0.909
ADS	4	2.42	1	1.92	
NOS	13	7.88	4	7.69	
Clinical stage					
IIIb	9	5.45	3	5.77	0.794
IV	156	94.55	49	94.23	
Distant metastases					
Brain	43	26.06	15	28.85	0.953
Bone	78	47.27	21	40.38	
Liver	10	6.06	1	1.92	
Other sites	109	66.06	34	65.38	
No metastases	12	7.27	3	5.77	
Mutation type					
19DEL	76	46.06	24	46.15	0.012
L858R	79	47.88	19	36.54	
Rare mutations	10	6.06	9	17.31	
Response rate					
Complete response	0	0.00	0	0.00	
Partial response	92	55.76	20	38.46	
Stable disease	48	29.09	21	40.38	
Progressive disease	25	151.50	11	21.15	
Disease control rate	140	84.85	41	78.85	0.310
Objective response rate	92	55.76	20	38.46	0.030
ADC, adenocarcinoma; ADS, adenosquamous carcinoma; CTC, circulating tumor cell.					

Conclusion: The current evidences suggest that FR-positive CTCs can be used for both the dynamic monitoring and prediction of outcome in EGFR-mutant NSCLC patients treated with EGFR-TKIs, which could serve as an alternative or supplement to CT scanning.

Keywords: Circulating tumor cell, non-small cell lung cancer, EGFR-TKI

MA15 COLLIDING APPROACHES - EGFR AND IMMUNOTHERAPY
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MA15.10 LOSS OF T790M MUTATION IS ASSOCIATED WITH EARLY PROGRESSION TO OSIMERTINIB IN CHINESE ADVANCED NSCLC PATIENTS HARBORING EGFR T790M

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Background: Osimertinib has demonstrated striking superior efficacy in non-small cell lung cancer (NSCLC) patients detected acuqired *T790M* mutation as resistant mechanism to upfront early-generation EGFR-TKIs. However, not all the T790M positive tumors are homogeneously sensitive to osimertinib, and the duration of response often varies. Previous studies suggest that loss of *T790M* mutation upon progression is related to decreased therapeutic benefit from osimertinib. The aim of this study is to investigate the association of T790M-mutant status and clinical outcomes after osimertinib treatment in Chinese NSCLC patients harboring acquired *EGFR T790M* mutation. **Method:** We reviewed the electric medical records of all patients receiving osimertinib monotherapy after detected acquired *T790M* mutation in rebiopsy after resistant to prior EGFR-TKIs, and underwent re-rebiopsy again upon progression to osimertinib at our hospital. Detailed clinicopathologic characteristics and response data were collected for all patients. **Result:** From January 2014 to December 2016, 230 patients were confirmed *T790M* mutation positive for acquired resistance to early-generation EGFR-TKIs (gefitinib, erlotinib, afatinib and icotinib). Among them, 90 patients received osimertinib monotherapy as subsequent treatment. Out of the patients, 84 (93.3%) were eligible for osimertinib-resistance analysis, and 31 (34.4%) patients underwent T790M detection in biopsy after disease progression to osimertinib. The most commonly used biopsy sample were tumor tissue, peripheral blood and hydrothorax. 16 patients remained *T790M* positive, while 15 patients lost *T790M* mutation in their re-rebiopsy samples. Loss of T790M upon progression was significantly associated with shorter duration of response to osimertinib (median time 5.93 vs 11.87 m, HR:0.325, 95%CI: 0.087 to 0.45, p=0.0005), while overall survival (OS) was not statistically different between T790M-loss and -remain groups. The objective response rates were also similar in two groups (85% and 100%, respectively). In multivariate analysis, T790M mutation loss remained significantly associated with early progression to osimertinib. **Conclusion:** Loss of *T790M* mutation was associated early progression to osimertinib in Chinese NSCLC patients harboring acquired T790M mutation. Dynamic detection during osimertinib treatment may be a potential strategy to timely reveal disease progression.

Keywords: EGFR T790M mutation, early progression to osimertinib, non-small cell lung cancer

MA15 COLLIDING APPROACHES - EGFR AND IMMUNOTHERAPY
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MA15.11 REAL WORLD BIOMARKER TESTING AND TREATMENT PATTERNS IN PATIENTS WITH ADVANCED NSCLC RECEIVING EGFR-TKIS

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Background: In patients who progress on treatment with first- or second-generation EGFR-TKIs, 50–60% will have an EGFR T790M resistance mutation. Osimertinib, a third-generation EGFR-TKI, is FDA approved for use in patients with metastatic EGFR T790M-positive NSCLC and disease progression on or after prior EGFR-TKI therapy, and recently gained additional approval for first-line treatment for patients with EGFR Ex19del/L858R positive advanced NSCLC. We sought to observe how many patients in the real world underwent biomarker testing on progression and subsequently received osimertinib, when T790M positive. **Method:** Flatiron Health EHR-derived database was used to identify adult patients with NSCLC treated with a first- or second-generation EGFR-TKI from 11/2015–09/2017, with the start of first EGFR-TKI defined as the index date. Patients were stratified by EGFR-TKI use as a first (1L) or later line (2L+) treatment. EGFRm status, including T790M testing and subsequent treatments received after initiating first- or second-generation EGFR-TKI, were described. Chart review was conducted on patients who received a subsequent therapy to confirm disease progression. **Result:** Patients in this study (n=782; 1L: n=435; 2L+: n=347) had a median age of 69 years, 64% were female, 56% were white, 87% were seen in the community, with a median follow-up of 307 days. During the study period, 30% (235/782; 1L: 96/435 [22%]; 2L+: 139/347 [40%]) of patients died without receiving a subsequent therapy, and 38% (294/782; 1L: 160/435 [37%]; 2L+: 134/347 [39%]) received subsequent therapies. From post-index date to initiation of subsequent therapies, 30% (88/294; 1L 63/160 [39%]; 2L+ 25/134 [19%]) of patients were tested for EGFR mutations including T790M. Among patients who received subsequent therapies, treatments included chemotherapies (1L=23%; 2L+=37%), immunotherapies (1L=16%; 2L+=43%), and targeted therapies (1L=64%; 2L+=30%). On progression, 25% (1L 40/160) and 5% (2L+ 7/134) of the patients received osimertinib. Of those tested for EGFR mutation post-index date (n=88), 28% (n=25) were positive for T790M and 96% of these (n=24) received osimertinib. Most patients (251/294 [85%]; 1L: 136/160 [85%]; 2L+: 115/134 [86%]) on subsequent therapies were confirmed to have disease progression at chart review. **Conclusion:** In this study, a third of patients were tested for subsequent EGFR mutations including EGFR T790M following treatment with first- or second-generation EGFR-TKI. Of these, a third were positive for T790M and nearly all of the T790M positive patients received osimertinib. These findings highlight low rates of biomarker testing at progression, and the need for optimal treatments that maximize benefits for patients with EGFRm NSCLC.

Keywords: NSCLC, biomarker testing, EGFR-TKI

MA16 NOVEL MECHANISMS FOR MOLECULAR PROFILING
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MA16.01 FREQUENCY AND GENOMIC CONTEXT OF EMERGING MARKERS FOR MOLECULAR TESTING IN LUNG ADENOCARCINOMA IN CELL-FREE DNA NGS ANALYSIS

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Background: The recently updated CAP/IASLC/AMP lung cancer molecular testing guideline (Lindeman et al 2018) recommends several genes be analyzed by next-generation sequencing (NGS) in lung adenocarcinoma (LUAD), including *EGFR, ALK, BRAF, KRAS,* and others. It also includes a list of 20 emerging markers (EMs) for molecular testing and suggests practitioners remain aware of these and other genes between guideline updates. We investigated the frequency of genomic alterations (GAs) in several of these EMs in a cohort of patients with advanced lung adenocarcinoma who underwent clinical cell-free DNA (cfDNA) NGS analysis and assessed co-occurrence with canonical driver GAs. **Method:** Genomic data was reviewed from 6530 patients with at least one GA detected on clinical Guardant360 cfDNA NGS testing (Guardant Health, Inc) with an indicated diagnosis of lung adenocarcinoma from 11/25/16-3/1/18. Synonymous alterations were excluded from further analyses. **Result:** 2600 patients (40%) had at least one nonsynonymous alteration in the EM genes assessed; excluding GAs classified as variants of unknown significance (VUS), 1350 patients (21%) had at least one characterized alteration. Table 1 shows number and frequency of GAs observed per patient by gene and alteration type. Of EMs assessed, GAs were observed most commonly in *NF1, PIK3CA, PDGFRA, KIT,* and *FGFR1-2.* GAs in multiple EMs, including *RIT1, NRAS, FGFR2-3, NTRK1, KIT,* and *AKT1,* were observed co-occurring with established driver alterations, often in a genomic context consistent with resistance to targeted therapy at allelic fractions suggestive of subclonality.

Table 1. Number (%) of patients with non-synonymous alterations observed, by gene and type, n=6530.

	All Alteration Types*	Missense	Nonsense	Splice	Indel	Copy Number Amplification	Fusion
AKT1	18 (0.28%)	10 (0.15%)	0 (0%)	8 (0.12%)	N/A	N/A	N/A
DDR2	96 (1.47%)	82 (1.26%)	11 (0.17%)	3 (0.05%)	N/A	N/A	N/A
FGFR1	235 (3.60%)	109 (1.67%)	4 (0.06%)	3 (0.05%)	N/A	125 (1.91%)	N/A
FGFR2	247 (3.78%)	202 (3.09%)	8 (0.12%)	16 (0.25%)	N/A	23 (0.35%)	1 (0.02%)
FGFR3	57 (0.87%)	43 (0.66%)	3 (0.05%)	6 (0.09%)	N/A	N/A	5 (0.08%)
KIT	318 (4.87%)	196 (3.00%)	6 (0.09%)	19 (0.29%)	13 (0.20%)	95 (11.45%)	N/A
MAP2K1	62 (0.95%)	61 (0.93%)	1 (0.02%)	0 (0%)	N/A	N/A	N/A
MTOR	246 (3.77%)	191 (2.92%)	16 (0.25%)	24 (0.37%)	18 (0.28%)	N/A	N/A
NF1	889 (13.61%)	457 (7.00%)	141 (2.16%)	116 (1.78%)	254 (3.89%)	N/A	N/A
NRAS	120 (1.84%)	254 (3.89%)	3 (0.05%)	1 (0.02%)	N/A	N/A	N/A
NTRK1	107 (1.64%)	89 (1.36%)	3 (0.05%)	13 (0.20%)	N/A	N/A	3 (0.05%)
NTRK3	101 (1.55%)	98 (1.50%)	1 (0.02%)	2 (0.03%)	N/A	N/A	N/A
PDGFRA	358 (5.48%)	191 (2.92%)	17 (0.26%)	27 (0.41%)	19 (0.29%)	113 (1.73%)	N/A
PIK3CA	650 (9.95%)	456 (6.98%)	15 (0.23%)	5 (0.08%)	N/A	215 (3.29%)	N/A
RIT1	34 (0.52%)	31 (0.47%)	2 (0.03%)	1 (0.02%)	N/A	N/A	N/A
TSC1	83 (1.27%)	43 (0.66%)	5 (0.08%)	0 (0%)	36 (0.55%)	N/A	N/A

N/A: not assessed by assay.
*May be less than sum of individual alteration types, as some patients had more than one type of alteration in the same gene.

Conclusion: Effective therapies are continually emerging for a growing number of molecular biomarkers in lung cancer. Comprehensive genomic profiling with cfDNA NGS can identify GAs in both recommended and EM genes to guide therapeutic decision-making and catalyze clinical trial enrollment. Further investigation of mutual exclusivity and co-occurrence of established drivers and EMs may reveal novel resistance mechanisms and facilitate identification of rational combination therapeutic strategies.

Keywords: emerging markers, cell-free DNA, next-generation sequencing

MA16 NOVEL MECHANISMS FOR MOLECULAR PROFILING
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MA16.02 PROSPECTIVE CLINICAL VALIDATION OF THE INVISIONFIRST™ CTDNA ASSAY FOR MOLECULAR PROFILING OF PATIENTS WITH ADVANCED NSCLC

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Background: Clinical practice guidelines advocate molecular profiling as a part of the evaluation of advanced NSCLC, with ctDNA based profiling being an option for those with insufficient tissue. Thorough prospective clinical validation studies of NGS based ctDNA assays are lacking. Here we report the multi-centered prospective clinical validation of a ctDNA NGS panel for stratification of patients with advanced untreated NSCLC. **Method:** InVisionFirst™ (Inivata) is a ctDNA NGS assay for detection of genomic alterations in 36 genes commonly mutated in NSCLC and other cancers. 264 patients with untreated advanced NSCLC were prospectively recruited by 41 US centers. 178 patients had tumour tissue available for molecular profiling (predominantly by NGS) and the remaining 86 patients without tissue were included to compare ctDNA profiles obtained from patients with and without tissue for profiling. **Result:** A total of 204 patients (77.3%) had detectable ctDNA alterations. Using tissue results as the reference, overall concordance for the full 36 genes in the InVisionFirst™ panel with matched tissue profiling was 97.8% with 82.9% PPV, 98.5% NPV, 70.6% sensitivity and 99.2% specificity. Considering a subgroup of 8 genes that can influence routine clinical patient management (EGFR, ALK, ROS1, ERBB2, MET, BRAF, KRAS, STK11) the PPV was 93.7%, 96.8% NPV, 72.4% sensitivity and 99.4% specificity. Excluding patients with undetectable ctDNA, these figures become 93.7% PPV, 98.4% NPV, 87.3% sensitivity and 99.3% specificity. The observed pattern of genomic changes seen in ctDNA was consistent across patients with and without tissue for profiling. Across the whole study, 44 patients with actionable alterations were identified by ctDNA testing compared to only 36 by tissue testing. 47% of patients tested by ctDNA had an actionable alteration or an alteration that is generally mutually exclusive for such actionable changes such as KRAS or STK11. **Conclusion:** The InVisionFirst™ assay demonstrates excellent concordance with tissue profiling in this multi-centered prospective clinical validation study. The performance of this assay in terms of overall sensitivity and specificity appears comparable if not higher than other established commercial ctDNA assays. Utilization of InVisionFirst™ ctDNA testing led to the detection of 22% more actionable alterations than standard of care tissue testing in this study supporting its use for the molecular stratification of patients with advanced NSCLC. Further analyses on the features associated with detectable ctDNA signatures are ongoing.

Keywords: NSCLC, ctDNA, InVisionFirst™

MA16 NOVEL MECHANISMS FOR MOLECULAR PROFILING
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MA16.04 CLINICAL AND MOLECULAR CHARACTERISTICS OF EGFR MUTANT LUNG CANCERS WITH CONCURRENT TP53 AND RB1 MUTATIONS.

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Background: 20% of patients with metastatic lung adenocarcinoma have activating *EGFR*-mutations. *EGFR*-mutant lung cancers can undergo histologic transformation to small cell lung cancer (SCLC) as a response to the selective pressure of EGFR-TKIs in <5% of patients after earlier-generation EGFR-TKIs and have been reported after osimertinib. SCLC nearly universally harbor *TP53*/RB1-alterations which are rarely seen in *EGFR*-mutant lung adenocarcinomas. We sought to identify this subset of patients, describe their clinical course and likelihood of SCLC transformation. **Method:** Retrospective review of targeted next generation sequencing (NGS, MSK-IMACT) at Memorial Sloan Kettering (MSK) was performed to identify patients with concurrent *EGFR*-activating mutations and *TP53*/*RB1*-mutations within the same tumor sample from NGS between April 2014 to February 2018 with a data cutoff of March 2018. For comparison, consecutive patients with lung cancers harboring *EGFR*-mutations who were EGFR-TKI naïve and *TP53*/*RB1*-wildtype were also collected during that time-period. **Result:** Of the 21% of lung cancer patients with activating *EGFR*-mutations (759/3662), 5% (40/759) had concurrent *TP53*/*RB1*-mutations. 43% (17/40) were female, 58% former-smokers (23/40, median pack-years: 8), and median age of 68 (range 25-86 years). 88% (35/40) were adenocarcinoma at diagnosis, of which 11% (4/35) transformed to SCLC during treatment; 10% (4/40) were de-novo SCLC at diagnosis, and 1 was large cell neuroendocrine. The transformation rate was significantly higher compared to previous work from MSK evaluating *EGFR*-mutant patients showing 4% (4/155) transformation (p=0.04). Concurrent *PIK3CA* mutations were more frequently seen in the *EGFR*/*TP53*/*RB1* mutant group compared to the *TP53*/*RB1*-wildtype group (17% (n=6/35) vs 7% (n=4/60), p=0.11). 20 patients were EGFR TKI-naïve at the time of NGS; the median time on EGFR-TKI (ToT) was 7.6 months versus 14.2 months in the *TP53*/*RB1*-wildtype group (HR 4.48, p=0.0003). The overall survival (OS) of this cohort versus *TP53*/*RB1*-wildtype was not different (4.3 vs 4.1 years, HR 1.35, p=0.51). In the 4 patients with SCLC transformation, the median time to transformation was 2.4 years after a median of 1.5 EGFR-TKI therapies (range 1-5 lines). Median OS from time of transformation was 7 months. 63% (25/40) of the *EGFR*/*TP53*/*RB1*-mutant cohort had brain metastases during their disease course as compared to 50% (n=30) in the *TP53*/*RB1*-wildtype group (p=0.30). **Conclusion:** SCLC transformation is enriched in *EGFR*/*TP53*/*RB1*-mutant lung cancers, occurring in 11% of patients. Once SCLC transformation occurs, overall survival is short. Patients with *EGFR*/*TP53*/*RB1* have a shorter time on EGFR-TKI. Further investigation into optimal treatment for this subset of *EGFR*/*TP53*/*RB1* mutant lung cancers is critical.

Keywords: Small cell lung cancer transformation, EGFR-mutant lung cancer, Lineage Plasticity

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TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MA16.05 MET KINASE DOMAIN REARRANGEMENTS (KDRE) IN NON-SMALL CELL LUNG CANCER (NSCLC) IDENTIFIED THROUGH COMPREHENSIVE GENOMIC PROFILING (CGP)

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Background: MET is a known oncogenic driver in NSCLC, and activation via various means including gene amplification, exon 14 skipping, and fusion has been reported to be targetable in the clinical setting. However, the prevalence and characteristics of NSCLCs harboring MET kinase fusions as well as diverse KDRE have not been comprehensively assessed. **Method:** Hybrid-capture based CGP was performed on 32,643 FFPE or 3,076 blood-based ctDNA NSCLC specimens during the course of clinical care. Tumor mutational burden (TMB) was determined on 0.83-1.1 megabases (Mb) of sequenced DNA and is reported as mutations/Mb. **Result:** In 35,719 unique NSCLC patient cases assayed, RE retaining the *MET* kinase domain were detected in 63 (0.2%) cases. These included *MET* fusions with an identified 5' fusion partner (n=8, 12.7%), probable *MET* fusions with an unidentified fusion partner (n=32, 50.8%), MET kinase domain duplications (KDD, n=7, 11.1%), *MET* exon 14 skipping rearrangements (n=6, 9.5%), and *MET* rearrangements of the 5' terminus (n=10, 15.9%). Fusion partners identified include *CAPZA2* (2 cases), *CAV2*, *CD47*, *INPPL1*, *LHFPL3*, *PRKAR2B* and *SPECC1*. MET kinase-inactivating rearrangements were also detected in the larger cohort (n=10, 0.03%). MET KDRE cases harbored at least one targetable NSCLC NCCN guidelines driver alteration in 27.0% (n=17) of cases including *EGFR* activating subs (L858R, L861Q) or exon 19 deletions (n=8), *MET* exon 14 skipping short variants (n=6), *ALK* fusions (n=2), and a BRAF V600E mutation. *KRAS* short variants were detected in 6 additional cases. *MET*

amplification also co-occurred in 36.5% of cases with MET KDRE (n=23, median copy number 16). The median TMB in cases with MET KDRE was 6.1 mut/Mb, as compared to a median of 7.0 mut/Mb for NSCLC samples overall. Clinical treatment information for a subset of cases will be presented, including paired cases in which the MET KDRE may represent an acquired mechanism of resistance to EGFR- or ALK-targeted therapy. **Conclusion:** Potentially targetable MET rearrangements retaining the kinase domain were observed in 0.2% of NSCLCs, which may be an underestimate considering that these assays sequence all *MET* exons, but do not specifically bait *MET* intronic breakpoints. These data suggest that MET KDRE, including, but not limited to fusions and KDD, may represent a distinct subset of driver alterations and potential resistance mechanisms. The value of testing for and potentially targeting these alterations as part of routine clinical care in NSCLC warrants further investigation.

Keywords: comprehensive genomic profiling, kinase rearrangement, MET

MA16 NOVEL MECHANISMS FOR MOLECULAR PROFILING
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MA16.06 EGFR CLONALITY AND TUMOR MUTATION BURDEN (TMB) BY CIRCULATING TUMOR DNA (CTDNA) SEQUENCING IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: TKI has significantly improved survival time of NSCLC pts with sensitive mutation. However, pts present different outcome while receiving TKI treatment. We conduct a prospective multicenter clinical trial to determine whether clonality of sensitive mutation is related to the efficacy of TKI. We also evaluate the consistency of TMB between tissue and blood in this cohort. **Method:** Paired tumor and plasma samples at diagnosis were obtained from systemic treatment naïve pts with advanced NSCLC. DNA was sequenced by target-capture deep sequencing of 1021 previously annotated genes related to solid tumors. Clonal *EGFR* mutation was defined if EGFR mutation was in the cluster with the highest mean variated allele frequency with PyClone, and otherwise subclonal *EGFR* mutation. TMB of tissue (tTMB) and blood (bTMB) analysis interrogated single nucleotide variants, small insertion and deletion, with VAF ≥3 % and ≥0.5 %, respectively. TMB-high pts were identified with ≥9 mut/MB (upper quartile of data from geneplus). **Result:** During February 2017 to April 2018, 127 advanced NSCLC pts were enrolled from 9 centers. A total of 653 somatic variations were detected in tissues. Mutations occurred most frequently in *EGFR* (57 %), *TP53* (54 %), *KRAS* (9 %), *ALK* (8 %). In matched plasma, 405 (62 %) tumor-derived mutations were detected by pan-caner panel sequencing. A total of 90 *EGFR* mutations were detected in 73 pts, most of which occurred in tyrosine kinase domain (L858R, 41%; Ex19del, 33%). Most *EGFR* mutation were clonal in tissue and plasma, with a consistence of 83 % in paired samples. In addition, bTMB was significantly correlated to tTMB (Pearson r= 0.85, p-value= 1.8e-30), with a consistence of 89 %. Interestingly, high TMB was observed in a small fraction of patients (8 %) with driver mutations, such as mutations in *EGFR*, *ALK* fusion, *ERBB2* and *PIK3CA*. **Conclusion:** Deep sequencing with the pan-cancer panel can effectively detect mutations and evaluate TMB in both tissue and blood with high consistence. *EGFR* mutations can be clonal or subclonal in both tissue and blood. Prospective multicenter study is ongoing to determine the *EGFR* clonality as a predictive factor for the TKI efficacy in NSCLC (TRACELib-NSCLC, NCT03059641).

Keywords: TMB, advance NSCLC, ctDNA sequencing

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MA16.08 CLINICAL UTILITY OF DETECTING ROS1 GENETIC ALTERATIONS IN PLASMA

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Background: ROS1-rearranged lung cancer harbors an oncogenic fusion protein created by the juxtaposition of the *ROS1* gene to various fusion partners. Due to the lack of a conserved breakpoint and inclusion of intronic segments, *ROS1* rearrangements can be challenging to identify with DNA-based sequencing approaches. The feasibility and clinical utility of detecting *ROS1* fusions in circulating tumor DNA is not well established. **Method:** The Guardant360 de-identified database was queried to identify lung cancer cases with plasma *ROS1* fusions and describe the molecular features of the ROS1-rearranged cohort. In addition, we performed longitudinal analysis of plasma specimens from four patients at our institution who were treated with next-generation ROS1 inhibitors after progressing on crizotinib. **Result:** From review of 24,009 plasma specimens from lung cancer patients, we identified 56 patients with *ROS1* fusions. *CD74* was the most common of 7 identified fusion partners [n=35 (62%) CD74, n=7 (12.5%) SDC4, n=7 (12.5%) EZR, n=3 (5%) TPM3, n=2 (4%) TFG, and n=1 (2%) each of CCDC6 and SLC34A2]. *ROS1* fusions commonly co-occurred with *TP53* mutations (n=36, 64%) and genes involved in cell-cycle regulation (n=11, 20%) or the WNT/ß-catenin pathway (n=16, 29%). In 4 (80%) of 5 cases where plasma genotyping occurred at crizotinib progression, we identified a putative resistance mechanism, including a *ROS1* resistance mutation in 3 patients (n=2 G2032R & n=1 L2026M) and a *BRAF* V600E mutation in 1 patient. We analyzed longitudinal plasma specimens from 4 patients with crizotinib-resistant lung cancer who were subsequently treated with a next-generation ROS1 inhibitor (n=3 lorlatinib, n=1 entrectinib). One patient treated with lorlatinib had a pretreatment *ROS1* G2032R mutation (in plasma and tissue); plasma analysis revealed stability of the G2032R allelic fraction in the setting of primary progression of pleural disease. Of the 2 patients without pretreatment *ROS1* mutations who received lorlatinib, one developed a *ROS1* G2032R mutation after initial response to treatment. The second patient experienced primary progression and plasma genotyping revealed low level *FGFR1* copy number gain (3.3 copies); pre-crizotinib plasma was not available for comparison. One patient had a plasma *PIK3CA* E545K mutation at the time of crizotinib progression, and did not respond to next-line entrectinib. **Conclusion:** Next-generation sequencing can be used to detect *ROS1* fusions and resistance mutations in plasma. Longitudinal plasma analysis may provide insight into the activity of investigational drugs against *ROS1* mutations that mediate resistance to crizotinib.

Keywords: ROS1, crizotinib, liquid biopsy

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MA16.09 FEASIBILITY, CLINICAL RELEVANCE OF ALK/ROS1 FUSION VARIANT DETECTION BY LIQUID BIOPSY IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Liquid biopsy offers an alternative non-invasive approach to reflect the tumor genomic landscape of NSCLC patients; however, the potential of liquid biopsies for *ALK/ROS1* fusion detection is poorly described. Herein, we evaluated an amplicon-based NGS assay for ctDNA detection of *ALK* and *ROS1* fusions in a large cohort of *ALK* and *ROS1* NSCLC patients and correlation of variants with clinical data.

Method: *ALK*- and *ROS1*-translocated advanced NSCLC patients, were prospectively enrolled from October 2015 to April 2018 in 9 French institutions. ALK or ROS1 positivity was as confirmed by immunochemistry and FISH or RNAseq. *ALK* (*EML4* variants v1, v2, v3), *ROS1* (*CD74, SLC34A2, SDC4 and EZR)* fusions, and mutations in a panel of 36 NSCLC-associated genes were investigated in ctDNA using InVisionFirst™ (Plagnol V PLoS ONE, 2018). **Result:** A total of 120 patients were included: 96 ALK and 24 ROS1. 30 samples were collected from patients who were TKI-treatment-naive, 257 during follow-up and 73 at progressive disease (PD) under TKI. The median age was 55 years-old (range 23-75); most patients were female (57%) and had a non-smoking history (59%). At diagnosis, 20% of patients presented with brain metastasis. All patients received at least 1 ALK-TKI (median: 1.6; range:1-6). Preliminary results are available for the first 54 patients: 21 at diagnosis and 33 at PD under TKI. *ALK/ROS1* fusions were detected in 13/21 patients (62%) at diagnosis: 12/20 *ALK*-fusions (7 v1, 2 v2 and 3 v3) and in 1/1 *ROS1*-fusion (*CD74-ROS1*). No fusion was detected in 8 patients, which may be due to partner genes or variants not covered by this panel. However, 5 of these 8 patients had exclusive thoracic or brain PD. Liquid biopsies collected at the radiographic evaluation under therapy revealed complete ctDNA clearance of the fusion when patients experienced PR (n=4). In samples at PD, fusion was detected in 44% of patients (24/55) with evidence of acquired resistance in patients both positive and negative for fusion. Results for the remaining samples, correlation between fusion variant and survival, fusion variant and mechanism of resistance will be presented at the Congress. **Conclusion:** Our results suggest that ctDNA profiling is a promising non-invasive tool for identification of *ALK/ROS1* fusions and monitoring of response in advanced NSCLC patients. Systematic identification of the fusion partner may help to better understand the heterogeneity and evolution (sensitivity profile to targeted inhibitors and associated-mechanisms of resistance) of NSCLC driven by ALK and ROS1 rearrangement.

Keywords: Fusion variant, ALK/ROS1-rearrangement, ctDNA

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MA16.10 CLINICAL UTILITY OF CEREBROSPINAL FLUID CELL-FREE DNA FOR CLARIFYING GENETIC FEATURES OF LEPTOMENINGEAL METASTASES IN ALK REARRANGEMENT NSCLC

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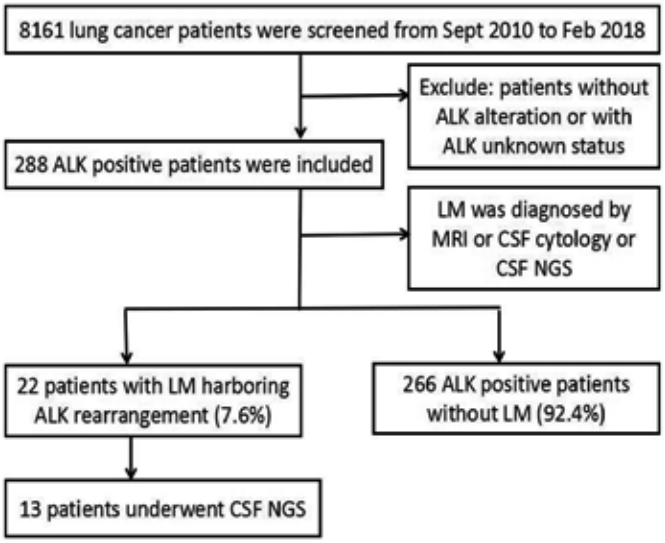
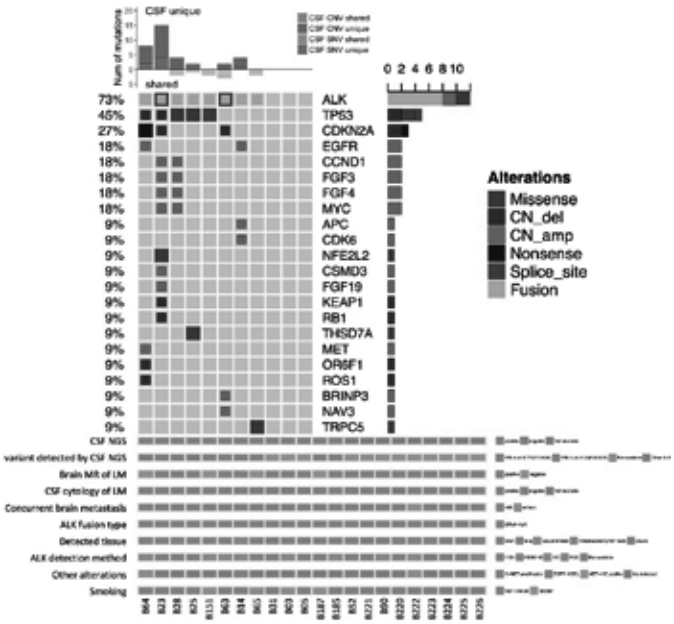
Background: Leptomeningeal metastases (LM) were associated with a poor prognosis in non small cell lung cancer (NSCLC). LM were much more frequent in *EGFR* mutant patients, and cerebrospinal fluid (CSF) cell-free DNA (cfDNA) has shown unique genetic profiles of LM in patients harboring *EGFR* mutations in our previous studies. However, studies in *ALK* positive NSCLC patients with LM are scarce. **Method:** Lung cancer patients with *ALK* rearrangement were screened from Sept 2011 to Feb 2018 at our institute. Leptomeningeal metastases were diagnosed by MRI or CSF cytology or next-generation sequencing (NGS) of CSF cfDNAs. Paired plasma were also tested by NGS. **Result:** LM were diagnosed in 22 (7.6%) of 288 *ALK* rearrangement patients with lung cancer. A total of 11 ALK positive patients with LM were enrolled with CSF cfDNA tested by NGS (one case used CSF precipitates instead of CSF cfDNA). Paired plasma were available in 11 patients. Driver genes were detected in 75.0% CSF samples and 45.5% plasma respectively (P=0.214). Max allele fractions were higher in CSF cfDNA than in plasma (40.8% versus 0%, P=0.021). *ALK* variant 1 (E13:A20) was detected in 3 cases of CSF and paired plasma, respectively. *ALK* variant 2 (E20:A20) was identified in 5 cases of CSF and 1 paired plasma. Multiple copy number variants (CNV) were mainly found in CSF cfDNA, including EGFR copy number gains. Resistance mutations including gatekeeper gene *ALK* G1202R was identified in CSF cfDNA with *ALK* variant 1 and *ALK* G1269A was detected in plasma. The detection rate of TP53 was 45.4% versus 27.3% in CSF cfDNA and plasma.





Conclusion: CSF cfDNA was more sensitive than plasma to reveal genetic features of ALK-fusion LM, confirming its role as a liquid biopsy medium for LM in driver gene positive NSCLC.

Keywords: Leptomeningeal metastases, non small cell lung cancer, Cerebrospinal fluid

MA17.01 A SENSE OF UNDERSTANDING AND BELONGING WHEN LIFE IS AT STAKE – OPERABLE LUNG CANCER PATIENTS' LIVED EXPERIENCES OF PARTICIPATION IN EXERCISE

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Background: Exercise has been introduced to improve physical capacity and quality of life and to reduce symptoms and side effects of treatment in surgically treated non-small cell lung cancer (NSCLC) patients. The effects of an exercise programme for this patient group has been tested in a randomized controlled trial – the PROLUCA study. The questions though, of how patients experience participation in group-based exercise studies and the impact of the shared community with fellow patients has not been previously examined. The objective was to explore lived experiences and social benefits among patients with operable NSCLC who participated in an exercise programme (the PROLUCA study) post-surgery. **Method:** Nineteen patients enrolled in an exercise intervention two weeks post-surgery participated in qualitative interviews at three time points. A phenomenological hermeneutical approach comprised the epistemological stance and the methodological basis was Ricoeur's narrative philosophy. The goal of the analysis and interpretation was to provide descriptions that captured the meaning of the lived experiences of the patients. **Result:** Patients included in this qualitative study had a mean age of 63 years (range 48-75), 58% were female, and 68% was retired. Eighty-four percent had performance status 0 (WHO) and almost all patients were used to some kind of physical activity. The analysis revealed social benefits of taking part in the group-based exercise intervention. The patients experienced themselves as part of a community, and the physical exercise intervention was significant in terms of the patients' social capital. In this sense, patients gained access to resources that derived from human interaction in the exercise group, and their illness and treatment became easier to manage when shared with others in the same situation. The exercise intervention helped to create a community for patients after lung cancer surgery, and the patients experienced a feeling of belonging and equality with the other participants. **Conclusion:** The group based exercise intervention created opportunities for mutual understanding between patients, making illness and treatment easier to manage. The patients experienced support to gain renewed balance in life during the exercise intervention in the interaction with peers in the group. It is relevant to inform operable NSCLC patients about the potential community of understanding and belonging in group-based exercise interventions.

Keywords: NSCLC, Surgery, exercise

MA17.02 EARLY ACCRUAL TO A PRECISION LUNG CANCER SURVIVORSHIP INTERVENTION: THE KENTUCKY LEADS COLLABORATIVE LUNG CANCER SURVIVORSHIP CARE PROGRAM

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Background: Recent advances in early detection and treatment of lung cancer have created a need for survivorship care interventions to reduce the psychosocial and symptom burden of lung cancer, but few interventions address the unique experience of lung cancer survivors and their caregivers. Leveraging shared decision making and motivational interviewing, the Kentucky LEADS Collaborative developed a precision psychosocial intervention addressing the unique experiences and challenges of individuals diagnosed with lung cancer and their caregivers. This sub-study describes the demographic, diagnostic, and psychosocial characteristics of the initial participants in the Kentucky LEADS Collaborative Lung Cancer Survivorship Care Program. **Method:** Participants include 61 lung cancer survivors across 9 lung cancer care sites in Kentucky, USA. Data were drawn from baseline surveys of demographic characteristics, disease/treatment information, symptom burden, psychosocial functioning and quality of life administered to lung cancer survivors and caregivers enrolled in the single-arm intervention trial. **Result:** Of the first 61 LC survivors enrolled, 32 had a caregiver join them as participants in the intervention (53%). Participants had a mean age of 62 years. Approximately 20% of LC survivors did not have a caregiver available to participate, and 27% declined to invite a caregiver join the program. Most participating caregivers were spouses (63%), but siblings (10%) and children (19%) were also included. Most survivors were female (66%), Caucasian (97%), and covered by health insurance (95%), and 59% were married or living in a committed relationship. Most participants had been diagnosed with non-small cell lung cancer (84%) and late-stage disease (IIIB-IV; 53%). Most participants had a history of smoking (95%); 30% had smoked within the past 30 days, and 29% were current smokers. Among current smokers, participants reported very high levels of quit planning (9.*23*±*2.77*) and quitting confidence (9.*14*±*2.89)*. Finally, approximately 55% reported clinically significant distress, with a mean level of distress of 3.98 (2.99) on a scale from 0-10. **Conclusion:** Early accrual to the trial has exceeded expectations. Most survivors had advanced disease and reported significant distress. A substantial minority continued to use tobacco. Data suggest that modifications made to the survivorship approach emphasizing empathy and patient preference may help improve intervention acceptability and feasibility. Subsequent analyses will evaluate the impact of the intervention on quality of life, psychosocial functioning, and symptom burden. Data will also be collected regarding acceptability of the intervention and potential program changes to optimize benefits.

Keywords: survivorship, behavioral oncology, quality of life

MA17.03 SHARED DECISION-MAKING FOR PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Lung cancer is the leading cause of cancer-related death in the world and more than half of the patients have metastatic disease at the time of diagnosis. Although, treatment options are developing rapidly, most patients are facing a poor prognosis. The role of 3rd or 4th line treatment with chemotherapy remains controversial with sparse evidence of efficacy. Therefore, the patient's preferences become central. Shared decision-making enables the patients to be actively involved in choosing the treatment option that best reflects both medical evidence and individual preferences. This study examines how patients with lung cancer and their relatives are empowered and supported when they have to make informed choices regarding 3rd or 4th line of treatment. The aim was to develop a model for shared decision-making and to test decision aid tools that enable a collaborative process that takes into account the best available scientific evidence, as well as the patient's values and preferences. **Method:** Patients diagnosed with advanced non-small cell lung cancer, their relatives and the health care professionals were involved in the process that included: 1) Multidisciplinary workshops and workshops with patients and relatives, 2) Training course in communication on existential issues and shared decision-making for health care professionals, 3) Designing and testing five decision aid tools, 4) Creating a Podcast and 5) Evaluation by patient satisfaction surveys. **Result:** Three strategic focus areas were identified: 1) The meaningful service, 2) considerations in end-of-life care and 3) patient involvement in decision making. The patient reported quality of communication was increased during the study period. The patient satisfaction surveys (n=77 baseline) and (n=60 final evaluation) demonstrated statistical significant improvements from baseline to final evaluation in regard to:1) involving patients in the treatment decisions to the extent they prefer (Pearson Chi-Square, P=0.048) and 2) encouraging patients to ask questions (Pearson Chi-Square, P=0.008). The study improved the health care professionals understanding of the importance of incorporating patients in shared decision-making processes in clinical practice. However, some barriers for implementation were identified, such as changing established behaviour among health care professionals. **Conclusion:** The findings indicate that decision aid tools are useful and related to significant changes in patient experience of the quality of communication. We suggest investigating the feasibility and potential concerns of integrating these tools to a larger extend in clinical practice.

Keywords: Patient involvement, shared decision-making, Advanced Non-Small Cell Lung Cancer

MA17.05 DEVELOPMENT OF A TELEPHONE CLINIC FOR PATIENTS UNDERGOING LONG TERM FOLLOW-UP AFTER THORACIC SURGERY

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Background: Patients undergoing long term follow-up after lung cancer surgery in our institution follow an imaging based follow-up programme. Protocol led CT imaging followed by an out-patient appointment is undertaken every 6 months for two years after surgery then annually until year 5. Feedback from patients indicated they find two trips to the hospital burdensome and they frequently requested results of surveillance imaging over the telephone. Limited capacity in the thoracic surgery clinics led to long waits for an appointment to be informed of imaging results. To address these issues, we developed a model of nurse led telephone follow-up after surveillance imaging. **Method:** A proposal to hold one telephone clinic per week was made to commissioners in the autumn of 2016. Following approval, the telephone clinic commenced in April 2017. Patients are triaged by the specialist nurse when CT results are available and allocated to the telephone clinic if appropriate. They are given a timed appointment and the telephone number they will be contacted on is confirmed prior to the appointment. A database is completed during the appointment, a record of the consultation is made in both paper and electronic patient records and a letter is sent to the GP and other teams who have contact with the patient. Patients with significant abnormalities on CT imaging are referred for discussion by the multidisciplinary team and seen in a face to face clinic. **Result:** In the first twelve months (April 2017 to March 2018) there were 254 patient appointments in 51 telephone clinics. Average call length is 10 minutes with a range of 3 to 22 minutes. One patient scheduled for a telephone appointment was not contactable at the appointed time (0.4%). Satisfaction with the clinic is high with 98% of patients requesting their next follow-up appointment in the telephone clinic. Clinic capacity was increased at reduced cost to commissioners as a telemedicine appointment is charged at £25.34 compared to £70.16 for a face to face appointment. **Conclusion:** Early results suggest nurse led telephone clinics are an effective way of providing follow-up to patients on an imaging based follow-up programme after surgery. They are well received by patients. We aim to introduce an online tool to objectively assess symptoms in this patient group. Further evaluation of patient experience in this clinic would be beneficial, along with an evaluation of the impact of introduction of telephone follow-up on the rest of the service.

Keywords: Surgery, Follow-up, Nurse-led

MA17.06 THE SPECIALIST LUNG CANCER NURSE AND SELF-MANAGEMENT FOR PEOPLE LIVING WITH LUNG CANCER: A MODEL OF ENGAGEMENT

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Background: There is increasing evidence that patient self-management strategies, used as adjuncts to traditional pharmacological interventions, can improve symptom control for people living with lung cancer. While it is acknowledged that the specialist lung cancer nurse (SLCN) is well positioned in the multidisciplinary team to facilitate patient self-management education (PSME), limited guidance is available to SLCNs on this role. The aim of this study was to understand the knowledge and skills required of SLCNs to facilitate PSME and how such skills might best be developed. The intent was to develop a pedagogy that enhances SLCN-patient interactions so that patients can be better supported to make self-care decisions and to act on these decisions. **Method:** The epistemological lens of the study drew on the sociocultural works of Vygotsky and Leontiev. Fifteen participants were purposively recruited through the Australia and New Zealand Lung Cancer Nurses Forum. The sample comprised Australian registered nurses employed at the level of clinical nurse consultant. Eligibility for the study required participants have a minimum of 5 years lung cancer nursing experience. Of the sample, the average was 13 years' experience. Through individual, face to face interviews, a biographical approach to data collection focused on participants' work and non-work lives. The theoretically informed analysis generated understanding about the salient influences on SLCN learning and how and why these influences shaped PSME. **Result:** PSME is an inherently complex activity. Although seeking to facilitate patient learning to empower patients to self-manage, the SLCN experiences challenges in the contemporary health care environment. Entrenched power relations, professional boundaries, minimal practice guidelines and issues of resourcing of lung cancer and lung cancer nursing are key factors that shape PSME. A model of engagement was designed to reflect the pedagogy that underpins optimal interactions between SLCNs and patients. The model brings forth the socially situated contexts of the SLCN and patient as central to the interaction. A reflective mode of practice creates a teaching and learning environment inclusive of sociocultural and individual processes on learning and thus the mechanisms of co-constructing knowledge for the purpose of shaping patient behaviour. **Conclusion:** The study assumes the strategic importance of addressing how best the SLCN workforce can support people living with lung cancer to self-manage. A key strength of the research is the focus on understanding the individual and social interrelatedness of SLCN learning for the purpose of enhancing educational interactions in complex environments with people living with lung cancer.

Keywords: nurse education, patient self-management, nurse-patient interaction

MA17.07 NURSE-LED TELEHEALTH CLINIC IN TREATMENT MONITORING AND FOLLOW UP

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Background: A clinical consultation is usually physician led and traditionally carried out in a direct person-person interaction in an outpatient clinic. The alternative is replacing it through electronic means via telehealth. This has already been exploited as a phone consultation and is gaining momentum as a video based consultation although it has not been widely introduced into oncology. **Method:** The aim was to ascertain the acceptance of the video consulting technology in real clinical settings and the effectiveness of video consultation in replacing conventional consultation. Eligible patients who attended a pre-existing nurse led clinic completed a checklist to ensure access to appropriate IT equipment. Those able to participate were asked to replace two nurse led appointments with nurse led teleheath appointments using iKonsult video consultation platform. After each consultation a satisfaction questionnaire was completed. **Result:** Patients were recruited from a protocolised nurse led clinic for mutation driven NSCLC on oral tyrosine kinase inhibitors (TKI). 42 patients were approached over a three month period; only 6 agreed and were followed up via the telehealth platform. 4 patients considered it as a possibility, 4 did not feel confident and 3 did not have the correct equipment. The remaining patients cited numerous reasons for not taking up this service. In the satisfaction analysis of 17 initial telemedicine consultations 5/6 patients (81%) were very satisfied with telemedicine follow up. 4 patients (66%) found the platform extremely easy and 2 (34%) easy to use. **Conclusion:** On treatment monitoring of oral TKI therapy could be effectively carried out using video consultation platform reducing the number of hospital visits. The consultations provided necessary information and allowed for adequate clinical assessment. However the initial take up rate is low mostly due to patient reluctance rather than unavailable technology. The overall feedback from participants was very positive and accepting of the service. The iKonsult video consultation is being introduced into other oncology settings.

MA17.09 REMOTE SYMPTOM REPORTING FOR TELE-NURSING TEAM IN THORACIC ONCOLOGY CLINICS: ENVIRONMENTAL SCAN AND STAKEHOLDER ENGAGEMENT

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Background: 50+% of cancer-related toxicities are under-reported. A real-time Remote (i.e., at-home) Symptom Reporting (RSR) system could help patients seek help when symptoms exceed thresholds, mitigating unplanned clinic/emergency room visits. A RSR system for solid-tumor patients undergoing chemotherapy is associated with improved health-

related quality of life and survival (Basch et al, 2017). Adapting RSR into the thoracic cancer clinic environment requires assessments of potential implementation barriers, and tailoring of the RSR-system. **Method:** Over a five month period, we performed an environmental scan to determine readiness of RSR implementation in our comprehensive thoracic oncology outpatient clinic. A qualitative assessment of potential RSR integration into the telephone triage environment was performed through one-on-one interviews and focus groups, followed by thematic analysis. Discussions were held with multiple stakeholders; key implementation champions were identified. We utilized the Canadian Institutes of Health Research Knowledge-to-Action Framework, Steps 2-4 as our guide. **Result:** In the environmental scan, 125 telephone triage calls were logged over randomly-chosen days in a 6-week period. The mean ± SEM call duration was 5.4 ± 0.62 minutes. Mean time until response was 44.4 ± 3.8 minutes. Nurses spent on average 2.7 ± 0.2 minutes documenting into the electronic-patient-record. The mean duration from initial contact to completion was 24.1 ± 4.5 minutes. Resolution of the triage calls involved telephone advice alone (87%; n=109), unplanned clinic visits (6%; n=8), and emergency visits (6%; n=7). In the qualitative analyses, top stakeholder-identified issues were: lack of assessment standardization; wasted time transcribing paper triage notes to electronic records; and a high patient/family burden in terms on understanding when to seek help. There was universal interest in adopting a RSR system from administrative assistants, nursing administration, clinic nurses, physicians and trainees. Perceived benefits of RSR were: standardized, focused telephone assessments; tailored symptom assessments in the thoracic setting (i.e., dyspnea, coughing, hemoptysis); patient empowerment; and improved efficiency in patient contact, intra-team communication, and documentation. Key stakeholder RSR features were: a phone/web application that assesses symptom severity and indicates when to contact the triage team; one-touch feature to reach team; longitudinal symptom trend display for tele-nursing team; and embedding of the COSTaRS framework to facilitate tele-nursing interventions and documentation. **Conclusion:** Integration of a RSR system integration was perceived favorably by stakeholders to increase nursing efficiency and improve health related patient outcomes, but success hinges on an identified set of key requirements.

Keywords: Telenursing, triage, patient reported outcomes

MA17 NEW METHODS TO IMPROVE LUNG CANCER PATIENTS OUTCOMES
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MA17.10 THE USE OF TECHNOLOGY IN THE DELIVERY OF SUPPORTIVE CARE OF LUNG CANCER PATIENTS AFTER TREATMENT

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Background: The NHS Lanarkshire Lung Cancer Project is part of the Transforming Care after Treatment (TCAT) programme. During phase one 58 patients participated in the project. 88% of patients opted for a telephone consultation, which was more time effective taking only on average 20 minutes compared to 48 minutes for a face to face consultation. 90% of patients rated the service as excellent and a review of additional Patient Reported Outcome Measures demonstarted an improvement in overall quality of life. Further funding was secured as part of Phase 3 of the TCAT programme allowing for continued testing. **Method:** Between November 2017 – May 2018 lung cancer patients living in Lanarkshire were offered two monthly SPARC assessments on completion of treatment . This was followed up with and a telephone consultation from a lung cancer clinical nurse specialist, the provision of a personalised care plan and access to self-management information. The choice of an electronic or paper SPARC assessment was offered. To support the evaluation a Functional Assessment of Cancer Therapy – Lung (FACT-L), Memorial Symptoms Assessment Scale (MSAS) and Supportive Care Needs Survey Long-Form 59 (SCNS) were completed prior to their first and after their final assessment. A patient experience questionnaire was also provided on completion of their final assessment. **Result:** 24 patients participated in phase 3. 53% opted to complete their assessment electronically with 47% preferring the paper option. 15 patients (63%) completed both assessments resulting in a total of 582 concerns being identified. Data analysis of these patients shows a 27% reduction in concerns with the number of high concerns falling by 62% between the first and second assessment. The average length of time for telephone review remained similar phase one at 22 minutes ranging from 7 minutes to 55 minutes. Patient satisfaction in the project continued to be high with 82% rating the service as excellent and 18% as good. Data analysis for 15 patients' who had completed 2 FACT-L, MSAS and SCNS yielded a significant reduction in symptom burden and psychological distress with a significant improvement in quality of life. **Conclusion:** Findings from this project are encouraging that this model of working is not only acceptable to patients but time efficient and clinically effective. However, a limitation of this project is its small sample size. Therefore, further work is needed to explore its transferability and cost effectiveness to allow it to be considered for implementation in standard practice.

Keywords: Transforming Care After Treatment, Patient Reported Outcome Measures, Electronic Holistic Care Needs Assessment

MA17 NEW METHODS TO IMPROVE LUNG CANCER PATIENTS OUTCOMES
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MA17.11 MULTI-CENTRED, PROSPECTIVE, AUDIT TO IDENTIFY READMISSION CAUSES AND COMPLICATIONS WITHIN 30 OF PRIMARY LUNG CANCER SURGERY

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Background: Surgery remains the first choice of curative treatment, for patients with non-small lung cancer, the proportion of patients undergoing surgery has risen in recent years. Post-operative complications are well recognised following curative lung cancer surgery but there is limited data on readmission rates and causes . The UK Thoracic Surgery Group (TSG), a subgroup of the National Lung Cancer Forum (NLCNF) conducted a multicentre audit to assess readmission potential causes and patient experience. **Method:** The audit involved 6 UK thoracic surgical centres with prospective data collection over 3 months from primary lung cancer resection patients. Patients were contacted 1 month post discharge by telephone. Data collection included demographics, socioeconomic, smoking status, comorbidities, surgery, postoperative recovery, discharge satisfaction and readmission details. **Result:** 268 patients underwent thoracic surgery, the overall readmission rate was 11% (30), with variable readmission rate across the centres (range 3-24%), most readmission occurred within 7 days of discharge 47% (14) with patients being readmitted to a hospital that did not performed the procedure 43%(17). The most common cause of readmission was mainly pulmonary related with chest infections being largest cause, pain, wound infection and pneumothorax were also common. Length of stay following readmission was longer than initial surgical stay median 8 (range 0-94) vs 5 (range 2-27).Type of surgical approach had no impact on readmission. However readmission was associated with smoking, post-operative complications, discharge with drain, length of stay post-surgery and the patient's readiness for discharge (see table 1).

Table 1	Non-Readmission Group (n=238)	Readmission Group (n=30)	P value
Did not feel ready to go home	10% (23)	30% (9)	0.003
Did not feel supported in the community	10% (23)	20% (6)	0.1065
Did not know who to contact for advice	18% (44)	3% (1)	0.0375
Number of patients who contacted their GP unwell	47% (113)	50% (15)	0.6899
Number of patients who visited casualty following discharge	6% (14)	70% (21)	0.0001

Conclusion: This audit provides a broad overview of the pattern and trend of readmissions rates within 30 days post discharge following lung cancer resection. Whilst not every readmission can be avoided, there is opportunity to identify and prevent patient readmission. Listening to patient's assessment of their readiness for discharge is crucial to facilitating patient compliance with discharge and confidence in community carers.

Keywords: Re-admission, Thoracic Surgery, NSCLC

MA18.01 NON-SMALL CELL LUNG CANCER RISK ASSESSMENT WITH ARTIFICIAL NEURAL NETWORKS

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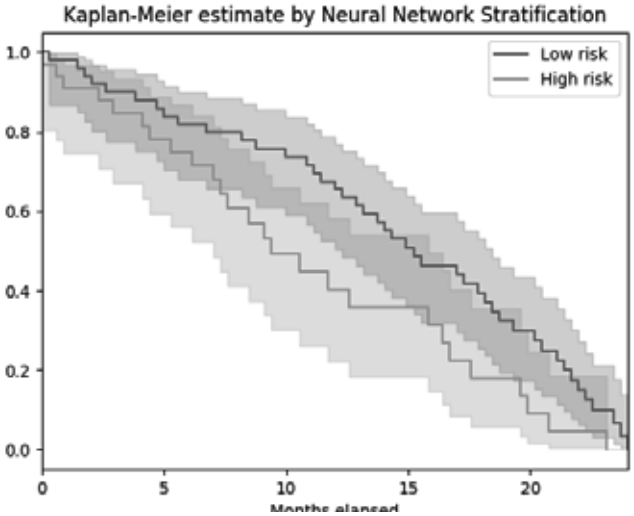
Background: Lung cancer is a heterogeneous disease with many clinically important subtypes. Given the complexity of classification, there is room for innovative risk assessment tools to help ascertain prognosis and management. In this work we tested an Artificial Neural Network (ANN) to stratify patients into clinically significant low and high risk categories. **Method:** CT imaging, survival, and cancer staging data was extracted for a sample of 311 patients with Stage-I (n = 186) and Stage-II (n = 125) non-small cell lung cancer (NSCLC) from the comprehensive Boston Lung Cancer Survival (BLCS) cohort. Median follow-up from time of diagnosis was 3.5 years, with 86% 2-year survival. A deep convolutional neural network pretrained on ImageNet was used, with fine-tuning of the last convolutional layers, dense layers, and softmax for stratification. Inputs of this model were 50 x 50 mm2 image patches. Training was performed on 182 labeled CT scans (112 Stage-I and 70 Stage-II). 46 cases were used for initial cross-validation, with an independent test set of 83 cases. The median prediction probability from the ANN was used as a cutoff to divide patients into low and high risk groups. **Result:** The model was able to perform classification of cancer stage on the heterogeneous test set (AUC = 0.73, p< 0.0005). The test set was split evenly into low risk (n = 42) and high risk (n= 41) groups based on model predictions. There was statistically significant separation in the Kaplan Meier-estimates for survivorship in the two stratified groups (p < 0.02).



Conclusion: ANNs can be effective tools for quantitative risk stratification in NSCLC. In addition to the potential for real-time clinical decision support, ANNs may also help create new paradigms in lung cancer risk assessment. The models have the capacity to perform suprahuman computations, which can help meet future demands of clinical practice, given expanding digital-imaging volumes.

Keywords: Neural network, Survival, Staging

MA18.02 THE IMPACT OF TREATMENT EVOLUTION IN NSCLC (ITEN) MODEL: DEVELOPMENT AND VALIDATION

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Background: The iTEN model was developed to estimate the survival impact of new treatments for advanced NSCLC (aNSCLC) patients. The structure and key assumptions of the iTEN model and outputs validated against published real-world survival data are presented. **Method:** The iTEN model is a discrete event simulation of aNSCLC patients' treatment plans. Individual patient characteristics (histology, molecular subtypes (EGFR, ALK, ROS1, BRAF, PD-L1), and performance status) are generated by random sampling from Canadian prevalence estimates. All Health Canada approved agents for treatment of aNSCLC are included. Simulated patients start on first-line therapy and move to subsequent lines of therapy in modelled progression events. Up to six-lines of therapy can be included. Time-of-event for progression or death for each patient is calculated based on random probabilities and progression-free survival (PFS) and overall survival (OS) curves modelled from published clinical trials. For example, a simulated ALK+ patient might receive first-line crizotinib, followed by second-line ceritinib and BSC, based on PFS/OS data from PROFILE 1014 and ASCEND-5. Predicted OS is calculated as the cumulative time spent on active therapy and BSC. PFS/OS data were extrapolated using best practices. Treatment on previous therapies was assumed to have no impact on the efficacy of subsequent therapies. Model survival predictions were validated against published real-world estimates from the Ontario Cancer and Austrian (TYROL) registries, by reproducing the same treatment mix in the simulated patients as in the publications. **Result:** iTEN estimated two- to five-year survival rates were similar to those reported by the Ontario Cancer and TYROL registries.

Source	Period examined	Treatment Mix	Overall Survival (months)				
			12	24	36	48	60
Ontario Cancer Registry[1]	2005-2009[a]	Two lines of	67%	29%	13%	8%	Unknown
iTEN estimate	2009[a]	chemotherapy	61%	25%	10%	5%	2%
Tyrol Registry[2]	2000-2009[b]	Chemotherapy,	38%	14%	7%	4%	2%
iTEN estimate	2009[b]	erlotinib, or gefitinib	39%	11%	4%	2%	1%

Notes: [a]All patients received two lines of chemotherapy; [b]Patients were eligible for 1-5L of therapy, but only approximately 23% of patients in the registry received a second-line therapy.
Sources: 1) Sacher et al. (2015) Cancer 121:2562-2569 2) Kocher et al. (2015) Lung Cancer 87: 193-200.

Conclusion: While further analyses are required, the iTEN model produces survival estimates comparable to published real-world data; therefore, the iTEN model may be a valid tool to estimate aNSCLC patient survival.

Keywords: aNSCLC, overall survival

MA18.03 HOW IN THE REAL WORLD ARE LUNG CANCER PATIENTS TREATED? THE ONTARIO, CANADA EXPERIENCE

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Background: Clinical trials define treatment recommendations but how patients are actually treated in the real world is poorly understood. The Canadian Partnership Against Cancer has developed a model of lung cancer (LC) management (OncoSim-lung) based on clinical trials data and expert advice. To credibly project the future clinical and economic impacts of cancer control measures using OncoSim, the model has been refined using real-world data. **Method:** Treatment data by histology and stage were extracted from the Ontario Cancer Registry for LC cohorts diagnosed in 2010 and 2013. All incident cases that satisfied the IARC rule of a new primary were included. Missing or unknown stage cases were excluded. Clinical pathways were validated by oncologists from different disciplines across Canada. **Result:** The 2013 cohort included 8,086 staged LC: NSCLC (n=7,143) Stage I 18.7%, II 8%, III/IIIa 11.4%, IIIb 4.9% IV 56.8%; SCLC (n= 943) limited 67.7%, extensive 32.3%. Of 1340 stage I NSCLC patients, 61% underwent surgery; 39% had no surgery and one third of these had no active treatment (NAT). 55% of those not receiving surgery underwent radical radiotherapy and 6% had palliative radiotherapy. Of 579 patients with stage II NSCLC, 60% underwent surgery and 47% of these received adjuvant chemotherapy; 40% had no surgery and 22% of these had NAT. Radical radiotherapy, radiotherapy plus chemotherapy or palliative radiotherapy were given in 33%, 19% and 18% of non-surgical cases, respectively. Of 813 stage III/IIIa patients, only 26% underwent surgery, 41% of whom received adjuvant chemotherapy or postoperative radical radiotherapy (16%); 13% received trimodality treatment. Of the 75% of Stage III not receiving surgery, 26% had NAT and 21% had palliative radiotherapy alone. Of those receiving active

treatment, 20% received combined chemo +radiotherapy and 13% each had chemotherapy alone or radical radiotherapy alone. Of 356 stage IIIb patients, 17% had NAT, 28% received palliative radiotherapy and only 30% had chemo + radical radiotherapy. 18% had chemo alone. Of 4055 stage IV NSCLC, 47% had NAT, 24% received chemotherapy alone and 23% had palliative radiotherapy only. Of those who received first-line chemotherapy (n= 1059), 47% received second line chemotherapy and of those, 37% received third line therapy. **Conclusion:** Compared to prior expert opinion, there was a higher use of radiotherapy for early stage disease, a lower frequency of chemo-radiotherapy in Stage III disease and a higher frequency of NAT across all stages of disease.

Keywords: real world, stage, treatment

MA18 MODELLING, DECISION-MAKING AND POPULATION-BASED OUTCOMES
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MA18.05 CHARACTERISTICS AND LONG-TERM OS OF NON-SMALL CELL LUNG CANCER PATIENTS RECEIVING EGFR TYROSINE KINASE INHIBITOR TREATMENT

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Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are important therapeutic agents in treatment of EGFR mutation-positive non-small cell lung cancer (NSCLC) patients. However, long-term follow-up and knowledge of clinical factors and TKI treatment patterns, which may be associated with longer OS, remains unclear. Using nationwide registry data, the aim was to investigate survival, prognostic factors for OS, and first line TKI treatment pattern of stage IIIB/IV NSCLC patients in Sweden. **Method:** In this cohort study, data on all patients diagnosed with stage IIIB-IV NSCLC during 2010—2015 from the nationwide Cancer Registry of Sweden were linked with data on dispensed EGFR-TKI drugs, comorbidity, and mortality data from Swedish national health registries. OS was defined as the interval from date of diagnosis until date of death. Survival rates were estimated using the Kaplan-Meier method. Assessment of predictive factors for OS was performed in multivariable Cox regression. **Result:** Of 9,992 stage IIIB/IV NSCLC patients (mean age 70 years, female 49%), 1419 (14%) received first-line TKI treatment. Overall, 59% of TKI treated patients (median age 68 years) were female, 44% had at least one comorbidity, 85% had adenocarcinoma, and 89% were stage IV. Median follow-up time was 15 months and median OS was 16 months; 1- and 3-years survival rates were 62% and 15%, respectively. Predictors of longer OS were younger age at diagnosis, adenocarcinoma, less advanced clinical stage, and less comorbid disease. Furthermore, patients included in the end of the period had a longer OS compared to earlier. TKI treatment switching/re-challenging, as well as prolonged TKI treatment, also predicted longer OS. **Conclusion:** This is the first nationwide study on NSCLC patients receiving first-line EGFR TKIs in routine clinical practice in Sweden. In addition to the reported prolonged TKI treatment length and TKI switching/re-challenging during the observation period, improvements and extension of EGFR testing targeting the appropriate NSCLC patient population may further have contributed to the observed relatively long overall survival.

Keywords: non small cell lung cancer, survival, Tyrosine kinase inhibitors

MA18 MODELLING, DECISION-MAKING AND POPULATION-BASED OUTCOMES
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MA18.06 PATTERNS OF LUNG CANCER CARE IN THE UNITED STATES: DEVELOPMENTS AND DISPARITIES

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Background: The level of adherence to lung cancer treatment guidelines is unclear. The aims of this current study were to provide an overview of current patterns of lung cancer care in the United States and to identify possible disparities in receiving standard of care. **Method:** Using the National Cancer Database, we evaluated the first course therapy of 468,422 lung cancer cases diagnosed between 2010-2014. We used a series of multivariate logistic regression models to identify relationships between patient, tumor, and health care provider characteristics and receiving predefined stage-specific standards of care. **Result:** Most common treatments were surgery only (15.2%), radiotherapy only (12.8%), chemotherapy only (13.5%), and radiotherapy and chemotherapy (26.2%). 22.1% of subjects received no treatment. Between 2010-2014, the use of Video-Assisted Thoracoscopic Surgery among surgically treated cases increased from 24.6% to 42.3%, while the rate of conversions to open surgery decreased from 18.3% to 10.4%. Among stage IA non-small cell lung cancer patients treated with thoracic radiotherapy, the use of Stereotactic Body Radiotherapy increased from 53.4% to 73.0%. Overall, only 63.3% of subjects received standard of care. Receiving surgery for early-stage non-small cell lung cancer was less likely with increasing age (for those 80 and over: odds ratio [OR], 0.08; 95% confidence interval [95%CI], 0.07-0.09), for non-Hispanic Blacks (OR, 0.59; 95%CI, 0.57-0.62), and for squamous cell histology (OR, 0.46; 95%CI, 0.45-0.47). These disparities were also present in other stages. **Conclusion:** Particularly elderly lung cancer patients, non-Hispanic Blacks, and those with squamous cell histology are less likely to receive standard of care. These disparities may have consequences for lung cancer screening, as the effectiveness depends on adequate treatment of lung cancer.

Keywords: Healthcare Disparities, Lung neoplasms, Practice patterns

MA18 MODELLING, DECISION-MAKING AND POPULATION-BASED OUTCOMES
TUESDAY, SEPTEMBER 25, 2018 - 13:30-15:00

MA18.07 AWARENESS OF THE HARMS OF CONTINUED SMOKING AMONG LUNG CANCER (LC) SURVIVORS

L. Eng[1], S. Liu[1], D. Farzanfar[1], D. Alton[1], E. Smith[2], A. Mccartney[2], S. Yeung[1], A. Basgaran[2], K. Balaratnam[2], K. Mattina[1], C. Harper[1], R. Mohan[1], M.C. Brown[2], A. Hope[3], P. Bradbury[1], A. Sacher[1], N. Leighl[4], F. Shepherd[2], A. Bezjak[3], D. Howell[2], J. Jones[2], W. Xu[2], D. Goldstein[2], W. Evans[5], P. Selby[6], M. Giuliani[7], G. Liu[1]

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Background: Continued smoking after a LC diagnosis is associated with poorer cancer outcomes including increased risk of treatment-related side-effects, reduced treatment efficacy and poorer prognosis. Smoking cessation is an integral part of LC survivorship by improving both cancer and non-cancer outcomes. To enhance survivorship education, clinicians should understand patient awareness of the harms of continued smoking. **Method:** LC survivors from Princess Margaret Cancer Centre, Toronto (2014-2017) were surveyed with respect to self-awareness of the harms of continued smoking on cancer-related outcomes. Univariable and multivariable logistic regression models assessed factors associated with awareness and whether awareness was associated with cessation among current smokers at diagnosis. **Result:** Of 553 patients, 181 were lifetime never-smokers. Among those smoking during the peri-diagnosis period (n=177), 65% quit after diagnosis. Among all, few patients were aware that smoking negatively impacts treatment-related outcomes [complications from cancer surgery (only 41% aware), radiation side-effects (30%), quality-of-life on chemotherapy (44%) and treatment efficacy (36%)]; half were aware that smoking negatively impacts cancer prognosis (51% aware) and risk of developing second primaries (50%). Compared to ex-smokers/never-smokers at diagnosis, current smokers at diagnosis were less aware of the impact of smoking on radiation side-effects (22% vs 31% aware, P=0.01), prognosis (44% vs 55%, P=0.02) and risk of second primaries (42% vs 55%, P=0.007). Among sociodemographic variables, only those speaking English at home were consistently found more likely unaware that smoking negatively impacts these outcomes (ORs=1.52-2.20, P<0.04). Patients with early stage disease were more likely unaware that smoking negative impacts radiation side-effects (OR=1.60, 95%CI[1.09-2.35], P=0.02); while patients on curative treatment (OR=1.53[1.08-2.17], P=0.02) and those exposed to second-hand smoke (SHS) were more likely unaware that smoking impacts quality-of-life on chemotherapy (OR=1.64[1.05-2.58], P=0.03). Exposure to SHS, treatment intent and stage were not associated with awareness of impact on prognosis or second primaries (*P*>0.11). Among smokers in the peri-diagnosis period, awareness of the impact of smoking on surgical complications (aOR=2.09 [0.96-4.54], P=0.06), quality-of-life while receiving chemotherapy (aOR=2.60[1.17-5.79], P=0.02) and on treatment efficacy (aOR =2.24[0.97-5.20], P=0.06) were each associated with subsequent quitting, adjusted for marital status, pack-years, self-rated health and SHS exposure. **Conclusion:** Many LC patients are unaware of the harms of continued smoking on cancer outcomes, particularly those smoking at diagnosis. Awareness of some of these outcomes was associated with subsequent tobacco cessation. Patient education on the health benefits of smoking cessation may increase quit rates and improve outcomes for LC patients.

Keywords: Patient Education and Awareness, Smoking Cessation, lung cancer

MA18.09 PREDICTORS OF HEALTH UTILITY SCORES (HUS) IN ADVANCED EGFR-MUTATED NSCLC.

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Background: Advanced NSCLC patients with EGFR mutations (EGFRm) are currently treated with first - to third-generation tyrosine kinase inhibitors (TKIs). In the advanced setting, quality of life is an important goal; we therefore evaluated determinants of HUS in this population. **Method:** In a prospective, observational study, patients with advanced *EGFR*m NSCLC completed EQ-5D surveys at outpatient visits generating HUS (range 0-1). Patients were allowed to enrol at any point in their disease course. Baseline clinical characteristics and outcome data were extracted from chart review. Patient imaging was reviewed and health states (stable/progressing) at each encounter recorded. Univariable analyses conducted using ANOVA and multivariable regression analyses with generalized estimating equations identified factors associated with HUS. **Result:** From November 2014 to July 2017, 782 encounters (follow-up visits) were collected for 244 patients. Median age at first encounter was 64 years (range:29-96); 54% were female and 54% Asian. Median time from diagnosis of stage IV NSCLC to first encounter was 23 months (range:0-67). The median number of HUS collected per patient was 2 (range:1-14). For patients with multiple visits the median time between completed questionnaires was 1.8 months (1-18). 105 patients (43%) presented with or developed brain metastases during the study period. In a univariable analysis, regardless of treatment line, mean HUS (mHUS) on osimertinib was 0.85 (standard deviation (SD):0.15) (n=33 patients; 114 encounters) compared to mHUS=0.80 (SD:0.17) on gefitinib (n=147, 351 encounters); mHUS=0.72 (SD:0.16) on chemotherapy (n=32, 76 encounters); and mHUS=0.79 (SD=0.15) on other TKIs (n=49, 133 encounters); p<0.001. In a multivariable analysis, disease progression (p=0.04) and ECOG performance status >0 (p<0.001) were associated with lower HUS. In contrast, treatment with osimertinib (when compared to a reference group of first-generation TKIs, gefitinib/erlotinib) was associated with improved HUS (p=0.01), while line of therapy and number of metastatic sites of disease were not associated with HUS. In addition, brain metastases had no significant impact on HUS (p=0.33). **Conclusion:** Progressive disease and worse performance status associate with lower HUS in patients with EGFRm NSCLC. Patients treated with osimertinib had the highest HUS when compared with a reference group of first-generation EGFR TKIs regardless of line of therapy. These results may help in the choice of EGFR-TKI, especially in patients with a poor performance status.

MA18.10 EVOLVING IMMUNOTHERAPY PRACTICE PATTERNS IN ADVANCED NSCLC: ANALYSIS OF AN ONLINE TREATMENT DECISION TOOL

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Background: Checkpoint immunotherapy (IO) is revolutionizing NSCLC therapy. We have previously published results of an online decision support tool designed to provide clinicians with education and expert guidance (Chow et al: JTO 2015). Here we report an analysis of a recently updated version of this online tool, capturing the impact of emerging IO options. **Method:** From June 2016 to July 2017, the NSCLC decision tool was updated to incorporate new treatment options for 280 different case scenarios. Briefly, oncologists entered patient and disease characteristics and then their planned treatment into the tool. Afterwards recommendations from 5 lung cancer experts were provided for that specific patient scenario. **Result:** This analysis includes 1481 individual cases entered by 863 practicing oncologists between June 2016 and April 2018 (USA 19%, Europe 33%, Rest of World 48%). During this time, treatment choices for EGFR and ALK cancers by oncologists closely resemble those of experts. After approval of 1st-line pembrolizumab for patients with high PD-L1 expression, oncologists recommended pembrolizumab less often than experts (67% vs 95%). In the 2nd-line setting following platinum chemotherapy, both tumor histology and PD-L1 expression level impacted treatment recommendations (see Table). For PD-L1 expression < 1%, recommendations between oncologists and experts differed substantially.

Second-line setting after platinum chemotherapy				
	Participants' Treatment Choice		Experts' Treatment Choice	
	2016	2017	2016	2017
Nonsquamous				
PD-L1 (≥ 1%)	54% IO 34% CT (n = 35)	79% IO 15% CT (n = 47)	100% IO	85% IO 15% CT
PD-L1 (< 1%)	28% IO 65% CT (n = 104)	49% IO 41% CT (n = 63)	40% IO 55% CT	75% IO 25% CT
Squamous				
PD-L1 (≥ 1%)	62% IO 25% CT (n = 24)	74% IO 4% CT (n = 23)	100% IO	100% IO
PD-L1 (< 1%)	28% IO 65% CT (n = 74)	38% IO 40% CT (n = 45)	85% IO 15% CT	80% IO 20% CT

Conclusion: This updated analysis of an online NSCLC decision-making tool integrates recent changes to the treatment landscape in 2017, capturing emerging patterns in IO therapy. Compared to earlier versions, practicing oncologist's choice of 1st-line EGFR- and ALK- targeted therapy more closely tracked with experts during this period, while selection of IO differs from expert recommendations. A detailed analysis of expert versus online user data will be presented.

Keywords: Immunotherapy, online tool

MA18.11 IMPLEMENTING A COMPREHENSIVE NATIONAL AUDIT OF LUNG CANCER SURGERY: THE ENGLISH LUNG CANCER CLINICAL OUTCOMES PUBLICATION (LCCOP) PROJECT

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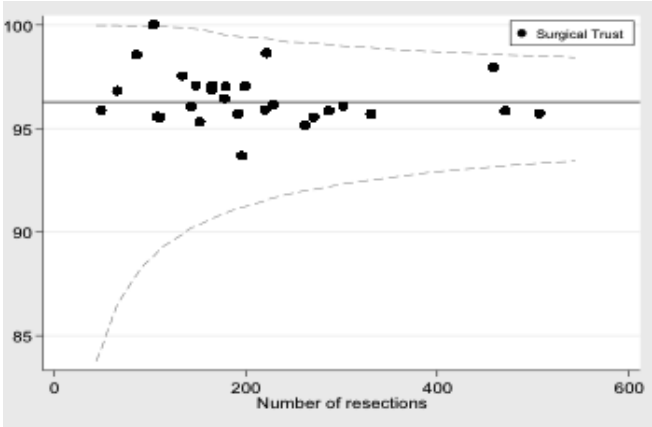
Background: We report the establishment of a national audit of outcomes after lung cancer resection (LCCOP) in the English National Health Service (NHS), a government healthcare system providing the great majority of lung cancer surgery. LCCOP is a compulsory audit commissioned by NHS England. **Method:** Unusually, for a surgical audit, data is initially obtained from the cancer registry, and matched to national Hospital Episode Data (HES), before local validation by clinical teams. After case mix adjustment, unit level survival rates at 30, 60 and 90 days, and length-of-stay data are published online and in an annual report. The first annual report was released in 2014. Survival is adjusted for age, sex, performance status, stage, laterality, FEV1 percentage, comorbidity and socioeconomic status **Result:** The number of resections rose by 21% between 2015-2017 (4892 to 5936). Median annual activity per surgeon rose from 30 to 49 cases between 2014-2017, a 63% increase. In 2015 survival at 30, 90 and 365 days was 98.1%, 96.3% and 87.9% respectively. Median length of stay was 6 days (IQR 4-9). In 2015, 43.9% of lobectomies were completed by VATS, 4.3% were started VATS and completed by open surgery and 0.7% completed by robotics. Adjusted 90 day survival by surgical unit: 2017 report (2015 data)



Conclusion: Using routinely collected NHS activity data for surgical audit is feasible, and reduces the data collection burden for hospital teams. Clinical validation remains important to correct discrepancies. Surgical activity has risen significantly. Increases in individual surgeon case volume may reflect increasing subspecialisation. Significant inter-provider variation remains, particularly in length of stay. More lung cancer surgery is being done in the English NHS. Surgeons are increasingly subspecialising, with higher case volumes. Local variation remains, particularly around length of stay. A mixed model of routinely collected data with local validation appears acceptable to clinical units.

Keywords: Surgery, audit, outcomes

MA19 GENOMIC MARKERS OF IO RESPONSE
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA19.01 EFFICACY AND GENOMIC CORRELATES OF RESPONSE TO ANTI-PD1/PD-L1 BLOCKADE IN NON-SMALL CELL LUNG CANCERS HARBORING TARGETABLE ONCOGENES

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Background: Immune-checkpoint inhibitors (ICIs) are associated with improved outcomes in a subset of patients with advanced non-small cell lung cancer (NSCLC). NSCLCs with targetable oncogenes are thought to be less responsive to ICI therapy, possibly due to association with never smoking status and reduced tumor mutational burden (TMB), but this has not been comprehensively characterized. We evaluated the responsiveness of NSCLCs with targetable oncogenes to ICIs, and if mutation type or TMB influence response. **Method:** Clinicopathologic, radiographic response, and sequencing data for patients with advanced NSCLC treated with ICI therapy was acquired from two separate cohorts (DFCI Oncopanel, n=296; MSKCC MSK-IMPACT, n=202). Durable clinical benefit (DCB) was defined as responsive/stable disease > 6 months. Samples with activating mutations in *EGFR*, *ALK*, *ROS*, *BRAF*, *MET*, and *RET* were identified. TMB was calculated as the sum of nonsynonymous mutations divided by the coding region captured in each panel. Objective response rates (ORR), DCB, and TMB were compared in targetable oncogene positive (TOP) vs oncogene negative (TON) patients. TMB was considered within each cohort to avoid confounding for differences in NGS panel technique. **Result:** Targetable oncogenes were identified in 16% (82/498) of patients; 44(9%) *EGFR*, 15(3%) *MET* exon 14 splice site mutated, 8(2%) *BRAF V600E*, 6(1%) *ROS1* rearranged, 5(1%) *ALK* rearranged, and 4(1%) *RET* re-arranged. Response to ICIs was similar in TOP vs TON patients, with ORR of 18% and 20%, and median PFS of 2.7 vs 2.8 months in TOP vs TON patients respectively. Among TOP patients, response rates differed by mutation type; ORR rate was 11%(5/44) in *EGFR* mutated, 40%(6/15) in *MET* mutated, 25%(2/8) in *BRAF* mutated, 33%(2/6) in *ROS1* rearranged, and 0% in *RET* and *ALK* rearranged cancers (0/4, 0/5 respectively). Compared to WT, TMB was lower in TOP tumors (OncoPanel median 9vs11, p=0.0064; IMPACT median 4vs8, p=2.25e-06). TMB did not correlate with objective response or DCB in TOP tumors when considered collectively or by mutation type (OncoPanel median TMB 10vs8 in DCB vs NDB, p=0.52; IMPACT median TMB 3vs5 in DCB vs NDB, p=0.31)(Mann-Whitney U for all). **Conclusion:** Despite lower TMB in oncogene positive NSCLC, these patients still derive clinical benefit from ICIs. ICI responsiveness is likely mutation specific, and is most pronounced in *MET* and *BRAF* mutated cancers. Among targetable oncogene positive NSCLC, TMB did not distinguish benefit. Taken together, low TMB in the presence of oncogenic driver mutations should not preclude ICI therapy.

Keywords: targetable oncogene, Immunotherapy, tumor mutational burden

MA19 GENOMIC MARKERS OF IO RESPONSE
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA19.02 PRIOR THERAPY AND INCREASED EXPRESSION OF PD-L1 IN NSCLC TUMOR SAMPLES

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Background: Tumor PD-L1 expression has been shown to enrich for response to immunotherapy in several indications, including advanced NSCLC. However, the stability of PD-L1 expression over time and its relationship with non-immunotherapy cancer treatment is currently uncertain. We hypothesized that prior chemotherapy or radiotherapy would increase PD-L1 expression. **Method:** In the Phase 2, open-label, single-arm durvalumab ATLANTIC study (NCT02087423), patients who had received ≥2 prior systemic regimens in the treatment of Stage IIIB or IV NSCLC were screened for tumor PD-L1 expression by immunohistochemistry using the VENTANA PD-L1 (SP263) Assay (25% tumor cell [TC] cutoff). PD-L1 expression was assessed using either a recent (<3 months) or archival sample; a subset of patients provided both. The relationship between non-immunotherapy cancer treatment and prevalence of tumor PD-L1 expression ≥25% (TC≥25%) was assessed in patients who received therapy prior to sample acquisition versus those who did not. Pearson's chi-squared test was used to examine the differences between patient subgroups. **Result:** Of the patients screened for participation in ATLANTIC, 1590 were successfully assessed for PD-L1 expression. PD-L1 TC≥25% prevalence was higher in patients who had received prior radiotherapy or chemotherapy before sample acquisition, with prevalence noticeably higher in those who had received ≥2 lines of prior chemotherapy. Prior EGFR inhibitor treatment did not have any noticeable relationship to TC≥25% prevalence (Table). In the subset of patients with paired recent and archival samples, TC≥25% prevalence remained the same in 74% of cases, increased over time in 19.5%, and decreased in 6.5%.

Treatment regimen	Subgroup (n)	PD-L1 TC≥25% prevalence (%)	P-value
Prior tyrosine kinase inhibitor (TKI)	No prior TKI (607)	39.9	0.947
	Prior TKI (411)	39.7	
	Prior EGFR inhibitor (379)	38.5	0.154
	Prior ALK inhibitor (15)	60.0	
Prior chemotherapy	No prior chemotherapy (145)	29.0	0.004
	Prior chemotherapy (873)	41.6	
Number of lines of prior chemotherapy	0 (155)	29.0	0.031
	1 (10)	30.0	
	2 (138)	42.8	
	>2 (725)	41.5	
Prior radiotherapy	No prior radiotherapy (599)	37.1	0.034
	Prior radiotherapy (419)	43.7	

Conclusion: PD-L1 expression may increase in response to chemotherapy or radiotherapy and is unlikely to decrease over time. Re-biopsy may provide a more accurate assessment of current tumor PD-L1 expression status when a low/negative result is seen in an archival sample, particularly if the patient has received multiple lines of intervening radiotherapy or chemotherapy.

Keywords: programmed cell death ligand-1, Diagnostic test, Immunotherapy

MA19 GENOMIC MARKERS OF IO RESPONSE
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA19.04 THE CLINICAL IMPLICATION OF FRAMESHIFT INDEL MUTATION BURDEN IN NON-SMALL CELL LUNG CANCER (NSCLC)

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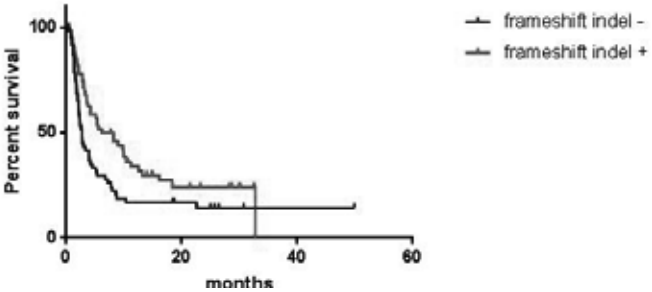
Background: Tumor mutational burden (TMB) has been proposed as a potential predictive marker for immune checkpoint inhibitor (ICI) response in many cancers, including NSCLC. Recently, research has revealed frameshift indel (fsindel) of all mutations to be significantly associated with ICI response in melanoma patients. However, little is currently known regarding its clinical implication in NSCLC patients treated with PD1/PD-L1 inhibitors (ICIs). **Method:** Next generation sequencing of 324 genes (FoundationOne™) was used to derive fsindel burden and TMB. A total of 128 patient data with NSCLC treated with ICIs were analyzed from Northwestern University (N=68) and the University of Miami (N=60). A total of 128 patients were divided into two groups with 0 fsindel (FS-) and more than 1 fsindel (FS+). Progression free survival (PFS) and overall survival (OS) were compared between FS+ and FS- groups. PFS and OS outcomes of TMB high group (H-TMB, upper¹/₄) and TMB low group (L-TMB, lower¹/₄) were also compared. **Result:**

Figure 1. Progression free survival of NSCLC patients on Immune checkpoint inhibitors by frameshift indel status



Among 128 patients, 51.6% belonged to FS+ group (N=66). Between FS-/FS+ groups, there were no significant differences in mean age (66.2/66.0) and performance status (0.9/0.9). Lines of ICIs used in the FS-/FS+ groups were 1st (19/19%), 2nd (47/56%), 3rd (24/11%), and 4th line or more (10/14%). FS+ group had significantly longer PFS compared with FS- group (median 6.2/2.7 months, P=0.02, Figure 1). No significant difference in OS was seen between the two groups (median 16.8/11.2 months, P=0.70). In contrast, however, H-TMB did not show any significant difference in PFS (median 5.6/4.0 months, P=0.14) and OS (median 15.8/15.1 months, P=0.69) compared to L-TMB. **Conclusion:** This is the first report to illustrate an association between fsindel and outcome in patients with NSLC treated with ICIs. Our findings suggest its potential role as a predictive marker for immunotherapy.

Keywords: NSCLC, frameshift indel, immuno checkpoints inhibitor

MA19 GENOMIC MARKERS OF IO RESPONSE
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA19.05 DIFFERENCE OF TUMOR MUTATIONAL BURDEN IS ASSOCIATED WITH DISTINCT IMMUNE MICROENVIROMENT IN THE T CELL-INFLAMED LUNG ADENOCARCINOMA

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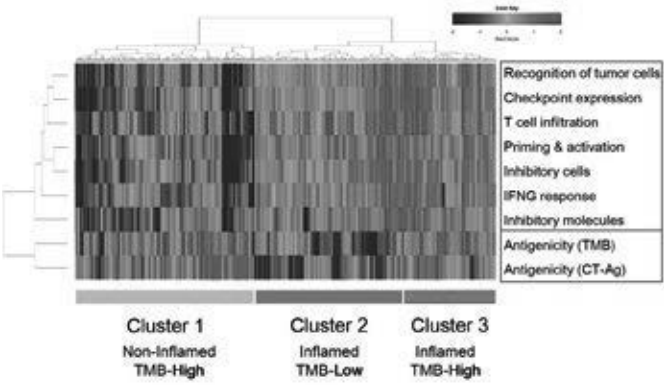
Background: PD-L1 expression on tumor cells, tumor infiltrating lymphocytes (TILs), and tumor mutational burden (TMB) have been reported as predictive biomarkers for checkpoint inhibitor immunotherapies. However, little is known about the relationship between each biomarkers. The aim of this study was to assess the relationship between these biomarkers, especially TIL and TMB. **Method:** RNA-seq data of 533 primary lung adenocarcinoma were downloaded from The Cancer Genome Atlas (TCGA). Gene expression and gene set enrichment were analyzed. Clinical information and somatic missense mutation data were also integrated. **Result:** Weak correlation between PD-L1 and CD8A expression (Spearman's R=0.32, P<0.001), and PD-L1 expression and TMB (R=0.10, P=0.019) were seen, but not between CD8A expression and TMB (R=0.03, P=0.45). Next, we performed gene signature analysis related to cancer-immunity cycle (ref. Karasaki et al. *J Thorac Oncol* 2017). Hierarchical clustering resulted in 3 clusters: T cell non-inflamed phenotype with high antigenicity (Cluster 1), inflamed phenotype with low antigenicity (Cluster 2), and inflamed phenotype with high antigenicity (Cluster 3).(Fig.1) Compared with Cluster 3, Cluster 2 was featured by lower gene expression signature of cytolytic activity (P<0.0001, U-test), as well as lower expression of PD-L1 (P<0.0001, U-test). To further investigate the relationship between TMB and TILs, T-cell inflamed phenotype tumors were divided into four groups according to the quartiles of TMB. We estimated immune cell phenotypes of TMB-high (upper quartile) and TMB-low (lower quartile) groups using ssGSEA and CIBERSORT. Either analysis showed significant enrichment of activated CD4 T cells in TMB-high group (P<0.0001, T-test). **Conclusion:** Existence of Cluster 1 and 2 suggested that tumor antigenicity (TMB) does not necessarily correlate with TIL enrichment. TMB-low tumors may form T cell-inflamed tumors (Cluster 2), although the immune status may differ from TMB-high inflamed tumors (Cluster 3). Integrating multiple biomarkers for the assessment of tumor immune microenvironment is important for optimal immunotherapy.

Figure 1. Hierarchical clustering of TCGA-LUAD using Immunogram Scores



Keywords: tumor mutational burden, immunogram, Tumor infiltrating lymphocytes

MA19 GENOMIC MARKERS OF IO RESPONSE
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA19.06 BLOOD BASED BIOMARKERS: RNA, KRAS AND PD-L1 STRONGLY MATCHING WITH TISSUE AND SHOWING CORRELATION WITH CLINICAL RESPONSES IN NSCLC PATIENT'S

L. Raez[1], J. Usher[2], C. Habaue[3], K. Danenberg[2], B. Hunis[1], Y. Jaimes[2], S. Rabizadeh[2], A. Castrellon[1], P. Danenberg[4]

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Background: Circulating cell-free tumor RNA (cfRNA) can be now safety isolated as cfDNA and used to measure changes in the tumor burden in the blood and changes in gene expression in non-small cell lung cancer (NSCLC) patients (pts). We are correlating these changes in cfRNA and PD-L1 with clinical response to therapy (chemotherapy, immunotherapy (IMMUNO) or targeted therapy) in stage IV NSCLC pts. Our group has been the first one to use cfRNA to detect PD-L1. **Method:** Blood was drawn from 31 pts under various treatments (tx) every 6-8 weeks, at the same time that CT scans were done. CfRNA was extracted from the resulting plasma and reverse transcribed with random hexamers to cDNA. Levels of cfRNA were quantitated by RT-qPCR and correlated with pts clinical response (CR/PR/SD/PD), as determined by CT scans. **Result:** A total of 31 lung cancer pts were enrolled in a 2-year clinical study. 25 of 31 pts completed already the first two cycles of tx and had CT scans done. Of these, 6/8 pts with progressive disease (PD) showed increased (INC) levels of cfRNA, 9/13 pts with stable disease (SD) showed either no change (NC) or decreased (DEC) cfRNA, and 4/4 pts with partial response (PR) had NC or DEC cfRNA, corresponding to 76% concordance between cfRNA and clinical responses. PD-L1 expression measured in plasma cfRNA matched the tissue expression in 7/10 pts. In the one pt where

PD-L1 was (-) in blood and (+) in tissue there was PD on IMMUNO. Among 8 pts treated with IMMUNO: 3/3 pts with PD showed INC PD-L1 cfRNA expression, 3/3 pts with SD had NC in negative PD-L1 status, and 2 pts with PR showed DEC PD-L1 cfRNA, corresponding to 100% correlation between PD-L1 expression levels and pt response. Of the 31 pts, 32% (10/31) harbored KRAS mutations in cfDNA. Of those with KRAS+ status by tissue-based testing, 83% matched with cfDNA results. Among KRAS+ pts, 80% (8/10) showed PD-L1 cfRNA expression in same blood draws with KRAS+ cfDNA, suggesting correlation between these cfDNA and cfRNA analyses. **Conclusion:** Significant association was observed between clinical response and changes in plasma cfRNA levels in NSCLC pts (76%). There was concordance between tissue- and blood-based testing in both DNA (KRAS mutations, 83%) and RNA (PD-L1 expression, 70%). While on IMMUNO levels of PD-L1 expression could be used to monitor response to immunotherapy.

Keywords: PDL-1, cfRNA, NSCLC

MA19 GENOMIC MARKERS OF IO RESPONSE
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA19.08 DETECTION OF PRIMARY IMMUNOTHERAPY RESISTANCE TO PD-1 CHECKPOINT INHIBITORS (PD1CI) IN 2ND LINE NSCLC

J. Aerts[1], E. Smit[2], M. Muller[2], A. Niemeijer[3], C. Oliveira[4], H. Roder[4], J. Roder[4]

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Background: PD1CI are capable of restoring immunity, but some patients do not benefit. While molecular tests like PD-L1 expression and TMB help in enriching response in respective subsets, a test identifying patients showing primary resistance to PD1CI which does not require tissue samples could help in optimizing treatment regimens. **Method:** Sophisticated mass spectrometry profiling data from a development set (S) of pre-treatment serum from 116 2nd line NSCLC patients treated with nivolumab were correlated with outcome data (PFS/OS)using multivariate machine learning techniques related to deep learning. The resulting test stratified patients into three groups: group A having very poor outcomes, group B having intermediate outcomes, and group C having very good outcomes. Development results were obtained using out-of-bag estimators. Two additional patient cohorts treated with nivolumab, V1(N=58) and V2(N=75), were used for validation. **Result:** The proportions of patients in A, B, and C were 41:43:32 in S, 23:18:17 in V1, and 32:19:24 in V2. Median PFS/OS in the poor prognosis group A was 43/132 days in S, 105/189 days in V1, 90/278 days in V2, and in the good prognosis group C 276/528 days in S, 192/459 days in V1, and 155/ not reached days in V2. In a comparison with historical controls treated with single agent chemotherapy and analyzed with the same technique, nivolumab appeared substantially superior in the good prognosis group C, while there was no evidence of superiority in the poor prognosis group A. In multivariate analysis including performance status, smoking history, and histology, the test remained an independent predictor of outcome. The patterns of protein expression related to poor prognosis in group A patients were associated with elevated complement, wound healing, and acute phase reactants. **Conclusion:** We developed and validated a test stratifying patients into three groups with significantly different outcomes on nivolumab. The poor prognosis group showed little benefit from nivolumab, and other treatments may be needed, while in the good prognosis group outcomes were very good for a 2nd line population. Our results emphasize the important role of the host immune response in the prediction of PD1CI efficacy. Data on PD-L1 IHC from these cohorts will be included in the multivariate analysis and presented at the meeting.

Keywords: Immunotherapy, advanced NSCLC, Checkpoint Inhibitor

MA19 GENOMIC MARKERS OF IO RESPONSE
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA19.09 CONCURRENT MUTATIONS IN STK11 AND KEAP1 IS ASSOCIATED WITH RESISTANCE TO PD-(L)1 BLOCKADE IN PATIENTS WITH NSCLC DESPITE HIGH TMB

K. Arbour, R. Shen, A. Plodkowski, H. Rizvi, A. Ni, N. Long, D. Halpenny, F. Sanchez-Vega, C. Rudin, G. Riely, M. Hellmann

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Background: Targeted next generation sequencing (NGS) testing for lung cancer patients identifies recurrent patterns of co-mutations. STK11 is known to be associated with poor outcomes with immunotherapy. We have identified that STK11 is commonly co-mutated with KEAP1, but the impact of this pattern of co-mutation on response to immunotherapy is not known. **Method:** We identified 308 patients with advanced lung cancer treated at Memorial Sloan Kettering Cancer Center who underwent NGS testing with MSK-IMPACT and received at least one dose of PD-(L)1 inhibitor. Progression free survival (PFS) and overall survival (OS) from treatment initiation of PD-(L)1 blockade were calculated using Kaplan-Meier methodology and compared using logrank method and t-test for continuous variables. **Result:** In a cohort of 308 patients with NSCLC treated with PD-(L)1 blockade, STK11 or KEAP1 mutations occurred frequently (23% and 22% respectively) and concurrent STK11 and KEAP1 mutations (STK11mut/KEAP1mut) were common (56% of all STK11 mutant patients and 13% of all lung cancers, Fisher's test of association p<0.0001). Other common co-mutations with STK11 included KRAS (50%) and TP53 (48%). STK11mut/KEAP1mut patients had higher TMB than STK11wt/KEAP1wt patients (median 9.4 vs 6.1, Mann-Whitney p= 0.0002). STK11mut/KEAP1mut (n=39) patients had diminished PFS and OS compared to patients with STK11wt/KEAP1wt (n=210) (PFS HR 1.5, p=0.02; OS HR 2.3, p=0.001). As context, outcomes in STK11mut/ KEAP1mut patients were similarly poor to EGFR mutant patients (n=28) treated with PD-(L)1 blockade (PFS p=0.7) despite substantially different tumor mutation burden (9.4 vs 4.9 mut/Mb, p<0.0001). Among STK11mut/KEAP1mut patients, poor outcomes were unchanged irrespective of KRAS status (PFS p=0.8, OS p=0.5). Patients with mutations in STK11 alone (n=31) or KEAP1 alone (n=28) had outcomes that more closely mirrored STK11wt/KEAP1wt patients (PFS p=0.9 and 0.1 respectively, OS p=0.1 and 0.2 respectively). **Conclusion:** KEAP1 plus STK11 co-mutation is a common event in NSCLC that is distinctly associated with poor outcomes with PD-(L)1 blockade despite otherwise favor molecular features.

Keywords: Immune checkpoint blockade, non-small cell lung cancer, STK11

MA19 GENOMIC MARKERS OF IO RESPONSE
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA19.10 IMPACT OF STK11/LKB1 GENOMIC ALTERATIONS ON CLINICAL OUTCOMES WITH CHEMO-IMMUNOTHERAPY IN NON-SQUAMOUS NSCLC

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Background: Chemo-immunotherapy with pemetrexed/carboplatin/ pembrolizumab represents a standard of care for the first-line treatment of patients with metastatic non-squamous NSCLC, irrespective of tumor cell PD-L1 expression. Genomic determinants of response to chemo-immunotherapy in NSCLC have not been reported thus far. We previously identified *STK11/LKB1* alterations as a major genomic driver of *de novo* resistance to PD-1/PD-L1 inhibitor monotherapy in NSCLC (Skoulidis et al., *Cancer Discovery*, 2018). Here, we examine the impact of *STK11/ LKB1* mutations on clinical outcomes with chemo-immunotherapy with pemetrexed/carboplatin/pembrolizumab. **Method:** Patients with metastatic non-squamous NSCLC that received at least 1 cycle of pemetrexed/carboplatin/pembrolizumab at MD Anderson Cancer Center, were alive for ≥14 days thereafter and had available next generation sequencing- based comprehensive tumor genomic profiling were eligible. Response assessment was based on RECIST1.1. PD-L1 expression on tumor cells was evaluated using the FDA-approved 22C3 pharmDx assay. All patients consented to collection of clinical and molecular data as part of the GEMINI protocol. **Result:** Among 49 eligible patients (median age 61 years, 51% female, 96% adenocarcinoma histology, 34.7% *KRAS*-mutant) the objective response rate to pemetrexed/carboplatin/ pembrolizumab was 51% (25/49) for the overall population. The disease control rate (PR+SD≥ 6 months) differed significantly between *STK11/ LKB1*-mutant and *STK11/LKB1*-wild-type tumors (31.3% vs 72.7%, P=0.011, two-tailed Fisher's exact test). The objective response rate was 31.3% for *STK11/LKB1*-mutant and 60.6% for *STK11/LKB1* wild-type tumors (P=0.07, two-tailed Fisher's exact test). 37.5% (6/16) of *STK11/ LKB1*-mutant tumors exhibited progressive disease as best overall response to chemo-immunotherapy compared with 6.1% (2/33) *STK11/ LKB1*-wild-type tumors (P=0.01, two-tailed Fisher's exact test). Patients bearing *STK11/LKB1*-mutant tumors exhibited shorter progression-free survival with chemo-immunotherapy (median PFS 4.4 months vs 11.0 months, P=0.039, log-rank test). *STK11/LKB1*-mutant tumors were less likely to be positive for PD-L1 expression (PD-L1 TPS ≥ 1%), although the difference did not reach statistical significance (43.8% vs 72%, P=0.1, two-tailed Fisher's exact test). **Conclusion:** *STK11/*

LKB1 genomic alterations are associated with inferior clinical outcomes with chemo-immunotherapy in non-squamous NSCLC, with response rates comparable to those previously reported for platinum doublet chemotherapy alone. Assessment of *STK11/LKB1* status may help refine treatment approaches in non-squamous NSCLC.

Keywords: chemo-immunotherapy, pemetrexed/carboplatin/pembrolizumab, STK11/LKB1

MA20 IMPLEMENTATION OF LUNG CANCER SCREENING
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA20.01 LUNG CANCER SCREENEE SELECTION BY USPSTF VERSUS PLCOM2012 CRITERIA – PRELIMINARY ILST FINDINGS

M. Tammemägi[1], R. Myers[2], M. Ruparel[3], N. Taghizadeh[4], S. Atkar-Khattra[5], J. Dickson[3], S. Quaife[6], A. Bhowmik[7], P. Burrowes[8], P. Maceachern[9], E. Bedard[10], J. Yee[11], J. Mayo[12], J. Liu[13], K. Fong[14], A. Tremblay[9], S. Janes[3], S. Lam[15]

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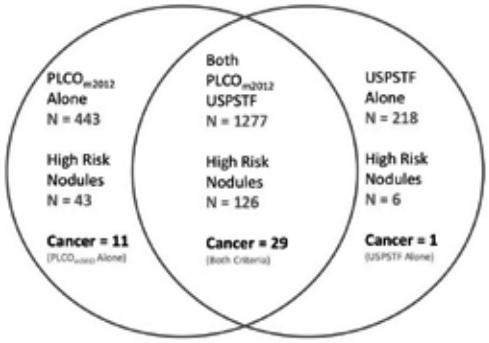
Background: The National Lung Screening Trial showed that lung cancer screening of high-risk individuals with low dose computed tomography can reduce lung cancer mortality by 20%. Critically important is enrolling high-risk individuals. Most current guidelines including the United States Preventive Services Task Force (USPSTF) and Center for Medicare and Medicaid Services (CMS) recommend screening using variants of the NLST eligibility criteria: smoking ≥30 pack-years, smoking within 15 years, and age 55-80 and 55-77 years. Many studies indicate that using accurate risk prediction models is superior for selecting individuals for screening, but these findings are based on retrospective analyses. The *International Lung Screen Trial*(ILST) was implemented to prospectively identify which approach is superior. **Method:** ILST is a multi-centred trial enrolling 4000 participants. Individuals will be offered screening if they are USPSTF criteria positive or have PLCOm2012 model 6-year risk ≥1.5%. Participants will receive two annual screens and will be followed for six years for lung cancer outcomes. Individuals not qualifying by either criteria will not be offered screening, but samples of them will be followed for lung cancer outcomes. Outcomes in discordant groups, USPSTF+ve/PLCOm2012-ve and USPSTF-ve/PLCOm2012+ve, are informative. Numbers of lung cancers, abnormal suspicious for lung cancer scans (a marker of future lung cancers) and individuals enrolled, and sensitivity and specificity and positive predictive values of the two criteria will be compared. **Result:** As of March 2018, ILST centers in Canada (British Columbia and Alberta), Australia, and the United Kingdom had enrolled and scanned 1938 individuals. Study results are summarized in Figure 1.

Figure 1. ILST Interim Results (N = 1938)



The proportion of lung cancers in PLCOm2012+ve individuals was 15.9% higher than in those who were USPSTF+ve (2.33% vs. 2.01%, p=0.34). The proportion abnormal suspicious for lung cancers scans in the PLCOm2012+ve were 11.3% higher than detected in those who were USPSTF+ve (9.83% vs. 8.83%, p=0.15).

Conclusion: Interim analysis of ILST data, suggests that classification accuracy of lung cancer screening outcomes support the PLCOm2012 criteria over the USPSTF criteria. Individuals who are USPSTF+ve and PLCOm2012-ve appear to be at such low baseline risk (0.46%) that they may be unlikely to benefit from screening.

Keywords: risk-based selection, lung cancer screenee selection

MA20 IMPLEMENTATION OF LUNG CANCER SCREENING
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MA20.02 "REDUCED" HUNT LUNG CANCER MODEL FOR PREDICTING LUNG CANCER IN THE PROSPECTIVE DANISH LUNG CANCER SCREENING STUDY - COMPARISON WITH THE NLST

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Background: Risk prediction is important for selection of individuals for lung cancer screening programs. We have recently published a validated calculator, the HUNT Lung Cancer Risk Model (https://www.ebiomedicine.com/article/S2352-3964(18)30114-2/fulltext) for all ages and smoking patterns. The Danish Lung Cancer Screening Trial (DLCST) was a randomized prospective study that included 4104 heavy smokers with a median age of 57.6, 33.8 pack-years and maximum 9 years quit time and 10 years follow-up. We tested the value of the HUNT model in this prospective Danish lung cancer study and compared with the NLST. **Method:** The DLCST study only had 5 of the 7 variables in the original HUNT Model, so we trained a "reduced" HUNT Model in the Norwegian HUNT2 cohort of 12 091 ever-smokers ages between 49-71 years (as the age span in the Danish cohort) based on age, pack-years, smoking intensity, quit time and BMI where sex was added for adjustment. The model was applied blindly in the 4051 individuals of the Danish cohort that had all 5 variables. **Result:** In the population selected by the "reduced" HUNT Model, 148/149 (99.33%) lung cancer cases were predicted (sensitivity 99.33%, negative predictive value 99.23%), thus only one individual that developed lung cancer was lost among those 52 not selected for screening. If the the NLST criteria were used (age 55-74, >30 pack-years and <15 years quit time), less than half of the Danish cohort (n=1870 (46.2%)) would have been considered eligible for screening, and 104/149 (69.80%) lung cancer cases would have been predicted. With these criteria, one would lose 45 (32.7%) lung cancer cases, and the sensitivity would be lower (69.80%). **Conclusion:** We were able to predict 99.33% of those that were diagnosed with lung cancer in 10 years, only one future lung cancer case was not included. Therefore, even the "reduced" HUNT model was highly sensitive in selecting persons at high risk for lung cancer in a screening cohort. The objection one could have for preferring the NLST criteria is that one screened about half of this population but at the same time lost 1/3 of the future lung cancers. *In a health system that can afford to screen more people than those included by the NLST criteria, the HUNT model may be useful, preferably the validated* ***HUNT Lung Cancer Model, for the selection of high risk individuals to a screening programme.***

Keywords: NLST, HUNT Lung Cancer Model, Screening

MA20 IMPLEMENTATION OF LUNG CANCER SCREENING
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MA20.03 SURPRISING IMPLICATIONS OF PROPOSED RISK-THRESHOLDS FOR SELECTING US EVER-SMOKERS INTO CT LUNG-CANCER SCREENING

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Background: Many studies show that using risk-models to select ever-smokers for screening may be more effective and efficient than current US Preventive Service Task Force (USPSTF) guidelines. Current National Comprehensive Cancer Network (NCCN) guidelines permit screening ever-smokers with at least 1.3% 6-year lung-cancer risk. Here we re-evaluate assertions, originally based on pre-2015 or non-representative data, that currently proposed risk-thresholds would screen no more ever-smokers than current USPSTF guidelines and at higher effectiveness and

efficiency. **Method:** Using the 2015 US National Health Interview Survey (NHIS), we estimate the number of ever-smokers eligible for lung-cancer screening according to 3 lung-cancer risk-thresholds: 1.3% (NCCN) and 1.51% 6-year risks by the $PLCO_{M2012}$ risk-model and 1.9% 5-year risk by the Lung Cancer Risk Assessment Tool (LCRAT). The NCCN and 1.51% thresholds were based on data from the Prostate Lung Colorectal and Ovarian (PLCO) cancer screening trial, a non-representative sample of US ever-smokers 1993-2001. The 1.9% threshold was based on pre-2015 but representative data (NHIS 2010-2012). Using previously published methodology to estimate 5-year outcomes following 3 annual CT lung-screens, we calculate screening effectiveness (the number needed to screen (NNS) to prevent 1 lung-cancer death) and efficiency (the number of false-positive CT screens per prevented lung-cancer death). **Result:** 8.0M US ever-smokers were eligible for lung-screening by USPSTF guidelines in 2015. Surprisingly, millions more were eligible according to risk-thresholds: 12.6M, 11.3M, and 9.2M ever-smokers were eligible at the 1.3% (NCCN), 1.51%, and 1.9% thresholds, respectively. We estimated effectiveness by USPSTF guidelines as NNS=194, which worsened to 222 and 207 for the 1.3% (NCCN) and 1.51% thresholds respectively, but improved to 172 for the 1.9% threshold. We estimated screening efficiency by USPSTF guidelines as 133 false-positives per prevented death, which worsened to 150 and 141 for the 1.3% (NCCN) and 1.51% thresholds respectively, but improved to 122 for the 1.9% threshold. The $PLCO_{m2012}$ risk threshold that would select 8.0M 2015 ever-smokers is substantially higher than NCCN guidelines (2.28% vs. 1.3% 6-year risk). **Conclusion:** Compared to current USPSTF guidelines, the 1.3% (NCCN) and 1.51% risk thresholds (6-year risks by $PLCO_{m2012}$) would screen many millions more US ever-smokers and likely at lower effectiveness and efficiency. Although the 1.9% threshold (5-year risk by LCRAT) also chose more ever-smokers than USPSTF guidelines, it may screen them more effectively and efficiently. Our findings demonstrate that risk-thresholds developed using older or non-representative data should be re-evaluated using current and representative data.

Keywords: lung cancer screening guidelines, lung cancer screening, individualized lung-cancer risk model

MA20 IMPLEMENTATION OF LUNG CANCER SCREENING
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MA20.05 WHO GETS SCREENED FOR LUNG CANCER? A SIMPLE ADJUSTMENT TO CURRENT GUIDELINES TO REDUCE RACIAL DISPARITIES

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Background: The United States Preventive Services Task Force (USPSTF) recommends low-dose computed tomography screening for lung cancer in current or former smokers age 55-80 years with a minimum 30 pack-year history and having quit no more than 15 years ago. However, these guidelines were developed in the predominantly white population of the National Lung Screening Trial and therefore may not be generalizable to African Americans who have different smoking patterns. We evaluated USPSTF lung cancer screening guidelines in a predominantly African American prospective cohort with an elevated incidence of lung cancer. **Method:** The Southern Community Cohort Study (SCCS) is a prospective observational cohort of approximately 86,000 adults (two-thirds African American) aged 40-79 years enrolled primarily at community health centers from 2002-2009 across 12 Southern U.S. states. Former and current smokers were included in the present study and were followed for up to 9 years. We examined the impact of race and smoking history on eligibility for lung cancer screening using USPSTF guidelines. **Result:** Among N=50,524 adult (67% African American, 33% white) ever smokers at baseline (64% current smokers, median age 50 years at enrollment) in the SCCS, we identified 1,359 incident lung cancers. Among lung cancer patients, 32% of African Americans were eligible for screening following USPTSF criteria compared with 55% of whites (p<0.001). The lower percentage of eligible African Americans was primarily due to African Americans having smoked fewer pack-years than whites (14 vs 27 median pack-years, respectively, p<0.001). Lowering the smoking pack-year eligibility criteria to a minimum 20-29 pack-year history, increased the number of African Americans eligible for screening by 38%. With a lower smoking pack-year criterion for African Americans, sensitivity increased from 32% to 50% and specificity decreased from 87% to 78% yielding sensitivity and specificity values that were similar to whites (55% sensitivity, 75% specificity) using the USPSTF guidelines. **Conclusion:** Current lung cancer screening guidelines are too conservative for African Americans. A greater percentage of African Americans are excluded from screening opportunities primarily due to lower smoking histories. Adjustment of pack-years in lung cancer screening guidelines by race will result in more equitable screening for smokers at high risk for lung cancer.

Keywords: Screening, eligibility, disparities

MA20 IMPLEMENTATION OF LUNG CANCER SCREENING
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MA20.06 LUNG CANCER SCREENING PILOT FOR PEOPLE AT HIGH RISK: EARLY RESULTS ON CANCER DETECTION AND STAGING

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Background: In June 2017, Cancer Care Ontario initiated organized lung cancer screening for people at high risk of developing lung cancer, using annual low-dose computed tomography (LDCT), at three pilot sites in Ontario. A key indicator of pilot success is detection of lung cancers at early stages. Ontario Cancer Registry (OCR) is used to track lung cancer diagnosis, stage and histology. **Method:** Patient abstracts were created using *Registry Plus CDC* abstracting software for pilot participants and patient-level data were collected from hospital data submissions, hospital electronic medical records via remote access, OCR pathology database (eMaRC) and OCR clinical source records (Resolink). Confirmed lung cancer cases were reviewed by a team of cancer staging analysts to achieve consensus on stage group using AJCC TNM 8th edition. A post-staging review was conducted for all staged cases to ensure accuracy and completeness. **Result:** As of February 2018, 1086 participants received a baseline LDCT scan. 37% (n=404) of participants had Lung-RADS™ scores of 1; 45% (n=487) had Lung-RADS™ scores of 2; 10% (n=112) had Lung-RADS™ scores of 3; and 8% (n=83) had Lung-RADS™ scores of 4A, 4B or 4X, which triggered additional follow-up or diagnostic workup. 18 lung cancers were confirmed and 11 were fully staged. Of the 11 staged cases: 45% (n=5) was stage I; 9% (n=1) stage II; 9% (n=1) stage III; and 36% (n=4) stage IV. This represents a statistically significant increase in the proportion of early stage lung cancers (stage I and II) compared to historical proportions (p<0.05). 73% (n=8) were adenocarcinoma. The median risk score (i.e., PLCOm2012 risk prediction model probability of developing lung cancer in 6 years) was 8.1%, considerably higher than the median risk score of the overall pilot cohort (2.9%). 82% (n=9) had baseline Lung-RADS™ scores of 4X and 18% (n=2) had 4B. The average age at diagnosis was 67. 45% (n=5) were male; 55% (n=6) were current smokers; and 55% (n=6) had high school education or less. In addition, the screening pilot facilitated the successful transition by the OCR from AJCC TNM 7th to TNM 8th edition in lung cancer staging. Results will be updated in the conference presentation. **Conclusion:** Early pilot results demonstrate success in detecting early stage lung cancers and a statistically significant stage shift to earlier cancer stages. We anticipate a greater proportion of early stage lung cancers on annual recall LDCT scans. The OCR efficiently enabled capturing important incidence, staging and histological pilot data.

Keywords: Screening, Early Detection, Cancer Staging

MA20 IMPLEMENTATION OF LUNG CANCER SCREENING
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MA20.07 LUNG CANCER SCREENING FOR LIMITED-RESOURCE PATIENTS: PRELIMINARY FINDINGS FROM A LOW-DOSE CT PILOT PROGRAM

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Background: Low-dose CT (LDCT) screening for lung cancer in adults at high-risk is associated with a reduction in lung cancer mortality in high-risk adults, yet screening rates remain low. Increasing access to high-quality lung cancer screening is critical to further reducing deaths from the disease. In 2015 the American Cancer Society implemented a pilot program to identify successful strategies for improving access to LDCT in Memphis, Tennessee and Charleston, West Virginia through partnerships with Federally Qualified Health Centers (FQHCs) that serve limited resource patients. The program focused on developing systems within FQHCs to identify and refer patients for LDCT, and helping FQHCs build relationships with local accredited screening facilities to deliver lung cancer screening and navigate patients through the screening process and any necessary follow-up. This program is novel because it brings emerging technology in lung cancer screening and early detection to

low-resource FQHCs that typically do not have access to state-of-the-art interventions. As such, the pilot affords important opportunities to identify facilitators and barriers to conducting LDCT in under-resourced areas. *This presentation focuses on evaluation results for the program to-date, emphasizing barriers to implementation experienced by FQHCs and their screening partners.* **Method:** Participating FQHCs submitted quarterly monitoring reports tracking the number of: patients assessed for LDCT eligibility, shared decision-making (SDM) visits, patients screened, and screening results. Evaluators conducted site visits and stakeholder interviews with staff from FQHCs and their screening partners in summer 2017 and 2018 to capture nuanced information about program implementation. **Result:** Participating FQHCs conducted 387 SDM discussions and have screened 252 patients to date. Participants expressed uncertainty about the definition and process of SDM, and difficulty with tracking and billing for these patient-provider encounters. During the project period, both sites established processes for follow-up screening and referrals based on initial screening results (LRADs 1-4). Interview data provided insight into the major challenges and successes to piloting and implementing a new protocol. Both sites struggled to agree on the correct follow-up for LRADS 3 and 4 patients. Through piloting and discussion with clinic leadership, one site successfully implemented clear, logical follow-up procedures based on staff capacity and clinical guidelines. **Conclusion:** Our evaluation findings, including key lessons learned and recommendations, add to the growing knowledge base of effective lung cancer screening practices and may be used to inform and guide health systems looking to initiate similar programs, particularly those in low-resource settings.

Keywords: Screening, low dose CT, health disparities

MA20 IMPLEMENTATION OF LUNG CANCER SCREENING
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MA20.09 IMPROVED LUNG CANCER AND MORTALITY PREDICTION ACCURACY USING SURVIVAL MODELS BASED ON SEMI-AUTOMATIC CT IMAGE MEASUREMENTS

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Background: In a lung cancer CT screening setting, imaging biomarkers are typically extracted by experienced human readers. We found that adding semi-automatic computer-aided detection (CAD) measurements to a base model significantly improved lung cancer and mortality risk prediction accuracy. **Method:** Participants' baseline CT scans, characteristics, and 7-year follow-up outcomes were obtained from the National Lung Screening Trial. The selection included all 1810 deceased and a random selection of 4190 surviving participants from the CT screening arm with an image available; the latter subcohort was sampled with replacement up to 24432 to approximate the full CT arm. Seventeen patient characteristics variables endorsed by literature were considered for each model. CAD was used to automatically measure normalized emphysema score, coronary calcium volume, and thoracic aorta calcium volume. Pulmonary nodule consistency, volume, solid core volume (if part-solid), and upper lobe location were annotated by an experienced radiologist with CAD support. Only the largest noncalcified nodule was considered for the model; having no nodules was the reference. Cox proportional hazard regression was performed on patient characteristics variables only (base model) and combined with CAD variables (new model). This was done for three outcomes: lung cancer diagnosis, lung cancer mortality, and overall mortality. The average continuous net reclassification improvements (NRI) between the base and new models were calculated for each year following the baseline scan. To calculate NRI, the net percentages of subjects with and without the event of interest correctly reclassified as high and low risk, respectively, are summed (maximum range: -2 to 2); positive scores indicate that the new model is more accurate. **Result:** CAD measures were successfully computed for 5575 baseline scans. After sampling, the test cohort consisted of 24370 participants. 3.9% were diagnosed with lung cancer (940/24370) and 6.9% died (1681/24370), of which 24.9% due to lung cancer (418/1681). For all outcomes, the new models were significantly superior to the base model. With lung cancer diagnosis as the outcome, the NRI at 1, 4, and 7 years follow-up were 0.628 (95% confidence interval: 0.373–0.700), 0.331 (0.261–0.390), and 0.349 (0.293–0.389), respectively. The respective NRIs were 0.501 (0.290–0.642), 0.288 (0.221–0.374), and 0.255 (0.218–0.339) when predicting lung cancer mortality and 0.496 (0.295–0.610), 0.301 (0.239–0.376), and 0.270 (0.201–0.320) when predicting overall mortality. **Conclusion:** CAD measures of emphysema and atherosclerosis and CAD-supported pulmonary nodule annotations are of added value for predicting lung cancer and mortality. These new models may be used to further personalize lung cancer CT screening follow-up protocols.

Keywords: CT, CAD, model

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MA20.10 LUNG CANCER PREDICTION USING DEEP LEARNING SOFTWARE: VALIDATION ON INDEPENDENT MULTI-CENTRE DATA

H. Peschl[1], D. Han[2], P. Van Ooijen[2], M. Oudkerk[3], M. Dorrius[2], M. Rook[4], R. Vliegenthart[2], C.P. Heussel[4], N. Batora[4], H. Kauczor[4], C. Da Silva[4], O. Von Stackelberg[4], R. Rubtsov[4], M. Wielputz[4], S. Ather[1], M. Tsakok[1], C. Arteta[5], L. Pickup[5], S. Hussain[1], W. Hickes[1], P. Novotny[5], C. Santos[5], E. Fay[5], J. Declerck[6], V. Potesil[5], T. Kadir[6], F. Gleeson[7]

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Background: Artificial Intelligence software has shown promise in predicting malignancy in indeterminate CT detected pulmonary nodules. This study aimed to assess the accuracy of a convolutional neural network (CNN) based lung cancer prediction software on an independent dataset of indeterminate incidentally detected nodules in a retrospective European multicentre trial. **Method:** The software was trained using the US National Lung Screening Trial (NLST) dataset which was manually curated, such that each reported nodule and cancer was located, contoured and diagnostically characterised (9310 benign nodule patients; 1058 cancer patients). From this complete dataset, a training set was built by selecting all patients with solid and part-solid lesions of 6mm and above, where benign nodules and cancers could be confidently identified by clinicians (5972 patients, of which 575 were cancer patients). A CNN classifier was trained using Deep Learning on this data to produce a malignancy score per nodule. We defined a benign nodule rule-out test by calculating thresholds on the malignancy score that achieve 100% and 99.5% sensitivity on the NLST data. The study was set up so that a malignancy score for each nodule was generated. Overall performance was evaluated using Area-Under-the-ROC-Curve analysis (AUC) and rule-out performance measured the specificity at the two thresholds, i.e. the proportion of benign nodules correctly stratified at each threshold. There were 2201 nodules, measuring between 5-15mm from 1719 patients from three tertiary referral centres in the UK, Germany and Netherlands. The CT data included heterogeneous scan parameters, scanner manufacturers and clinical indications. Diagnostic ground-truth was established according to Fleischner or British Thoracic Society guidelines. The dataset contained 222 unique cancers from 215 patients. **Result:** AUC on all-site data was 0.92 (95%CI = 0.89-0.93) and broken down per-site the AUC was 0.97 (Netherlands, n=883, 26 cancers), 0.93 (UK, n= 698, 51 cancers), and 0.84 (Germany, 620, 145 cancers). The score thresholds used for the target sensitivity of 100% and 99.5% were the same and achieved an overall sensitivity on the data of 99.1% with a specificity of 25.0%. Per-site results were 25.6% (Netherlands), 27.8% (UK) and 20.6% (Germany) specificity with 100%, 100% and 98.6% sensitivity respectively. **Conclusion:** Performance of the AI software on independent European multicentre data was comparable to that achieved on the NLST training data, although there was some variability in the performance of the system across the three centres, potentially providing an opportunity for further optimisation.

Keywords: nodule, Artificial Intelligence, Deep learning

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MA20.11 AUTOMATIC NODULE SIZE MEASUREMENTS CAN IMPROVE PREDICTION ACCURACY WITHIN A BROCK RISK MODEL

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Background: The intrinsic variance of manually measured nodule diameters may limit the predictive accuracy of the Brock University Cancer Prediction Model, especially given the relative weight of its coefficient within the model. Size measurements that are automatically derived may improve this prediction performance. This study aims to examine whether automatic nodule segmentation can improve the predictive efficacy of the Brock model. **Method:** A retrospective analysis was performed on all images from the third annual screening

study (T2) of the US National Lung Cancer Screening Trial (NLST). Following BTS guidelines, all nodules >=5mm were selected with no other exclusions whether on type, attenuation margin, or otherwise. This resulted in 7551 benign and 314 malignant nodules from 5373 patients with mean age 62±5 years and 3180 males. An automatic segmentation method, based on Deep Learning, was used to segment the nodule volume using a single point placed within the nodule on the CT image as an initialization. The nodule volume, V, was calculated from the segmentation and then converted to an *equivalent* spherical diameter, $D_{sph}=\sqrt[3]{(6/\pi\ V)}$. We evaluated four implementations: 1) the original Brock model using as input the manual nodule sizes provided in the NLST dataset (BaselineManual); 2) the original Brock model using as input automatically calculated equivalent spherical diameter, D_{sph}, (BaselineAuto); 3) a Brock model re-fitted to the NLST dataset, using the manual nodule sizes (OptimManual); 4) a Brock model re-fitted to the NLST dataset, using the automatic nodule sizes (OptimAuto). Statistics were computed by bootstrapping across 1000 draws without replacement with 70%/30% training/testing per-patient splits. The performance of each combination was measured using Area-Under-the-Receiver-Operating-Curve (AUC-ROC) of predicting nodule malignancy. The relative weighting of size coefficients was also compared. **Result:** The AUC-ROC was 86.5% (95% confidence interval (CI): 83.2, 89.7) for BaselineManual, 87.4% for OptManual (84.3, 90.5), 88.5% for BaselineAuto (85.7, 91.4), and 89.0% for OptAuto (86.2, 91.8). The relative absolute weight of the size coefficient is 0.46 in OptManual (95% CI: 0.42,0.49) increasing to 0.53 (0.49, 0.57) in OptAuto, an increase of 0.07 (0.06, 0.09) **Conclusion:** Automatic segmentation appears to improve the prediction accuracy of both the original Brock model and the NLST optimized version. The benefits of repeatable measurements from automatic segmentations are apparent even as direct replacements within the original model, i.e. without re-fitting. However, re-fitting the parameters increases the relative weight of the nodule size coefficient and further improves performance.

Keywords: pulmonary nodule, AI, Automatic segmentation

MA21 MOLECULAR SUBTYPING, CBL3, AND NON CODING RNA
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MA21.01 CBL MUTATIONS (MT) AS IMPORTANT MEDIATORS OF ONCOGENIC RTK SIGNALING IN NSCLC

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Background: Casitas B-lineage lymphoma (Cbl), an E3 ubiquitin ligase, selectively regulates receptor tyrosine kinase (RTKs), e.g. EGFR, MET. Cbl loss of function (LOF) mt can can prevent ubiquitination of EGFR and potentiate EGFR signaling. Cbl mt have been described in cases of EGFR-TKI resistance but because EGFR signaling can activate signaling of fusion kinases and other ERBB family members, the implications of Cbl mt warrant broad characterization **Method:** Biopsies from NSCLC pts tested with Next-Generation Sequencing on a 592-gene panel (Illumina NextSeq, ArcherDx) were analyzed retrospectively. Cbl domains of interest: LOF [tyrosine kinase binding (TKB), linker (L), ring finger (RF) and ubiquitin-associated (UBA)] and unclear function [N-terminal (NT) and proline-rich (PR)]. Chi-square analysis was used to compare co-alteration rates. **Result:** Among 4,484 NSCLC pts' tumors (50% M/50% F; age range: 20-90, profiled 11/16-12/17), 222 had Cbl mt (5%), of which 65 (29% of mt, 1.4% of cohort) were LOF: 13% TKB (29), 7% L (15), 5% RF (13), and 3.6% UBA (8). Cbl LOF mt were primarily observed in adenocarcinomas (48/65), metastatic sites (35/65) and equal between M/F. Cbl mt in other domains: 23% PR (51) and 14% NT (31). Co-mutation distribution is shown in table below. Cbl LOF mt that disrupt Cbl function (H398N, S407C, C396R, Y371D, T377I/H) or interactions w/ RTK (S216G, P288S, F325L) co-occurred w/ oncogenes in nine pts: EGFR (L858R, S768I, exon19del+T790M), ERBB3 (V104M, G284R), EML4-ALK (n = 2), CD74-ROS1 (n = 1), and HER2 (D1125E).

	LOF	WT	
Oncogene	pos/total (%)		P
ERBB3 mt	2/65 (3.1)	6/4329 (0.1)	< 0.001
EGFR mt	3/65 (4.6)	491/4329 (11.3)	0.08
METex14	0/65 (0)	100/4329 (2.3)	0.2
ROS	1/60 (1.7)	22/3976 (0.6)	0.2
KRAS mt	14/65 (21)	1242/3086 (29)	0.2
BRAF V600E	0/65 (0)	56/4312 (1.3)	0.3
ALK	2/60 (3.3)	97/4175 (2.3)	0.6
ERBB4 mt	0/65 (0)	6/4329 (0.1)	0.7
HER2 mt	1/65 (1.5)	58/4328 (1.3)	0.9

Conclusion: Regulation of RTK signaling through Cbl-mediated degradative pathways represents an important node for dysregulation in cancer. Presence of Cbl LOF mt in oncogene-driven tumors may provide a bypass signaling-enabled molecular landscape. Further analysis of the role of Cbl LOF mt in *de-novo* or acquired TKI resistance in pts identified is planned.

Keywords: CBL, NSCLC, RTK signaling

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MA21.02 IDENTIFICATION OF AN E2 UBIQUITIN CONJUGASE CDC34 THAT COMPETES WITH E3 LIGASE C-CBL TO STABILIZE EGFR AND PROMOTES LUNG CARCINOGENESIS

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Background: The ubiquitin (Ub)-proteasome system (UPS) is the principal pathway for diverse intracellular protein degradation, in which the E2 ubiquitin-conjugating enzymes play critical roles by transferring the Ub on their conserved cysteine residue to the ε-amino group of lysine residues on substrates. **Method:** To systematically identify ubiquitin pathway genes that are critical to lung carcinogenesis, we used a highthrough-put silencing method to knockdown 696 genes in non-small cell lung cancer (NSCLC) cells, and investigated the significance of the candidates in patient samples, cellular and animal models. **Result:** We identified 31 candidates that were required for cell proliferation in two NSCLC lines, among which the E2 ubiquitin conjugase CDC34 represented the most significant one. CDC34 was elevated in tumor tissues in 67 of 102 (65.7%) NSCLCs, and smokers had higher CDC34 than nonsmokers. The expression of CDC34 was inversely associated with overall survival of the patients. Forced expression of CDC34 promoted, whereas knockdown of CDC34 inhibited lung cancer in vitro and in vivo. CDC34 bound EGFR and competed with E3 ligase c-Cbl to inhibit the polyubiquitination and subsequent degradation of EGFR. In EGFR-L858R and EGFR-T790M/Del(exon 19)-driven lung cancer in mice, nockdown of CDC34 by lentivirus mediated transfection of short hairpin RNA significantly inhibited tumor formation. **Conclusion:** These results demonstrate that an E2 enzyme is capable of competing with E3 ligase to inhibit ubiquitination and subsequent degradation of oncoprotein substrate, and CDC34 represents an attractive therapeutic target for NSCLCs with or without drug-resistant EGFR mutations.

Keywords: ubiquitin pathway genes, CDC34, EGFR

MA21 MOLECULAR SUBTYPING, CBL3, AND NON CODING RNA
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MA21.03 HETEROGENEITY IN MET COPY NUMBER AND INTRATUMOURAL SUBSETS IN PLEOMORPHIC LUNG CARCINOMA: IMPLICATIONS FOR MET DIRECTED THERAPY IN NSCLC

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Background: Pleomorphic Lung Carcinoma (PC) is a rare subtype of NSCLC poorly responsive to systemic therapy. Both epithelial and sarcomatoid phenotypes exist, suggesting an important role of epithelial-to-mesenchymal transition. We aimed to determine *MET* copy number (CN) within individual tumour components and establish its correlation with immunohistochemistry (IHC) expression. **Method:** Histopathological assessment and diagnosis was confirmed for 57 cases of resected PCs from the Royal Brompton Hospital Biobank. DNA was isolated from multiple regions and *MET* copy number determined by digital droplet PCR (ddPCR). IHC using c-MET (EP1454Y) and H-scores were assigned independently by two histopathologists. **Result:** Cases: median age 66 years, 36.2% T3, 41.4% T2 and 13.8% T1. In the epithelial areas, adenocarcinoma was the most common (45.6%) followed by undifferentiated NSCLC (22.8%) and squamous (17.5%): in pleomorphic areas, mixed giant/spindle cell (35%), spindle cell (31%) and giant cell (26%). *MET*-CN gain by ddPCR was seen in 25/58 (44%) of cases (CN>2.3). 3/58 (5%) had CN>5. There was a significantly higher *MET*-CN in pleomorphic compared to epithelial areas (2.7 versus 2.2 $P = 0.046$). While this did not correlate with c-MET IHC, an H-score of >223 had 75% sensitivity and 52.4% specificity for *MET*-CN >5.0 (Figure).

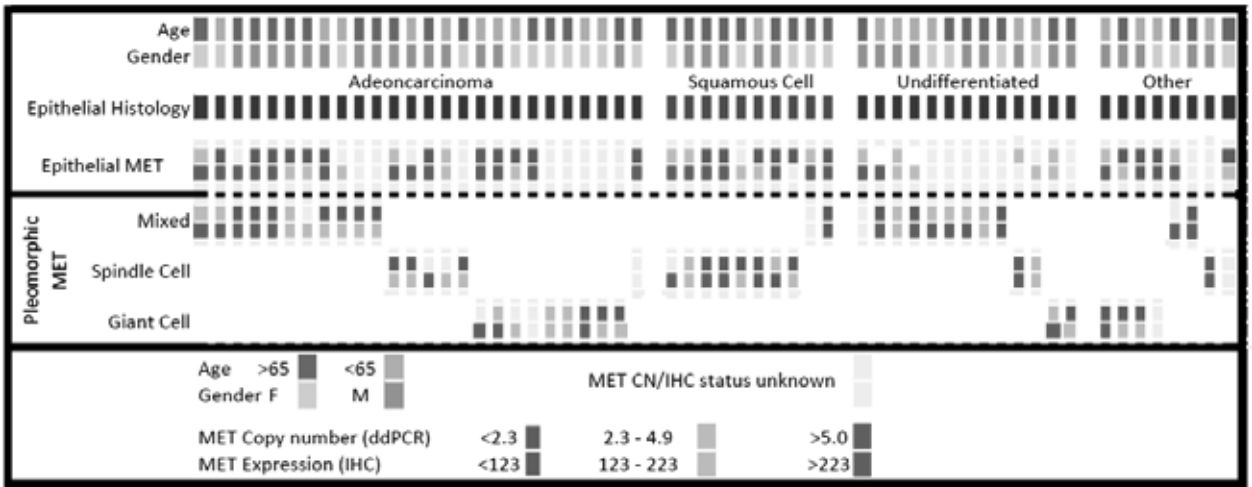

Figure 1: Distribution of MET copy number and expression according to epithelial and pleomorphic histolologies

Conclusion: There is intra-tumoral heterogeneity in *MET*-CN between tumoural subsets. This may account for the development of pleomorphic phenotypes in PC. Consequently *MET*-directed therapies such as crizotinib may be highly effective only against the MET-amplified component in PC and may not impact on overall tumoural control due to minimal efficacy in the non-amplified epithelial component. MET expression using IHC does not correlate with *MET*-CN determined by ddPCR, although may provide a screening tool for MET amplification. MET aberrations are potentially druggable and therefore this has implications for sampling and MET testing.

Keywords: MET, pleomorphic

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MA21.05 COMPREHENSIVE GENOMIC CHARACTERIZATION AND PROGNOSTIC NOMOGRAM DEVELOPED BY 295-GENE PANEL TARGETED SEQUENCING

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Background: The genomic landscape of lung cancer has been thoroughly studied in the western population. But comprehensive genetic profiling reports have been limited for the Chinese patients. Here we conducted deep targeted sequencing on a large cohort of Chinese treatment-naïve lung cancer patients and identified novel molecular patterns. We developed nomogram models for prognosis prediction by integrating genetic and clinical characteristics and aim to explore more precise models for risk stratification beyond TNM staging. **Method:** This was a retrospective study, enrolling diagnosed lung cancer patients at Tianjin Medical University Cancer Institute & Hospital from 2009 to 2012. We developed genomic landscape by targeted sequencing using a panel consisting of exons and critical introns of 295 cancer-related genes. Nomogram models were established to provide risk stratification in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) patients **Result:** 513 tumor tissue samples were collected at very beginning of treatment (stage I, n=193; stage II, n=140; stage IIIA, n=140; stage IIIB, n=5; stage IV, n=28; unknown, n=7). The most frequently mutated oncogenic genes in LUAD were EGFR (55%) and KRAS (11%), compared to 14% and 33% in TCGA. Heterogeneity existed in terms of mutual exclusive and co-occurrent mutated gene pairs between LUAD and LUSC. In LUAD, pairs with most significant exclusivity was EGFR/KRAS and co-occurrent was NOTCH3/GRIN2A, whereas the most significant concurrent gene pair in LUSC was ZNF703/FGFR1. To predict survival, our nomograms identified that, in stage I-IIIA LUAD and LUSC, mutated TET2 contributed to more favorable DFS while mutations in EPHA3 and ETV5 indicated better OS. Stage and mutated KRAS were associated with inferior DFS and OS (DFS, n=222, c-index=0.714; OS, n=308, c-index=0.706). In the T1+2&N0&M0 subgroup, which is considered clinically low risk for relapse, older patients who carry BRCA2 mutations were found to strongly correlate with poor DFS (n=121, c-index=0.709), while age and mutated KRAS were distinct indicators of inferior OS (n=163, c-index=0.725). The calibration for survival probability displayed well agreement between nomogram prediction and actual outcomes. Stratification of different risk groups based on nomogram prediction displayed significant differences among Kaplan-Meier curves for survival outcomes (p<0.0001). **Conclusion:** This is the so far largest cohort of

Chinese lung cancer patients with comprehensive genomic profiling reported. We revealed unique molecular profiles than TCGA and distinct mutual exclusivity and co-occurrence patterns between LUAD and LUSC. In addition, the nomogram models show promise of more precise prognostic prediction of NSCLC patients when integrating genetic information with clinical characteristics.

Keywords: targeted sequencing, lung cancer, Prognostic nomogram

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MA21.06 PROTEINS ASSOCIATED WITH SURVIVAL DIFFER DEPENDING ON MOLECULAR SUBTYPES, AND MUTATIONAL- AND SMOKING-STATUS IN NSCLC BIOPSIES

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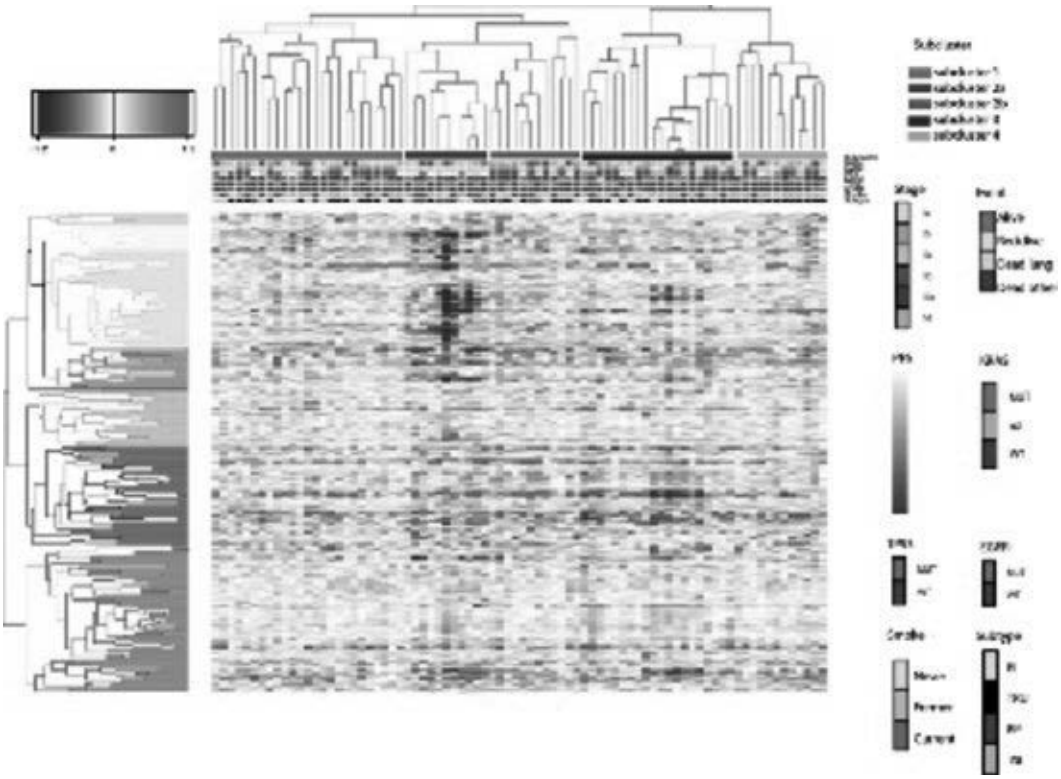
Background: Purpose: Proteins are the functional players driving both normal and disease physiology. The proteomic changes observed in lung cancer may be a consequence of mutations in essential driver-genes. The purpose of this study was to identify proteins in lung cancer biopsies associated with survival in groups stratified by smoking status, and *EGFR*-, *TP53*- and *KRAS*-mutations. **Method:** We have performed a profiling of 295 cancer relevant proteins, of which 60 were in a phosphorylated state, using reverse phase protein arrays (RPPA). We analyzed biopsies from 80 lung cancer patients (adenocarcinoma) and correlated the protein expression pattern with progression free survival (PFS) based on mutational- and smoking-status. **Result:** Spearman correlation analysis revealed a higher number of proteins with significant association to PFS ($p<0.05$) among the wild type samples compared to the mutated samples. High expression of protein kinase C (PKC) and the isoforms alpha, beta and delta, included the phosporylated state, showed the strongest association with better PFS, especially in the wild type samples. Ten proteins were associated with PFS in never-smokers, where eight of these were unique for this group. Unsupervised hierarchical clustering separated the samples into four subclusters, each enriched with one of the three molecular subtypes TRU, PI and PP (*Comprehensive molecular profiling of lung adenocarcinoma, Nature, 2014*). Subcluster 2 contained two smaller clusters (2a and 2b) enriched with samples of subtype PP, where subcluster 2a was associated with poor PFS ($p=0.003$, Figure 1).

Conclusion: As of today, we do not have any effective treatment targeting *KRAS*- and *TP53*- mutated cells. This study shows that expression of specific proteins and phospho-proteins associated with PFS differ depending on molecular subtype, and mutational- and smoking-status. Proteins associated with PFS may serve as therapeutic targets to circumvent treatment resistance.

Keywords: PROGRESSION FREE SURVIVAL, subtypes, protein profiling



MA21.07 A NATION-WIDE POPULATION-BASED MAPPING OF TARGETABLE ALTERATIONS IN SMOKING-INDEPENDENT LUNG CANCER

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Background: Smoking is by far the most important cause of lung cancer. However, lung cancer among never-smokers is common and increasing [1]. A smoking-independent subgroup of lung adenocarcinoma with certain molecular and clinical features exists [2-3]. Therefore, as 1st project within the Swedish Molecular Initiative against Lung cancer (SMIL) we aim to characterize never-smoking lung cancer for etiological, diagnostic and therapeutic purposes. **Method:** Through the Swedish National Lung Cancer Registry [1], we identified all individuals who underwent surgery for lung cancer in Sweden 2005-2014 and who were registered as never-smokers (n=540). At each study site (n=6), clinical data were reviewed by a thoracic oncologist/pulmonologist through patients' medical charts and archived tumor tissues were retrieved and reviewed by a thoracic pathologist. For subsequent studies, we extracted DNA and RNA (using the Qiagen AllPrep kit for FFPE tissue) and constructed tissue microarrays. As a first pre-planned analysis, we performed fusion gene mapping using an RNA-based NanoString nCounter Elements assay, as previously described [4]. **Result:** In the first 212 (out of 540) analyzed samples, we detected 17 fusions involving *ALK*, 8 involving *RET,* and 2 involving *NRG1*. In addition, *MET* exon 14 skipping was found in 17 samples. In total, these findings involved 21% of analyzed cases. Additional results from further studies on the cohort will be presented. **Conclusion:** SMIL is an ongoing nation-wide molecular research collaboration on lung cancer where we currently collect one of the largest never-smoking lung tumor cohorts worldwide. From the first pre-planned analyses, we conclude that, in a population-based cohort of early stage lung cancer from never-smokers, druggable oncogenic fusions are frequent. **References** 1. http://www.cancercentrum.se/vast/cancerdiagnoser/lunga-och-lungsack/kvalitetsregister 2. Staaf J, Jönsson G, Jönsson M, Karlsson A, Isaksson S, Salomonsson A,Pettersson HM, Soller M, Ewers SB, Johansson L, Jönsson P, Planck M. **Relation between smoking history and gene expression profiles in lung adenocarcinomas**. *BMC Med Genomics*. 2012 Jun 7;5:22. 3. Karlsson A, Ringnér M, Lauss M, Botling J, Micke P, Planck M, Staaf J. **Genomic and transcriptional alterations in lung adenocarcinoma in relation to smoking history**. *Clin Cancer Res*. 2014 Sep 15;20(18):4912-24. 4. Lindquist KE, Karlsson A, Levéen P, Brunnström H, Reuterswärd C, Holm K, Jönsson M, Annersten K, Rosengren F, Jirström K, Kosieradzki J, Ek L, Borg Å, Planck M, Jönsson G, Staaf J. **Clinical framework for next generation sequencing based analysis of treatment predictive mutations and multiplexed gene fusion detection in non-small cell lung cancer**. *Oncotarget*. 2017 May 23;8(21):34796-34810.

Keywords: population-based, never-smoker, gene fusion

MA21.09 DIFFERENTIAL GENE EXPRESSION IN TUMOR AND NORMAL TISSUE REVEALS NEW INSIGHTS IN THE BIOLOGY OF NON-SMALL CELL LUNG CARCINOMA.

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Background: Effective use of targeted cancer therapies typically depends upon the identification of actionable genomics somatic alterations, benefiting only a minority of Non-Small Cell Lung Carcinoma (NSCLC) patients. To integrate transcriptomic assessment in cancer precision medicine, we have evaluated the mRNA expression levels in tumors and their matched normal lung tissues with the hypothesis that mRNA quantification in tumors relative to their matched normal tissue may better reveal small transcriptional differences that are associated with major biological effects. **Method:** The discovery set used 123 frozen macrodissected treament-naive NSCLC tumors and matched normal tissues from surgical resections performed at the Mutualiste Montsouris Institute (Paris, France), and the validation set used 143 FFPE macrodissected treatment-naive NSCLC tumors and matched normal tissues from surgical resections performed at the Jewish General Hospital (Montreal, QC, Canada). A pathology review was performed in all cases. In the discovery set, expression levels of 17,318 genes were analysed using an Agilent Technologies platform; in the validation set, the NanoString nCoutner technology was used with a customized 148 probeset that was designed according to the results of the discovery phase. The primary objective of the study was post-surgery progression-free survival (PFS). The secondary objectives were post-surgery overall survival (OS) and the identification of pathway-driven expression signatures. **Result:** A set of highly expressed genes correlated with post-surgery PFS. Details of the prognostic signature will be presented at the meeting. Importantly, mRNA levels in normal tissues were highly variable between individuals. Organ matched reference enabled to control for the noise signals related to individual background genetic variability. The cell cycle G2/M checkpoint was the most significantly deregulated expression pathway in this cohort; nine genes in the signature are involved in this pathway and were upregulated in tumors, dependending on their histology: *CHEK1*, *TOP2A, AURKA, CDC2, PLK1, CDC2, CDC25A, CDC25B, and CDC25C*. *CHEK1 is a* pivotal gene in regulating the G2/M cell cycle pathway that triggers the double-strand base excision repair in which the main effector is PARP1. *CHEK1 was* overexpressed in 86% of adenocarcinomas, versus 42% for *PARP1.* **Conclusion:** Conventional transcriptomic approaches using expression metrics obtained in tumor pools may miss important changes due to individual variability in non-tumoral tissue.The present work illustrates that paired matched tumor and normal tissues can identify new key genes involved in the biology and pathogenesis of NSCLC, and opens new avenues for integrating transcriptomic investigations in the precision medicine arena.

Keywords: transcriptome, Prognosis, Pathology

MA21.10 LARGE-SCALE DISCOVERY OF NOVEL HUMAN ONCOFETAL TRANSCRIPTS IN LUNG

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Background: Oncofetal genes are those expressed during both embryogenesis and tumourigenesis, but silenced in normal adult tissues. Although most described oncofetal genes have been shown to play important roles in tumour development and display potential as diagnostic and prognostic markers, this area of research remains largely unexplored. The advent of high-throughput technologies has not only allowed for large-scale discovery of biomarkers, but has also highlighted the role of non-coding RNAs from tissue development to malignant transformation. Small non-coding RNAs (sncRNAs, e.g., miRNA, snoRNA, piRNA, snRNA) are key players in gene-regulatory networks, and have shown promise as fluid-based biomarkers. In this study, we performed a comprehensive characterization of the sncRNA transcriptome of fetal, non-malignant and tumour lung tissues to identify development-associated (oncofetal) sncRNAs with roles in lung cancer, including the discovery of previously unannotated miRNAs. **Method:** Here, 209 paired non-malignant/tumour lung samples from two cohorts (BCCA, n=118 and TCGA, n=91) and 25 fetal lung samples were analyzed through the platform miRMaster. This platform aligns sequence reads to the hg38 genomic build, quantifies known sncRNA species and predicts novel miRNA candidates using the mirDeep2 algorithm. The sncRNA species that had no significant alterations in expression between fetal and tumours samples, but displayed significant differential expression between fetal/non-malignant and tumour/non-malignant tissues were classified as oncofetal sncRNAs. The biological relevance of the

oncofetal sncRNAs and the novel miRNA candidates was investigated by gene-target prediction and pathway enrichment analyses, using mirDIP, IID and pathDIP databases. **Result:** Our study provides the first large-scale characterization of the lung sncRNA transcriptome in fetal, non-malignant and tumour tissues. In particular, we discovered the expression of 464 novel miRNA candidates and identified a large subset of oncofetal sncRNAs. Target prediction analysis showed that the novel miRNA candidates discovered in all lung tissues are involved in cellular processes associated with cell proliferation, migration and survival, including the Wnt, MAPK and Notch signaling pathways, which are known to be associated with the development and progression of lung cancer. Additionally, oncofetal sncRNAs were found to be associated with cell cycle control and differentiation, highlighting the functional relevance of these molecules. **Conclusion:** We have not only expanded the lung sncRNA transcriptome, but also revealed the expression of a large number of sncRNAs relevant to lung tumourigenesis that are not expressed in normal adult tissues. Our results will aid in the development of more accurate fluid-based biomarkers for the early-detection of lung cancer.

Keywords: small non-coding RNAs, novel microRNAs, Oncofetal

MA21 MOLECULAR SUBTYPING, CBL3, AND NON CODING RNA
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA21.11 EPIGENOMIC MAPPING OF CELL-FREE DNA IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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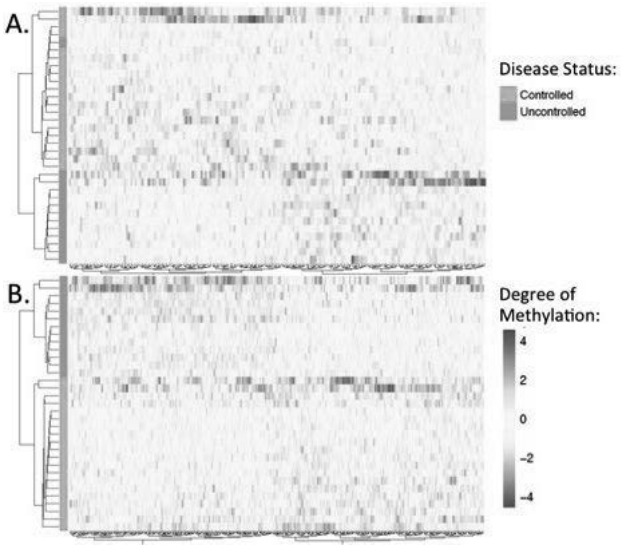
Background: Epigenetic modifications such as DNA methylation play an important role in human cancers, and have been implicated in tumor progression and drug resistance. Prior studies suggest 5-hydroxymethylcytosine (5hmC) has many important regulatory functions, given the colocalization of 5hmC within regulatory regions such as transcription factor binding sites, promotors and enhancers. Elevated 5hmC levels have been associated with increased gene expression. Genome-wide mapping of 5hmC has been performed in several different cells and tissues including brain and bone, though this has not previously been studied in lung cancer. It is possible the 5hmC profile can serve as a valuable biomarker for diagnosis, assessment for resistance, and surveillance for recurrence in non-small cell lung cancer (NSCLC). **Method:** This was an exploratory study with a primary objective to perform genome-wide 5-hydroxymethylcytosine profiling of circulating cell-free DNA (cfDNA) in patients with epidermal growth factor receptor (EGFR)-mutated lung cancer. Thirty-three different patient samples were collected from 32 different patients with advanced NSCLC with a known EGFR mutation by prior tissue genotyping such as FoundationMedicine or cfDNA such as Guardant. Samples were classified as "controlled" if the disease burden was stable or decreasing, versus "uncontrolled" if disease burden was increasing. Patients ranged from previously untreated to heavily pretreated. Full profiling of 5hmC in cfDNA was performed. **Result:** A difference in modification between "controlled" and "uncontrolled" disease was found in 311 differentially modified regions ($p<0.01$), and in 189 differentially modified genes($p<0.01$). Figure 1: Degree of methylation of a) 311 differentially modified regions b) 189 differentially modified genes.



Conclusion: In a retrospective analysis, a strong correlation exists between the methylation of specific regions and genes and the state of disease control. Future research should focus on if 5hmC profiling can be used to monitor disease status, to predict response to treatment, or alongside ctDNA for diagnostic accuracy.

Keywords: cell-free DNA, DNA methylation, Gene Expression Regulation

MA22 NEW THERAPEUTICS, PATHOLOGY, AND BRAIN METASTASES FOR SMALL CELL AND NEUROENDOCRINE TUMOUR
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA22.01 PARP INHIBITOR RADIOSENSITIZATION OF SMALL CELL LUNG CANCER DIFFERS BY PARP TRAPPING POTENCY

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Background: Small cell lung cancer (SCLC) is an aggressive malignancy with a critical need for novel therapies. Our goal was to determine whether PARP inhibition could sensitize SCLC cells to ionizing radiation (IR) and if so, to determine the contribution of PARP trapping to radiosensitization. **Method:** Short-term viability assays and clonogenic survival assays (CSA) were used to assess radiosensitization in six SCLC cell lines. Doses of veliparib and talazoparib with equivalent enzymatic inhibitory activity but differing PARP trapping activity were identified and compared in CSAs. The dose modification factor (DMF), defined as the ratio of RT dose needed to achieve an equivalent level of survival with RT alone compared to that for RT plus drug, was calculated at 37% survival. Phosphorylated gH2AX sub-nuclear foci were assessed by immunofluorescence to quantify double-stranded DNA breaks (DSBs). Talazoparib, IR, and their combination were tested in three patient-derived xenograft (PDX) models. **Result:** Talazoparib radiosensitized 5 of 6 SCLC cell lines in short-term viability assays with a talazoparib dose of 20 nM demonstrating a DMF ranging from 1.61 – 2.88 in 4 cell lines with 0.2 nM demonstrating a DMF of 1.56 in 1 additional cell line. We confirmed radiosensitization in 3 of 3 cell lines by CSAs with DMF ranging from 1.40 – 2.20. To determine effects of PARP trapping on radiosensitization, we identified that concentrations of 200 nM talazoparib and 1600 nM veliparib similarly inhibited PAR polymerization; however, talazoparib exhibited greater PARP trapping activity that was associated with superior radiosensitization (DMF 3.3 with talazoparib vs DMF 1.0 with veliparib). This observation further correlated with an increased number of DSBs induced by talazoparib as compared to veliparib, where we found that talazoparib produced more residual DSBs than veliparib and DMSO with IR (gH2AX foci mean per cell: talazoparib 53.5, veliparib 33.5, DMSO 25.5) and without IR (40.0, 19.6, 14.6). Finally, a dose of 0.2 mg/kg talazoparib *in vivo* caused tumor growth inhibition in combination with IR but not as a single agent in 3 SCLC PDX models. **Conclusion:** PARP inhibition effectively sensitizes SCLC cell lines and PDXs to RT, and PARP trapping activity enhances this effect. PARP inhibitors, especially those with high PARP trapping activity, may provide a powerful tool to improve the efficacy of RT in SCLC.

Keywords: small cell lung cancer, PARP INHIBITOR, radiosensitization

MA22 NEW THERAPEUTICS, PATHOLOGY, AND BRAIN METASTASES FOR SMALL CELL AND NEUROENDOCRINE TUMOUR
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA22.02 ACTIVATION OF MAPK SUPPRESSES NEUROENDOCRINE TRANSCRIPTION FACTORS AND CAUSES TRANSDIFFERENTIATION OF SMALL CELL LUNG CANCER

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Background: Gene alterations involved in activating signaling through receptor tyrosine kinases/RAS/RAF/MEK/ERK pathway are extremely rare in small cell lung cancer (SCLC). In addition, EGFR expression is lost during the histological reprogramming of *EGFR* mutation-positive lung adenocarcinoma (LUAD) to SCLC, despite the cancer retaining the original *EGFR* mutation. These observations imply that signaling through mitogen-activated protein kinases (MAPKs) - critically important in non-small cell lung cancer - might be detrimental in SCLC biology. Here we investigated the impact of induction of two mutated oncogenic proteins, $EGFR^{L858R}$ and $KRAS^{G12V}$ the most common drivers of LUAD, on the phenotype and signaling profiles of SCLC. **Method:** $EGFR^{L858R}$ or $KRAS^{G12V}$

were aberrantly expressed in an inducible manner in three SCLC cell lines (H2107, H82, and H524). The effects of induction of these oncogenes were determined through cell viability analysis and Western blotting analysis particularly focusing on the regulation of master neuroendocrine transcription factors such as insulinoma-associated protein 1 (INSM1), POU class 3 homeobox 2 (BRN2), achaete-scute hologue 1 (ASCL1), and neurogenic differentiation factor 1 (NEUROD1). Genome-wide expression profiles were assessed in a longitudinal manner after oncogene induction and specific gene sets driven by MAPK activation in each SCLC cell line were defined. **Result:** INSM1 and BRN2 were expressed in all the SCLC cell lines assessed. ASCL1 was expressed only in H2107 (classic type). Alternatively, NEUROD1 was expressed in the variant type SCLC cell lines, H82 and H524. Induction of mutant-EGFR or -KRAS resulted in different cell viability according to cell lines: H82 cells showed higher proliferation rate and the others showed lower proliferative ability. Furthermore, induction of these oncogenes caused transition from suspension to adherent phenotype in all the three cell lines. Importantly, EGFR/KRAS induction downregulated neuroendocrine transcription factors and these effects were more strongly observed after KRAS induction than after EGFR induction, which was concordant with the difference in degrees of phospho-ERK1/2 upregulation after induction of these mutant-oncogenes. Notably, treatment with SCH772984, an ERK1/2 inhibitor, rescued the repression of neuroendocrine factors by KRAS induction. Gene expression profiling is currently underway to reveal specific factors mediating ERK induced suppression of neuroendocrine programs. **Conclusion:** Activation of the RAS/RAF/MEK/ERK pathway causes phenotypic transition in SCLC growing in suspension to the adherent phenotype and suppresses neuroendocrine differentiation. Thus, ERK signaling has an fundamental role in repression of neuroendocrine differentiation programs and may be important in regulating histological transversion of SCLC to and from NSCLC with implications to drug resistance.

Keywords: MAPK, neuroendocrine factors, small cell lung cancer

MA22 NEW THERAPEUTICS, PATHOLOGY, AND BRAIN METASTASES FOR SMALL CELL AND NEUROENDOCRINE TUMOUR
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA22.03 SCLC CIRCULATING TUMOUR CELL DERIVED EXPLANTS: THE CLINICAL CHARACTERISTICS OF PATIENTS WHOSE SAMPLES GENERATE CDX

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Background: Small cell lung cancer (SCLC) prognosis is dismal, with minimal improvement in recent years. Work with SCLC cell lines and targeted therapies have been disappointing when translated into clinical practice. Circulating tumour cells (CTCs) represent a readily accessible liquid biopsy, which can be used to generate CTC derived explants (CDXs) for the study of SCLC biology and the investigation of biomarkers and therapeutics. These clinically relevant models appear to mirror patient response to therapeutics. Our aim was to assess if the patients whose samples generated a CDX represent the SCLC population, and determine if the clinical features of these patients offer insight into CTC biology. **Method:** This was a single centre, retrospective analysis of 147 SCLC patients who had participated in The CHEMORES Study in which SCLC patients were asked to donate blood samples for the discovery and validation of novel biomarkers. Paired patient blood samples were taken for CTC enumeration using CellSearch Technology and for attempted CDX model generation. We obtained demographic and clinical information on these patients, and analysed the data for differences between patients whose blood samples generated a CDX and those whose did not. **Result:** 231 paired blood samples were taken from 147 patients, with 45 CDXs successfully generated from 34 patients. CTC number was significantly higher in samples which generated a CDX than those which didn't, p=0.001. Successful progression samples had a significantly lower CTC number than successful baseline samples, p=0.026. There was no significant difference in age, gender, pack year history, performance status, stage, chemosensitivity or the presence of liver or brain metastases between patients whose samples did and did not generate a CDX. Metastatic burden was significantly higher in patients whose samples generated a CDX, p=<0.001. Progression free (PFS) and overall survival were significantly shorter in patients whose samples generated a CDX, p=<0.001 **Conclusion:** CTC number correlates with CDX success, although a specific CTC phenotype may be more important. CTCs at progression may have a more aggressive phenotype than those at baseline. CDXs appeared to represent the SCLC population which is important when translating knowledge gained by studying CDXs into clinical practice. CTCs may play a role in the widespread metastatic dissemination of SCLC and thus survival of patients. Shortened PFS in the absence of difference in chemosensitivity may be due to outliers with particularly long PFS in the unsuccessful group. Further genomic and phenotypic analysis of subpopulations of CTCs may provide further insight.

Keywords: Cell Derived Explants, Circulating Tumour Cells, small cell lung cancer

MA22 NEW THERAPEUTICS, PATHOLOGY, AND BRAIN METASTASES FOR SMALL CELL AND NEUROENDOCRINE TUMOUR
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA22.05 IMPACT OF TUMOR SPREAD THROUGH AIR SPACES (STAS) IN LUNG NEUROENDOCRINE TUMORS (NETS)

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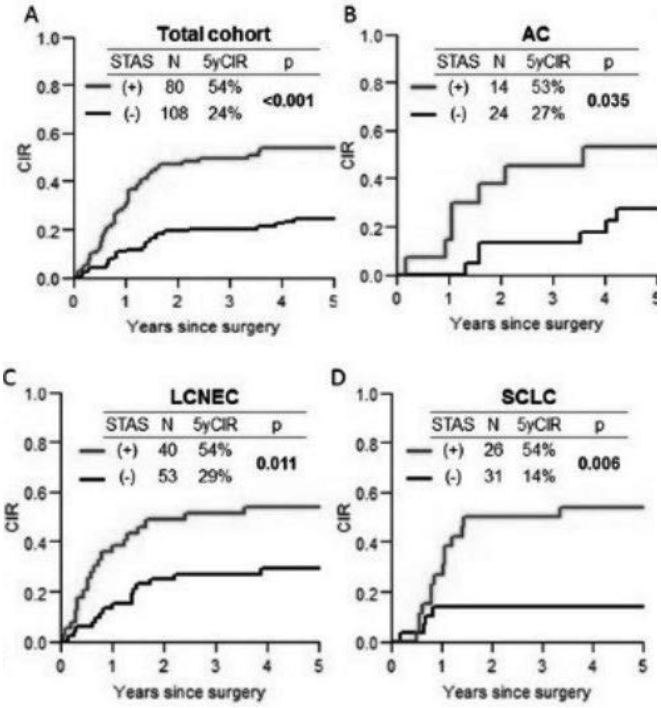
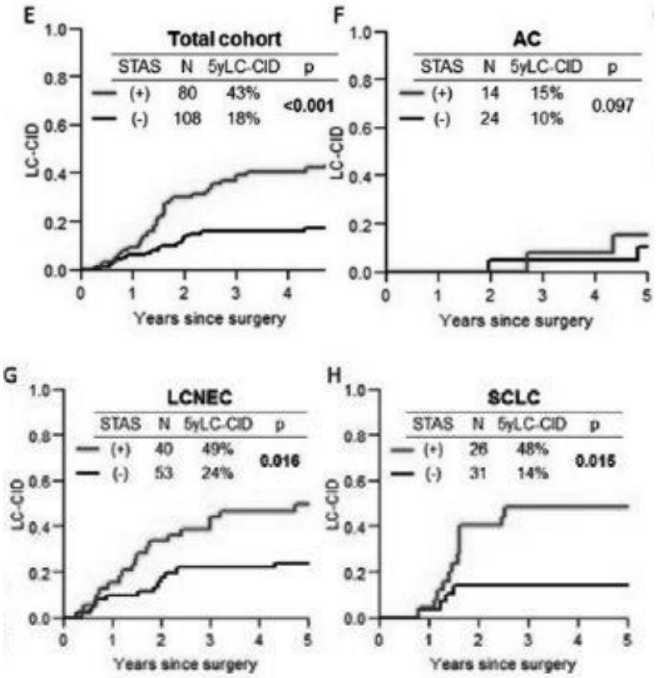
Background: We have previously reported the prognostic significance of STAS in lung adenocarcinoma and squamous cell carcinoma. The aim of this study was to investigate the incidence and prognostic impact of STAS in lung NETs. **Method:** We evaluated all tumor slides (range 2-7, median 3) for presence of STAS from patients with p-Stage I-III primary lung NETs [n=628, typical carcinoid (TC, n=305), atypical carcinoid (AC, n=38), large cell neuroendocrine carcinoma (LCNEC, n=93) and small cell lung carcinoma (SCLC, n=57)]. Patients with combined NETs were excluded from this analysis (n=19). Cumulative incidence of recurrence (CIR) and lung cancer-specific cumulative incidence of death (LC-CID) were analyzed by competing risks approach. **Result:** STAS was identified in 25% of NETs (15% in TC, 37% in AC, 43% in LCNEC, and 46% in SCLC). Prognostic analysis in TC cohort was not conducted due to the small number of events (<5 events). Patients with STAS positive tumors were associated with higher CIR than STAS negative tumors in the total (AC-LCNEC-SCLC) cohort as well as individual AC, LCNEC and SCLC cohorts (Figure 1, A-D). STAS was also associated with higher LC-CID in all cohorts except for AC (Figure 1, E-H). In multivariable analysis, STAS was a significant risk factor for recurrence and lung cancer specific-death, independent of stage and histologic subtype. Stratified by stage, STAS was an independent predictor of recurrence (subhazard ratio [SHR] 2.39, 95% CI 1.26-4.54, p= 0.007) and lung cancer-specific death (SHR 2.42, 95% CI 1.21- 4.84, p= 0.012) in LCNEC. In SCLC, STAS was also an independent risk factor of lung cancer-specific death (SHR 4.06, 95% CI 1.33- 12.35, p= 0.014).





Conclusion: STAS is a significant prognosticator in individual NET subtypes; AC, LCNEC, and SCLC. STAS is an independent poor prognostic factor in LCNEC and SCLC for lung cancer-specific death.

Keywords: Prognosis, Neuroendocrine tumors, Spread Through Air Spaces

MA22 NEW THERAPEUTICS, PATHOLOGY, AND BRAIN METASTASES FOR SMALL CELL AND NEUROENDOCRINE TUMOUR
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA22.06 PREINVASIVE MULTIFOCAL NEUROENDOCRINE LESIONS WITH PRIMARY TYPICAL CARCINOID LUNG TUMORS: A NEGATIVE PROGNOSTIC FACTOR?

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Background: Impact on survival in patients with surgically resected multifocal neuroendocrine lesions (MNET), such as diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) or tumorlets, along with primary typical lung carcinoid (TC) is unclear. Aim of this study is to analyze whether synchronous preinvasive multifocal neuroendocrine lesions of the lung with primary TC tumors (MTNET+TC) may represent a negative prognostic factor. **Method:** A retrospective study, prospectively collected, for TC from two institutional databases was evaluated with a lifelong follow-up from surgery. Patients who did not receive surgery, underwent bronchial resection or lung transplant were excluded. Pathology specimens were all reclassified according the 2015 WHO and the eight AJCC Staging system. Kaplan-Meier(KM) method and Log-rank test reports significance between TC and were MTNET+TC were used. Hence a 1:1 propensity score matching analyses was done by adjusting the imbalance and comparing the overall survival and progression free rate between matched groups with a Cox proportional hazards regression model. A p value of 0.05 or less was considered significant. **Result:** From January 1983 to December 2013 a total of 234 patients was outlined from the databases (TABLE). A total of 41 patients (17.5%) with MNET+TC were identified. Overall KM progression free survival achieved at 5 and 10 years respectively MNET+TC 93.2% and 83.8% compare to TC 98.4% and 96.1% (p =0.00039). Thirty-six MNET+TC were matched pairs vs. TC alone. Univariate Cox proportional hazards model for matched patients MNET+TC compared to TC was 2.78 (95% CI=0.84-9.3, p=0.095). Difference in progression free rate between matched groups was p<0.001.

Covariate	Full Sample n=234 (%)	TC n=193 (%)	MNET+TC n=41 (%)	p-value
CENTRE				0.39
Perugia (ITALY)	135 (58)	114 (59)	21 (51)	
Toronto (CANADA)	99 (42)	79 (41)	20 (49)	
AGE CATEGORY				0.07
<=65	155 (66)	133 (69)	22 (54)	
>65	79 (34)	60 (31)	19 (46)	
SMOKE				0.15
No	83 (35)	71 (37)	10 (24)	
Yes (also second-hand smoke)	155 (65)	122 (63)	31 (76)	
LOCATION				**0.0032**
Central	106 (45)	96 (50)	10 (24)	
Peripheral	128 (55)	97 (50)	31 (76)	
SIDE				0.23
Left	101 (43)	87 (45)	14 (34)	
Right	133 (57)	106 (55)	27 (66)	
SEX				0.3
Female	136 (58)	109 (56)	27 (66)	
Male	98 (42)	84 (44)	14 (34)	
LUNG				0.24
Bronchus	12 (5)	10 (5)	2 (5)	
Lower	104 (44)	89 (46)	15 (37)	
Middle	47 (20)	34 (18)	13 (32)	
Upper	71 (30)	60 (31)	11 (27)	
SURGERY				0.12
Wedge + Sub-lobar	35 (15)	24 (12)	11 (27)	
Lobectomy + Sleeve Lobectomy	186 (79)	158 (82)	28 (68)	
Pneumonectomy	12 (5)	10 (5)	2 (5)	
LYMPHADENECTOMY				**0.035**
No	19 (8)	12 (6)	7 (17)	
Yes	215 (92)	181 (94)	34 (83)	
TC DIAMETER				**0.011**
Mean (SD)	20.4 (11.7)	21.3 (11.7)	16.2 (10.9)	
8TH AJCC STAGING SYSTEM				**0.02**
IA1	30 (13)	20 (10)	10 (24)	
IA2	87 (37)	71 (37)	16 (39)	
IA3	52 (22)	47 (24)	5 (12)	
IB	20 (9)	20 (10)	0 (0)	
IIA	3 (1)	3 (2)	0 (0)	
IIB	12 (5)	11 (6)	1 (2)	
IIIA	10 (4)	8 (4)	2 (5)	
IIIB	1 (0)	1 (1)	0 (0)	
X	19 (8)	12 (6)	7 (17)	
FOLLOW-UP TIME (YEARS)				
Mean (SD)	9.6 (5.2)	9.9 (5.3)	7.9 (4.6)	
STATUS				
Alive	195 (83)	170 (88)	25 (61)	
Alive with Evidence of Disease	11 (5)	7 (4)	4 (10)	
Dead for other Causes	24 (10)	16 (8)	8 (20)	
Dead Disease Related	4 (2)	0 (0)	4 (10)	

Conclusion: Synchronous multifocal neuroendocrine preinvasive lesions (MNET) with primary typical carcinoid (TC) lung tumors can be a negative prognostic factor. Careful search of MNET should be always performed in clinical and pathological staging of a suspected primary TC. The increased risk of progression of MNET+TC warrants an accurate and lifelong follow-up.

Keywords: diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, tumorlets, Typical pulmonary carcinoid tumor

MA22 NEW THERAPEUTICS, PATHOLOGY, AND BRAIN METASTASES FOR SMALL CELL AND NEUROENDOCRINE TUMOUR
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA22.07 PROGNOSTIC VALUE OF DISTANT ORGAN-SPECIFIC METASTASES IN NEWLY DIAGNOSED LUNG NEUROENDOCRINE TUMORS: A POPULATION-BASED STUDY

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Background: Lung neuroendocrine tumors (Lung NETs) are rare neoplasms with inferior outcomes for patients with distant metastases. AJCC cancer staging system for the classification of NETs was first introduced in 2010. However, the prognostic impact of metastatic sites for lung NETs are poorly explored. We aimed to fill this gap of our knowledge using the SEER database. **Method:** Clinical-pathological characteristics, specific metastatic sites and outcomes of stage IV lung NETs (according to AJCC 7th edition) were extracted from the SEER database from 2010-2014. Overall survival (OS) and Lung cancer-specific survival (LCSS) were estimated by the Kaplan-Meier method and comparisons conducted using log-rank tests and Cox regression models. **Result:** A total of 2337 stage IV lung NETs patients were identified. The 5-year OS and LCSS were 10.7% and 18.3%, respectively. Among them, 2159 patients had specific organ metastases (liver, lung, bone or brain) at diagnosis. Liver was the most common metastatic site (1183, 50.6%), followed by bone (801,34.3%), lung (701,29.9%) and brain (616,26.4%). Patients with isolated lung metastases (1-, 5-year OS: 63.2%, 43.2%; 1-, 5-year LCSS: 74.0%, 62.9%,) had significantly better outcomes

comparing to other patterns of metastases. The outcomes of patients with any brain metastases was most unfavorable (1-, 5-year OS: 20.3%, 2.1%, p<0.001; 1-, 5-year LCSS: 26.8%, 7.7%, p<0.001). Multivariate Cox regression analysis on OS and LCSS revealed that age > 60 years (p<0.001), male gender (p<0.001), poorer differentiation (p<0.001) and brain metastases (p<0.001) were independently poor prognostic factors for stage IV lung NETs patients. **Conclusion:** The prognostic impact of metastatic site was unambiguous in stage IV patients with lung NETs. Comparing other metastatic patterns, brain metastases was associated with significant worse survival outcomes. Nearly twenty-fold difference in 5-year survival was revealed between isolated lung and brain metastases. For advanced lung NETs patients, brain metastases might be considered as a distinct category of dismal outcomes.

Keywords: Lung neuroendocrine tumors, Distant organ metastases, survival

MA22 NEW THERAPEUTICS, PATHOLOGY, AND BRAIN METASTASES FOR SMALL CELL AND NEUROENDOCRINE TUMOUR
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA22.09 SHOULD STEREOTACTIC RADIOSURGERY BE CONSIDERED FOR SALVAGE OF INTRACRANIAL RECURRENCE IN SMALL CELL LUNG CANCER?

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Background: Prophylactic cranial irradiation (PCI) remains a standard of care for small cell lung cancer (SCLC) to improve overall survival (OS) and prevent recurrence in limited (LS) and extensive stage (ES) disease. Intracranial recurrence (IC) after PCI affects 12-33%. Limited published data describe outcomes of salvage reirradiation (ReRT). Our purpose was to review outcomes after IC post-PCI or therapeutic whole brain radiotherapy (WBRT). **Method:** Consecutive patients with pathologically-confirmed SCLC assessed (01/2013-12/2015) at a tertiary cancer centre (catchment 1.5M) were retrospectively reviewed. Demographics, treatment and outcomes were abstracted and summary statistics calculated. Kaplan-Meier estimates and univariate and multivariate analysis (MVA) via the Cox proportional hazard model were performed. **Result:** Median age was 66.1yrs, 53% female, and 80% ECOG 0-2 (N =372). Median survival (MS) was 24 months (95%CI 18.3-29.7 mos) for 103 LS, and 7 months (95%CI 6.1-7.9 mos) for 269 ES patients. 72/103 LS received PCI (69.9%), 84.7% of whom had radical thoracic radiotherapy (RT). 54/269 ES patients presented with brain metastases (BM); 98/215 of the remaining received PCI, and 72 of those thoracic RT (84.7% 25-30Gy/10). PCI dose was 25Gy/10 in 95.9%. PCI patients had better performance status (PS), and were more likely to receive chemotherapy (CT) and thoracic RT (all p<0.013). 18.8% (32/170) recurred post-PCI (13 LS; 19 ES) at a median of 11.5 mos. 45/54 presenting with BM received WBRT (83.3% 20Gy/5), 14 of whom recurred. MS after PCI was 28 mos vs 12 mos for LS and ES, respectively. For LS patients with IC post-PCI, MS was 20 mos vs 38 mos without IC (p=0.03). On MVA, interval between brain RT predicted OS after PCI (HR 0.87; p<0.001), while stage (HR 3.56; p=0.008) and cranial RT dose predicted IC (HR 0.65; p=0.047). At IC, 56.5% (26/46) had <5 BM, median 1.7cm (range 0.5-5cm), 39.1% had no extracranial disease, 6 were asymptomatic, and 50% had ECOG 0-2. 30/46 had ReRT: 27 WBRT and 3 stereotactic radiosurgery (SRS). In retrospect, 17/46 would have been candidates for salvage SRS: 5 LS post-PCI; 8 ES post-PCI; and 4 ES post-WBRT. **Conclusion:** This cohort seems to challenge the belief that in-brain progression is always: diffuse; associated with clinical deterioration; and synchronous with systemic failure. With potential for OS >6 months, repeat WBRT risks meaningful neurocognitive toxicity. Further data are required; however, approximately 1 in 3 SCLC patients who recur after PCI or WBRT appear clinically appropriate for salvage SRS.

Keywords: Stereotactic Radiosurgery, brain metastases, reirradiation

MA22 NEW THERAPEUTICS, PATHOLOGY, AND BRAIN METASTASES FOR SMALL CELL AND NEUROENDOCRINE TUMOUR
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA22.10 PREVALENCE AND RISK FACTORS OF BRAIN METASTASES IN LIMITED STAGE SMALL CELL LUNG CANCER IMMEDIATELY BEFORE PROPHYLACTIC CRANIAL IRRADIATION

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Background: Prophylactic cranial irradiation (PCI) reduces the incidence of brain metastasis (BM) and improves overall survival (OS) in limited-stage Small Cell Lung Cancer (LS-SCLC) patients with complete or partial remission after receiving chemoradiotherapy. However, cranial magnetic resonance imaging (CMRI) before scheduled PCI is not mandatory, and its necessity remains controversial. Therefore, we conducted this study to evaluate LS-SCLC patients' BM rate revealed by CMRI immediately before PCI. **Method:** 283 consecutive LS-SCLC patients diagnosed at our center between 2014 and 2017 were evaluated, all have negative base-line CMRI. Patients received platinum-based chemotherapy plus concurrent or sequential thoracic radiation. 119 complete or partial responders were identified. All received another CMRI immediately before PCI and constituted the cohort of interest. Logistic regression was employed to assess the relationship between pre-PCI BM risk and the following variables: age, gender, smoking history, lymph node stage or time from treatment initiation to pre-PCI MRI (TTPCI). Cox regression was employed to evaluate relations between these risk factors and OS. Two-sided *P* value <0.05 was considered statistical significant. **Result:** 25 out of 119 (21%) LS-SCLC patients developed pre-PCI BMs, TTPCI (2.83 to 13.03 months) was revealed as an independent risk factor for pre-PCI BM (risk ratio: 1.653, 95% CI: 1.312 – 2.084, *P* < 0.001, **Table 1**). Patients with pre-PCI BM have significantly shorter OS (hazard ratio: 1.653, 95% CI: 1.312 – 2.084, *P* < 0.001, **Table 1**).

Table 1. Risk Factor Analyses for pre-PCI Brain Metastasis and Overal survival.

Covariates for pre-PCI BM	RR (95% CI)	P
Gender	0.402 (0.011 - 14.242)	0.617
Age at diagnosis	0.999 (0.933 - 1.069)	0.977
Smoking status	0.117 (0.003 - 4.048)	0.235
Lymph Node Stage (0-2 vs 3)	1.457 (0.437 - 4.854)	0.540
TTPCI (months)	**1.653 (1.312 - 2.084)**	**< 0.001**
Covariates for Overal Survival	**HR (95% CI)**	**P**
Gender	0.349 (0.097 - 1.254)	0.108
Age at diagnosis	1.041 (0.997 - 1.087)	0.069
Smoking status	1.404 (0.792 - 2.489)	0.184
Lymph Node Stage (0-2 vs 3)	1.293 (0.634 - 2.637)	0.480
pre-PCI BM	**4.411 (2.330 - 8.351)**	**< 0.001**

Abbrevation: RR: risk ratio; HR: hazard ratio; CI: confidence interval; PCI: prophylactic cranial irradiation; BM: brain metastasis. TTPCI: time interval from treatment initiation to pre-PCI cranial magnetic resonance imaging, as a continuous variable (range: 2.83 to 13.03 months).
Binary logistic regression was employed for pre-PCI BM risk analysis. Cox regression was employed for survival risk analysis.

Conclusion: A considerable portion of LS-SCLC patients developed BM after definitive chemoradiotherapy and immediately before PCI. We recommend mandatory CMRI before PCI in these patients. Earlier scheduled PCI may reduce BM rate in selected LS-SCLC patients, further studies are warranted to determine the optimal PCI timing for LS-SCLC patients.

Keywords: small cell lung cancer, Brain metastasis, prophylactic cranial irradiation

MA22 NEW THERAPEUTICS, PATHOLOGY, AND BRAIN METASTASES FOR SMALL CELL AND NEUROENDOCRINE TUMOUR
TUESDAY, SEPTEMBER 25, 2018 - 15:15-16:45

MA22.11 RISK OF HIPPOCAMPAL METASTASES IN SMALL CELL LUNG CANCER: IMPLICATIONS FOR HIPPOCAMPAL SPARING CRANIAL IRRADIATION

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Background: Prophylactic cranial irradiation (PCI) in patients with small cell lung cancer (SCLC) decreases the incidence of brain metastases (BMs) and can improve overall survival. However whole brain radiation therapy is associated with a decline in neurocognitive function. Hippocampal-sparing whole brain radiation therapy (HS-WBRT) aims to minimise damage to neural progenitor cells (NPCs) within the hippocampus and reduce the toxicity of PCI, although there may be an increased risk of treatment failure in the hippocampal region. The incidence of hippocampal metastases was investigated in patients with BMs from SCLC to evaluate the feasibility of HS-WBRT in this population. **Method:** Patients with SCLC presenting between 2000 and 2016 with BMs at presentation or during their disease course without previous cranial irradiation were identified from a prospectively maintained database. Hippocampal metastases (HMs) were defined as metastases within the hippocampus and a 5-mm radial expansion (hippocampus avoidance zone, according to the Radiation Therapy Oncology Group 0933 atlas). The rate of hippocampal metastases and associated clinical features were analysed. **Result:** One hundred and twenty eligible patients

with a total of 754 brain metastases were identified. In 67 (55.8%) patients BMs were detected at diagnosis of SCLC and in 53 (44.2%) patients BMs developed later without previous PCI. The median number of metastases was 3, and 27 (22.5%) patients had a single BM. There were 22 (18.3%) patients with hippocampal metastases. A total of 23 (3.1%) metastases involved the hippocampal avoidance area. On logistic regression analysis, the number of brain metastases was an independent risk factor for HMs. **Conclusion:** The overall incidence of hippocampal metastases in our cohort of SCLC patients is high. As HS-WBRT may increase the risk of treatment failure in the spared region, prospective randomised trials are encouraged.

Keywords: small cell lung cancer, Brain metastasis, Whole Brain Radiotherapy

MINI ORAL ABSTRACT SESSIONS WEDNESDAY, SEPTEMBER 26, 2018

MA23 EARLY STAGE LUNG CANCER: PRESENT AND FUTURE
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MA23.01 BUFFY COAT IMMUNOONCOLOGIC DIAGNOSIS AND PROGNOSIS OF PSTAGE I LUNG ADENOCARCINOMA

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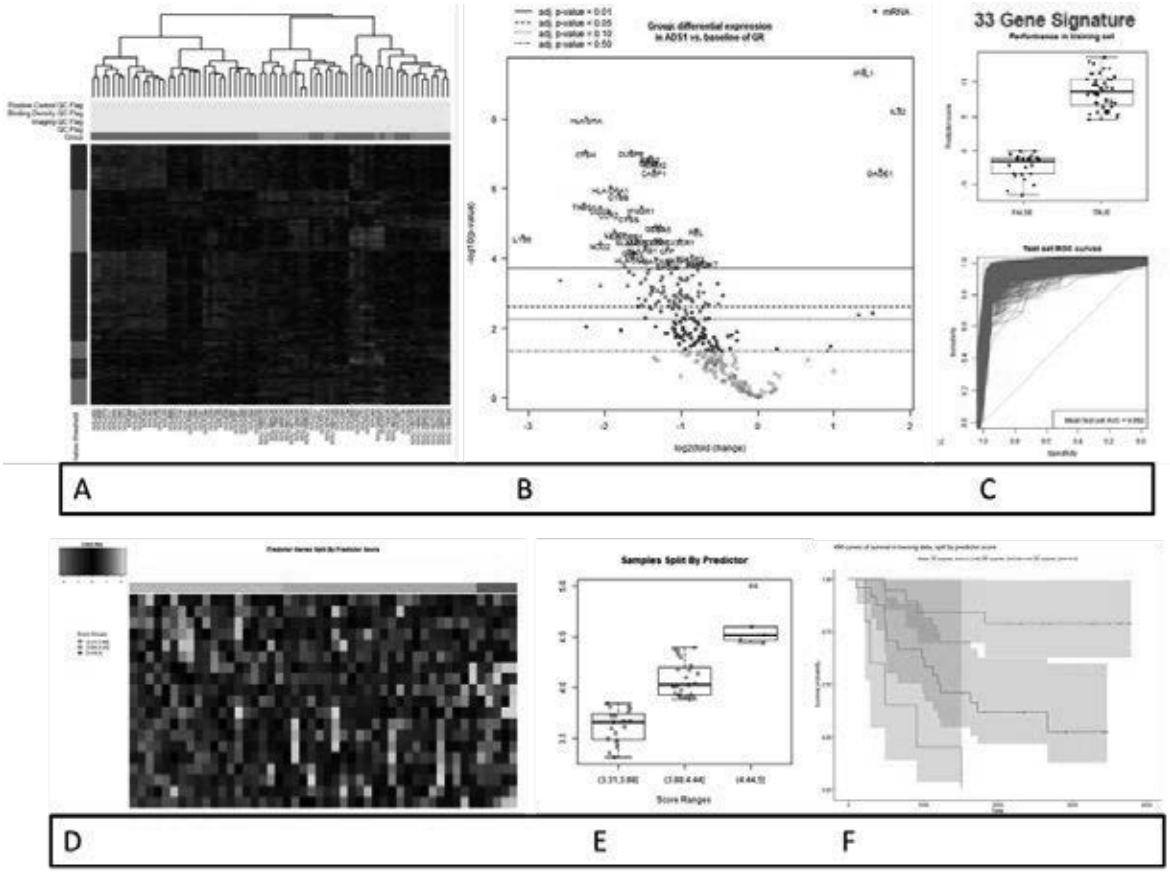
Background: Accurate diagnosis of CT detected pulmonary nodules is crucial to decrease futile minimally invasive resections. We hypothesize that the circulating cellular microenvironment (buffy coat [BC]) containing granulocytes, mononuclear cells, and platelets presents immunologic transcriptional profiles for distinguishing adenocarcinoma from granulomas, and can prognosticate pStage I adenocarcinomas. **Method:** BC total RNA was extracted from 48 pStage I adenocarcinomas having R0 resection and 23 granuloma patients found at surgery. Of the cancers, 23 did not recur either systemically or locoregionally and were matched by age, gender, and pack-years to progressors. RNA was profiled using Nanostring PanImmune Oncology panel for 770 immune genes and cytokines. A machine learning algorithm based on Elastic Net using 1000 loops of cross validation was run to estimate AUC, and logistic regression models used for prognostic classification. **Result:**



The figure depicts the results of the diagnostic profiling in the upper panel (A-C), and prognostication in lower panel (D-F). Unsupervised heat map separated adenocarcinomas (grey) from granulomas, and among the gene set analysis, differences in interleukins, microglial function, antigen processing, cytokines and macrophage functions were the most significant for cohort discrimination. A 33 gene set signature was able to separate granuloma from cancer with mean AUCs of 0.982. Expresion of BC immune related genes were remarkably different between the patients who recurred, and there were differences in profiles of locoregional recurrences compared to systemic recurrences (data not shown).Patients with elevated T-regs but decreased T-cells were characterized by distant progression, while decreased mast cells and increased CD-8 and total T-cells were associated with local recurrence. A three step prognostication index using 19 genes could stratify these patients by time to progression (E,F). **Conclusion:** These encouraging data offer the potential for immune transcriptional signatures to better select patients for diagnosis/management of early stage adenocarcinoma. Further validation studies are underway for possible presentation at WCLC18.

Keywords: immunotranscriptomics, diagnosis, Prognosis

MA23.02 CIRCULATING TUMOR DNA ANALYSIS WITH A NOVEL VARIANT CLASSIFIER FOR RECURRENCE DETECTION IN RESECTED, EARLY-STAGE LUNG CANCER

V. Lam[1], H. Tran[1], M. Vasquez[1], K. Li[2], K. Yuen[2], F. Vang[2], A. Jaimovich[2], D. Kennedy[2], J. Odegaard[2], S. Mortimer[2], S. Olsen[2], V. Raymond[2], A. Vaporciyan[3], M.B. Antonoff[4], G. Walsh[3], E. Roarty[5], L. Lacerda[1], J. Roth[3], S. Swisher[6], C. Bernatchez[7], B. Sepesi[3], D. Gibbons[8], J. Zhang[9], J. Heymach[10]

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Background: ctDNA is a blood-based biomarker with promising potential in lung cancer for minimal residual disease (MRD) assessment and early detection of recurrence. However, data regarding feasibility are limited, especially for stage I-II disease. **Method:** We performed longitudinal plasma ctDNA profiling of early-stage lung cancer patients (pts) that underwent resection at MD Anderson Cancer Center from Apr 2016 to Jan 2017. Plasma ctDNA was analyzed from pre-operative and multiple post-operative time points until disease recurrence. ctDNA profiling was performed using a 30kb Digital Sequencing panel (Guardant Health) covering SNVs in 21 genes and indels in 9 genes that are commonly present in lung cancer. ctDNA profiles from ~30,000 lung cancer pts were used to train a classifier to exclude non-tumor related mutations. **Result:** A total of 40 pts were included in this analysis, comprised of the first 17 pts with recurrence in the longitudinal study and 23 consecutive pts without recurrence. This cohort was primarily stage I and II (15 [38%], 16 [40%]). Histology included adenocarcinoma (29 [73%]), SCC (6 [15%]), and SCLC (2 [5%]). 58% had adjuvant therapy. Median follow-up was 17.7 (3.4 – 24.5) months and median time to recurrence was 7.1 (3.4 – 16.5) months in this selected cohort. At least one ctDNA alteration was detected in 55% (21/38) of pts with evaluable pre-op samples and in 22% (8/37) of pts at 4 weeks post-op. Presence of ctDNA at 4 weeks post-op heralded eventual recurrence with 43% sensitivity and 91% specificity (75% PPV, 73% NPV) and was significantly associated with worse recurrence free survival (p=0.022, HR 6.52; 95% CI 1.3 – 32.6), while also accounting for stage. In the absence of the variant classifier, an additional 7/37 pts had non-tumor alterations detected at 4 weeks post-op with a recurrence sensitivity and specificity of 57.1% and 69.6%. ctDNA was identified in 76% (13/17) of pts prior to or at the time of recurrence. The median interval between ctDNA detection and radiographic recurrence was 91 days. **Conclusion:** Detection of post-op ctDNA, as early as 4 weeks after resection of early-stage lung cancer, is associated with significantly increased risk of recurrence. Accurate detection of ctDNA in this MRD setting is enabled by a highly sensitive sequencing platform that incorporates a novel variant classifier to enhance clinical specificity.

Keywords: ctDNA, liquid biopsy, minimal residual disease

MA23.03 RISK ASSESSMENT FOR INDETERMINATE PULMONARY NODULES USING A NOVEL, PLASMA-PROTEIN BASED BIOMARKER ASSAY

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Background: To reduce overdiagnosis and overtreatment of non-cancerous pulmonary nodules found on CT scans, a noninvasive and easily administered test is needed to assess clinically significant disease risk. Such an assay should also accurately inform whether additional aggressive evaluation, including lung biopsy or thoracic surgery, is warranted. **Objective**: To determine the performance of a novel, plasma-based multiplexed protein test model when compared to the Veterans Affairs Clinical Factors Model (VA model) for discriminating between a lung cancer diagnosis established pathologically and an Indeterminate Pulmonary Nodule (IPN) found to be clinically and radiographically stable for at least one year. **Method:** The protein biomarker-based risk model had been trained and tested with a cohort of 277 subjects at high risk of lung cancer, aged 25-85, who were current smokers with an indeterminate lung nodule 4-30mm in diameter (121 subject training set; 59 subject test set) from eight medical centers across the US. Using retrospective plasma samples, we compared the protein biomarker model results with the malignant or benign outcomes in an independent validation cohort comprised of 97 subjects from the Vanderbilt University medical center. **Result:** Among the 97 validation study subjects (average age 60.1 years, range 42-83; average nodule size 16.1mm), the protein biomarker model correctly identified as benign or malignant an additional 44 of the 68 (65%) indeterminate pulmonary nodules classified as having intermediate risk by the VA model. Negative predictive value was 0.94. Only three patients with malignant disease were missed (94% sensitivity) while an additional 28 intermediate risk samples (41%) were properly classified as true positive, thus potentially avoiding aggressive interventions in those subjects with benign disease. **Conclusion:** This study evaluated a novel plasma protein biomarker assay model as a noninvasive risk assessment aid for characterizing indeterminate pulmonary nodules. When the model results are combined with the VA model, risk stratification for benign nodules is improved compared to current methods in clinical practice. We hypothesize patients with benign disease may benefit the most from this assay by avoiding unnecessary lung biopsy and subsequent overtreatment, while improving patient quality of care and reducing risks from these procedures. Providers and their patients in whom they suspect lung cancer may consider using this novel assay prior to proceeding with more aggressive interventions.

Keywords: lung cancer, pulmonary nodules, Screening, Early Detection

MA23.05 POST-OPERATIVE RADIATION IMPROVES OVERALL SURVIVAL IN PATIENTS WITH NODE-POSITIVE NON-SMALL CELL LUNG CANCER UNDERGOING SUBLOBAR RESECTIONS

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Background: The incidence and prognosis associated with patients undergoing sub-lobar resections and having positive lymph nodes(PLN) has been rarely studied. Our investigation will retrospectively review this topic. **Method:** The National Cancer Database(NCDB) was queried during the years 2004-2014 to assess patients undergoing sub-lobar resection (wedge, segmentectomy, and sub-lobar-NOS, N = 38,599) and specifically the patients with PLN (N = 5484). Patients were excluded who had any pre-op chemotherapy and/or radiation, had follow-up of less than 3 months, had stage IV disease or >1 tumor nodule. Multi-variable modeling(MVA) was used to determine factors for overall survival (OS). Propensity score matching(PSM) was used to determine pre-operative risk factors for PLN in patients having at least one node examined(N=22712) (matched by median number of nodes examined) and to assess the role of radiation in those patients with node positive disease (matched by age, sex, stage, chemotherapy, and number of nodes positive). **Result:** The incidence of PLN decreased progressively during our study from 17.9% in 2004 to 9.4% in 2014 (N1 8.3-5.0% and N2 9.6-4.4%). A lower risk of PLN was noted for squamous cell carcinomas, bronchoalveolar (minimally invasive) adenocarcinomas, and right upper lobe locations; but the risk increased with age, tumor size and clinical stage. In the node positive group, MVA demonstrated that OS was worse with males, older ages, non-Hispanic Whites (compared to Asian and Hispanic Whites), lowest

income quartile, Charlson co-morbidity > 0, grade, tumor size, number of positive nodes, positive surgical margins, length of stay, and not receiving chemotherapy or radiation. PSM demonstrated that radiation increased OS in patients having PLN regardless of margin status or N level involvement. **Conclusion:** The incidence of node positive sub-lobar resections has decreased during the years of our study, but still can be found in nearly 10%. In both MVA and PSM, post-operative radiation improves OS.

Keywords: Post-operative radiation, sublobar resection, non-small cell lung cancer

MA23 EARLY STAGE LUNG CANCER: PRESENT AND FUTURE
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MA23.06 SMALL RESIDUAL SETUP ERRORS AFTER IMAGE-GUIDED RADIOTHERAPY AFFECT HEART DOSE AND ARE LINKED TO OVERALL SURVIVAL

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Background: There is limited evidence of the effect of radiotherapy image guidance on survival. This work investigates the relationship between small residual set-up errors following IGRT and overall survival in lung cancer patients (mostly with significant comorbidities), and explores which anatomy may be responsible for observed differences. **Method:** Residual setup errors of 546 NSCLC patients treated with an off-line 5mm action threshold correction protocol for bony anatomy were summarized per patient as the mean and standard deviation for each axis, as well as the vector magnitude in a direction from tumour towards the heart, and included in multivariate Cox regression. Delivered dose distributions including residual setup errors were estimated and the difference between the delivered and planned dose was compared for patients who did/did not survive longer than 1 year. Permutation testing (n=1000) assessed significance. **Result:** Residual setup errors were not correlated with any pre-treatment clinical variable. Patients with a residual shift towards the heart (mean ~2 mm, max 5mm) have significantly worse overall survival (hazard ratio 1.310, p = 0.001). The average dose in the heart region changes linearly with the residual shift magnitude towards the heart (~0.8Gy/mm). A higher delivered dose than planned in a region at the heart base (Figure 1, arrow) is associated with poorer survival in multivariate analysis (hazard ratio 1.214/Gy, p<0.001).

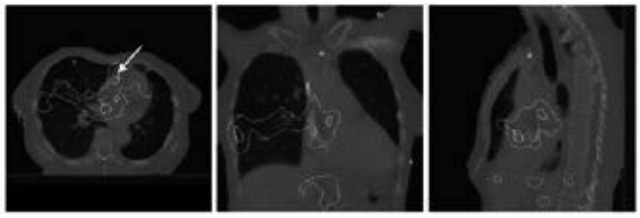

Figure 1: Data mining results (t-statistics map) of delivered – planned dose vs survival at one year. Axial, coronal and sagittal views of the reference patient CT, with the significance levels overlaid (defined at t-values of 3.9, 3.5, 3.0, 2.6 and 2.2). The most significant region is highlighted in the axial view by the arrow. Patients who did not survive one year had a significantly higher delivered than planned dose in this region. It indicates the base of the heart as responsible for poorer survival.

Conclusion: Small residual shifts after IGRT are strongly associated with overall survival in NSCLC patients, with shifts of the high dose region towards the heart leading to worse survival. The most likely cause of shorter survival is a corresponding increase in dose to the heart base. This analysis provides direct evidence of the importance of accurate patient positioning and highlights the significance of the heart base as a dose sensitive organ in thoracic radiotherapy patients with early effects on survival.

Keywords: Cardiac toxicity, Image Guided Radiotherapy, non small cell lung cancer

MA23 EARLY STAGE LUNG CANCER: PRESENT AND FUTURE
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MA23.07 DEFINING THE ROLE OF ADJUVANT THERAPY FOR EARLY STAGE LARGE CELL NEUROENDOCRINE LUNG CANCER

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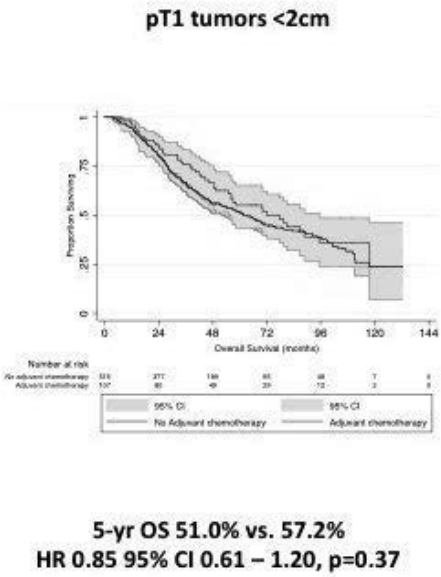
Background: Large cell neuroendocrine lung cancer (LC-NEC) is a rare, high-grade neuroendocrine tumor. Patterns of adjuvant treatment after surgical resection have not been well defined. **Method:** Patients with a pathologic diagnosis of LC-NEC were identified in the National Cancer Database 2004-2014. Patient demographics, tumor and treatment characteristics were examined. Survival differences in patients receiving chemotherapy were evaluated using Kaplan-Meier curves, and multivariate hierarchical Cox models were constructed to evaluate the impact of patient, histologic, tumor, treatment and hospital characteristics on overall survival (OS). A conditional landmark of 90-day postoperative survival was used to address immortal time bias and propensity-matching was used to address imbalance in covariates between groups. **Result:** 1,793 patients were identified with pathologically stage I LC-NEC, of which 482 (26.9%) received adjuvant chemotherapy. Use of adjuvant chemotherapy remained similar across the study period. Patients receiving adjuvant chemo were younger, less comorbid and more likely to have T2 tumors. Significantly longer survival was observed with the receipt of adjuvant chemotherapy (5-year OS 59.2% vs. 45.3%), which persisted after adjustment in multivariable Cox models (HR 0.69, 95%CI0.58 – 0.82, p<0.0001). Adjuvant chemotherapy was associated with longer survival in patients with tumors 2-3cm (60.4% vs. 41.8%; HR 0.64, 95%CI 0.46-0.89, p<0.0001), and T2 tumors (59.8% vs. 42.1%; HR 0.63, 95%CI 0.50-0.81, p<0.0001), but no differences were observed for LC-NEC patients with tumor size <2cm. Adjuvant chest radiotherapy was not associated with improved survival. T-stage specific propensity-matching confirmed these findings, however the association between survival and adjuvant chemotherapy for patients with tumors 2-3cm was no longer significant.

Figure 1. Kaplan-Meier curves for patients with pT1 tumors <2cm, pT1 tumors 2-3cm and pT2 LC-NEC tumors treated with surgery, with their associated hazard ratios (HR) for death in the derived from adjusted multivariable Cox models, reflecting the hazard for death for patients receiving adjuvant chemotherapy.



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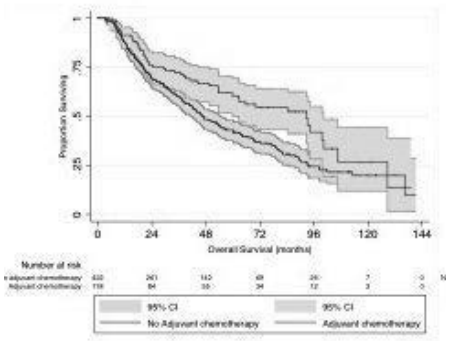
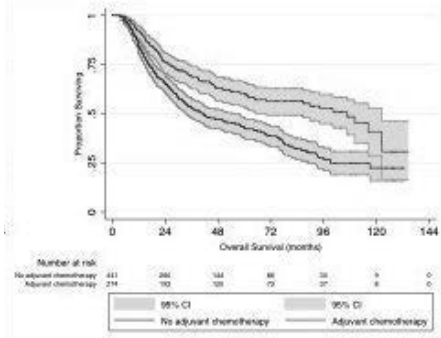
pT1 tumors 2-3cm



5-yr. OS 60.4% vs. 41.8%
HR 0.64 95% CI 0.46 - 0.89, p<0.0001

pT2 (tumors >3cm)



5-yr. OS 59.8% vs. 42.1%
HR 0.63 95% CI 0.50-0.81, p<0.0001

Conclusion: In this national study of LC-NEC, adjuvant chemotherapy was associated with significantly longer survival in Stage I tumors greater than 2cm. Adjuvant radiation was not associated with survival. A randomized trial of stage T2-4N0 LCNEC is needed to clarify the role of adjuvant chemotherapy in this population.

Keywords: adjuvant chemotherapy, large cell neuroendocrine lung cancer

MA23 EARLY STAGE LUNG CANCER: PRESENT AND FUTURE
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MA23.09 MINIMALLY INVASIVE APPROACHES DO NOT COMPROMISE OUTCOMES FOR PNEUMONECTOMY, A COMPARISON UTILIZING THE NATIONAL CANCER DATABASE

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Background: Minimally invasive approaches are increasingly being used for the conduct of complex surgical procedures. Whether the benefits of minimally invasive approaches compared to thoracotomy for sublobar and lobar lung resection for nonsmall cell lung carcinoma are realized for patients undergoing pneumonectomy is not clear. **Method:** The National Cancer Database was queried for patients who underwent pneumonectomy for NSCLC from 2010-2014. Those who underwent resection by a minimally invasive approach (MIS) were compared with those who were done by thoracotomy (Open) in an intent-to-treat analysis. Associations between potential covariates and treatment were analyzed using the Pearson Chi-square test for categorical variables and Wilcoxon Rank Sum test for continuous variables. Univariable and multivariable logistic models and proportional hazards model were used to assess the effect of surgical approach on 30 day and 90 day mortality and overall survival. Relative prognosis was summarized using odds ratios (OR) and hazards ratios (HR) estimates and 95% confidence limits. **Result:** A total of 4,938 patients underwent pneumonectomy during the study period, of which 755 (15.3%) were completed by minimally invasive approaches (MIS). No difference was noted in 30 and 90-day mortality rates for MIS compared to Open approaches (6.8% and 12.3% vs 6.7% and 11.9% respectively, p = 0.9 and 0.86). Tumor histology and stage characteristics were similar between the two groups. Mean lymph nodes examined was higher in the MIS group compared to Open (17.1± 0.4 vs 16.1 ± 0.2, p=0.034). Surgical approach was not associated with any difference in perioperative mortality with univariable or multivariable analysis. MIS was associated with improved overall survival on univariable analysis, but this was not evident with multivariable analysis. **Conclusion:** Pneumonectomy performed by minimally invasive approaches does not compromise perioperative mortality or long term outcomes. Further investigation into the impact of minimally invasive approaches on perioperative outcomes for whole lung resection is warranted.

Keywords: pneumonectomy, VATS, Nonsmall Cell Lung Carcinoma

MA23 EARLY STAGE LUNG CANCER: PRESENT AND FUTURE
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MA23.10 CONE-BEAM COMPUTED TOMOGRAPHY-GUIDED MICROCOIL LOCALIZATION OF PULMONARY NODULES DURING VIDEO-ASSISTED THORACIC SURGERY

H. Ujiie[1], A. Gregor[1], T. Kinoshita[1], K. Fujino[1], C. Lee[1], Y. Motooka[1], T. Inage[1], T. Kato[1], E. Nguyen[2], K. Yasufuku[1]

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Background: The standard procedure at our institution for intraoperative localization of non-palpable small lung nodules is computed tomography (CT)-guided microcoil placement prior to video-assisted thoracic surgery (VATS). Typically, microcoil placement is performed in the radiology suite followed by transfer to the operation room (OR). Our institution has built the Guided Therapeutics (GTx) OR, which includes a robotic cone-beam CT (CBCT). The GTx OR allows imaging and therapy to occur in one location. This can improve workflow and reduce patient transportation, which may increase the risk for microcoil dislodgement or the development of pneumothorax/hemothorax. Our objective was to determine the safety and efficacy of CBCT-guided microcoil placement for nodule localization during VATS. **Method:** This is a single center phase I clinical trial (NCT02496624). Patients with small lung nodules who were candidates for standard CT-guided microcoil localization were enrolled. CBCT was used to generate a 3D reconstruction. The lesion was then segmented using Syngo iGuide software. This reconstruction was next integrated into the digital workspace and automatically registered onto the fluoroscopic images, creating 'augmented fluoroscopy'. The microcoil was placed percutaneously using 'augmented' guidance, proximal to the lesion, using local anesthetic. Patients were subsequently induced into general anesthesia, intubated, and positioned for VATS. Minimally invasive resection of the nodule together with the microcoil was performed under standard fluoroscopic guidance. **Result:** A total of 11 patients were enrolled (mean age 70 ± 11SD). The average tumor size on CT was 1.3 cm (range 0.9-1.7). The average deepest depth from the pleural surface was 2.3 cm (1.3-3.8). The average CBCT-guided intervention time was 39 minutes (25-54), and VATS procedural time was 54 minutes (14-78). We were able to detect and successfully resect all nodules. Average total radiation dose was in an acceptable low range (8307μGy*m^2, range, 2402–18,371). There were no intraoperative complications. Average post-operative length of stay was 1.8 days. A pathological diagnosis was made for all patients: 8 primary lung cancers and 3 lung metastases. All surgical margins were negative on final pathology. **Conclusion:** CBCT-guided microcoil insertion followed by VATS was safe, with short operative times, short length of stay and 100% diagnostic yield. With the GTx OR's real-time guidance capabilities, surgeons can operate with increased confidence of finding and removing the target lesion. This technique will become increasingly important in the future with growing numbers of small nodules being detected on CT by lung cancer screening programs.

Keywords: Localization Lung cancer, Cone beam computed tomography (CBCT), video-assisted thoracic surgery (VATS)

MA23.11 LOBE-SPECIFIC NODAL DISSECTION FOR CLINICAL STAGE I AND II NON-SMALL CELL LUNG CANCER: JAPANESE MULTI-INSTITUTIONAL RETROSPECTIVE STUDY

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Background: Systematic nodal dissection (SND) is an international standard of lymph node dissection for non-small cell lung cancer (NSCLC). Recently, lobe-specific patterns of mediastinal lymph node metastases have been recognized, and lobe-specific nodal dissection (LSD) has been proposed for early-stage NSCLC. The purpose of this study was to assess the surgical outcomes according to the extent of mediastinal lymph node dissection for patients with NSCLC by using a nationwide registry database. **Method:** From among 11,663 patients in a Japanese lung cancer registry study for 2004, 5392 patients with clinical stage (c-stage) I or II NSCLC that was completely resected by lobectomy and either SND or LSD were enrolled. Patients who received preoperative therapy or had middle lobe tumor were excluded. In the LSD group, inferior mediastinal (subcarinal) nodes were not dissected for upper lobe tumors, and superior mediastinal nodes were not dissected for lower lobe tumors. To reduce the selection bias, an inverse probability of treatment weighting (IPTW) method using a propensity score was implemented. **Result:** LSD and SND were performed in 1,268 (23.5%) and 4,124 (76.5%) patients, respectively. LSD group included more c-IA and upper lobe tumors relative to SND group, although there was no significant differences in age and preoperative comorbidity. There was no significant difference in postoperative morbidity and mortality between 2 groups. Extended pathological N2 disease outside LSD area was found in 3.2% of the SND group, but recurrences were not different between 2 groups (all recurrences: 22.0% in LSD, 26.9% in SND; local recurrence: 6.1% in LSD, 7.7% in SND; p=0.788). The 5-year overall survival (OS) was 81.5% in LSD and SND in 75.9%. An IPTW–adjusted Cox model showed that LSD did not have a negative prognostic impact and instead was associated with favorable survival (hazard ratio: 0.68, 95% confidence interval: 0.60-0.77). **Conclusion:** This retrospective registry study suggested that LSD is an alternative to SND for selected patients with c-stage I or II NSCLC. Future prospective studies are warranted to determine whether LSD is applicable and provides clinical benefit for the general population of patients with cstage I or II NSCLC.

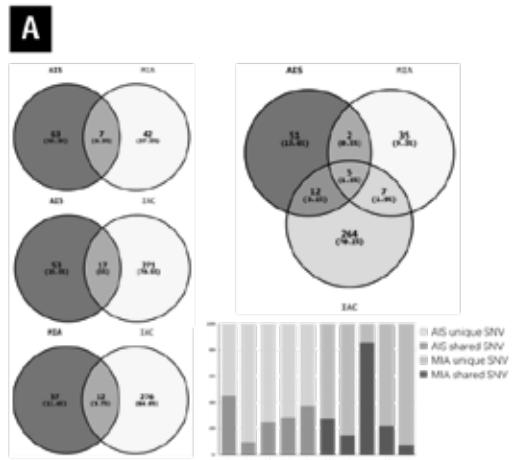
Keywords: Lymph node dissection, non-small cell lung cancer, Surgery

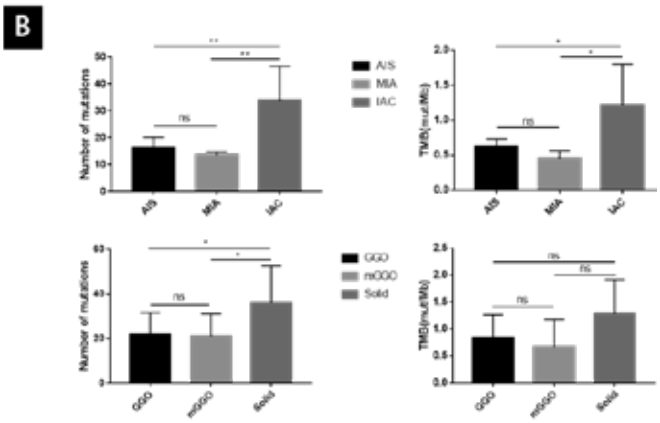
MA24.01 GENOMIC EVOLUTION TRAJECTORY DEPICTS INVASIVENESS ACQUISITION FROM PRE-INVASIVE TO INVASIVE ADENOCARCINOMA

C. Zhang[1], Z. Xie[1], F. Xu[2], J. Su[2], S. Dong[1], Q. Nie[1], Y.W. Shao[3], Q. Zhou[1], J.-. Yang[1], X. Yang[1], X. Zhang[1], Y. Wu[1], W. Zhong[3]

[1]Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou/CN, [2]Department of Pathology, Guangdong General Hospital, Guangzhou/CN, [3]Translational Medicine Research Institute, Geneseeq Technology Inc., Toronto/CA

Background: Accumulation of molecular abnormalities may depict evolution trajectories of tumor initiation and development. However, the genomic profile of early stage adenocarcinoma and molecular mechanism of invasiveness acquisition from pre-invasive to invasive adenocarcinoma remains barely explored. **Method:** We simultaneously collected 20 patients with adenocarcinoma in situ (AIS) (n=5), minimally invasive adenocarcinoma (MIA) (n=5) and stage IA adenocarcinoma (lepidic/acinar predominant) (n=10). Whole exon sequencing (WES) was performed in pre-invasive adenocarcinoma with multi-region specimens and stage IA adenocarcinoma. Analysis of genomic alteration among different pathological status was performed and tumor mutation burden (TMB) was calculated as well as six mutation types individually. Enriched pathways of each pathology were measured through KEGG analysis. **Result:** Baseline characteristics was generated through heatmap with smokers (2/20, 10%) and EGFR mutation (13/20, 65%) among whole population. AIS/MIA indicated much lower number of mutations than invasive adenocarcinoma (IAC) while TMB revealed the same trend without statistical significance. Multi-region sequencing showed high heterogeneity of single nucleotide variation (SNV) in AIS and MIA. Unique SNV presented dominant proportion in initial status. Cluster analysis showed higher copy number variation in AIS/MIA than IAC with cell adhesion molecules (CAMs) enriched in AIS/MIA while variety pathway enrichment in IAC through KEGG analysis. C>A transversions held major proportion in early stage adenocarcinoma and a significant increase in the proportion of C>T and C>G mutation was exhibited when evolving into IAC.





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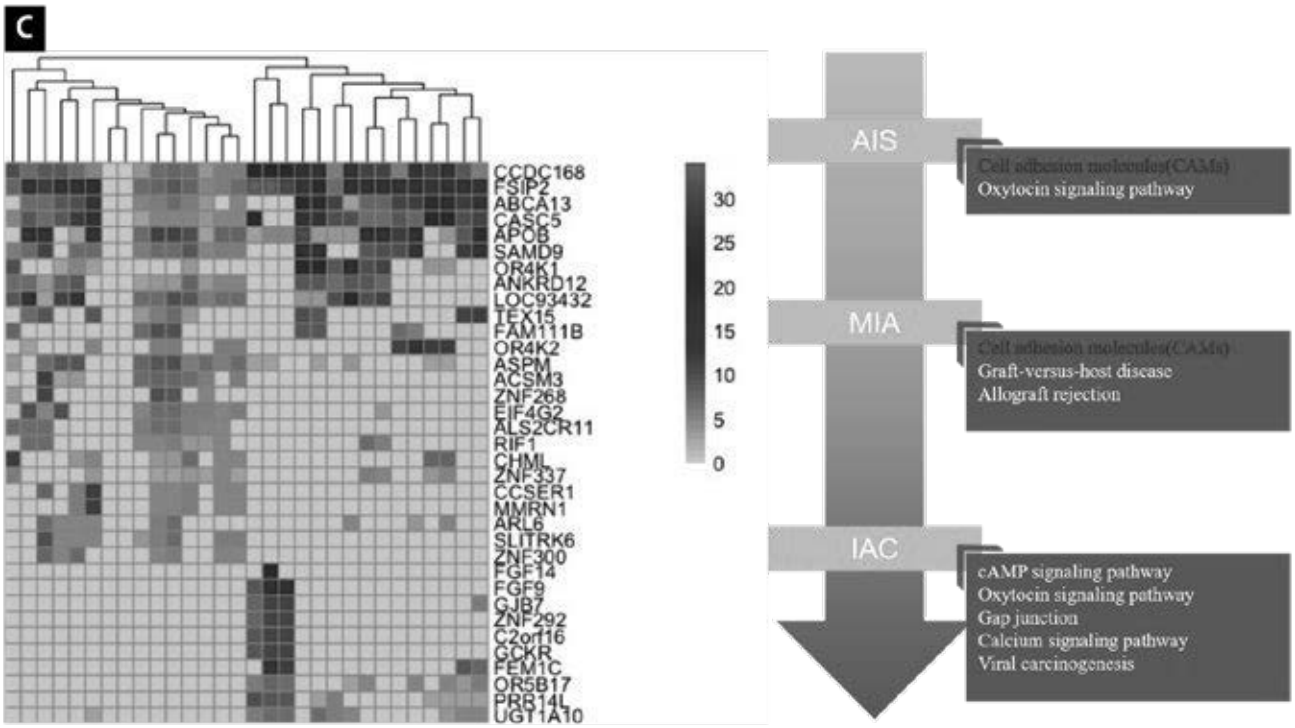

Fig. A) Venn diagram of single nuclear variants (SNV) among different pathological status and intratumor heterogeneity analysis of SNV for AIS and MIA. B) Number of mutations and tumor mutation burden (TMB) among different pathological status and radiological pattern. C) Cluster analysis of copy number variation among different pathology and KEGG analysis of enrichment functional pathway.

Conclusion: Intratumor heterogeneity may occur in the very beginning of adenocarcinoma. High copy number variation was dominant event for AIS/MIA while higher tumor mutation burden was seen in IAC. Tobacco signature encompassing C>A transversions dominates the early development of adenocarcinoma and APOBEC signature may play a potential role in acquisition of cancer invasiveness.

Keywords: multi-region squencing, Adenocarcinoma, evolution trajectory

MA24 GENOMIC EVOLUTION, KEAP 3 AND MORE NON-CODING RNA
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MA24.02 GENOMIC ALTERATIONS IN LUNG ADENOCARCINOMA PRECURSOR LESIONS

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Background: Adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma (MIA) are thought to be precursor lesions of invasive disease. Genomic alterations in these lesions have not been described. **Method:** Genomic analysis including whole genome and exome sequencing, and SNP array analysis were performed on 9 AIS and 18 MIA pathologically confirmed samples to identify single nucleotide variants (SNVs), structural variations and copy number variations. Mutation significance and signature analysis were determined by MutSig and NMF analyses. Pathway analysis was performed using ingenuity IPA. **Result:** The range of mutation burden for AIS and MIA was 0.7 to 12/Mb with a median of 1.7/Mb. This compared to a mean of 7.2/Mb for invasive lung adenocarcinoma. Significantly mutated genes identified in AIS and MIA were ELAVL4, LIN37, XCL1, ELK3, RPS9, FBXO2, HLA-B and MYOG, which affected pathways regulating ESR1, ELAVL1 and TP53. Genes with recurrent mutations included MTPN, CDC27, GGT2, CTBP2, EGFR, NCOR1 and TGIF1 and implicated EGFR, MYC and MAPK1 pathways. Somatic mutations were characterized by C>T and T>C transition signature, whereas CNV analysis found high concentrations of copy number amplifications at 6p21.3 to 6p22.1, 8q24.12 to 8q24.3 and at 21q22.3. There were comparable structural variations in the AIS cases compared to MIA. **Conclusion:** In contrast to hypothesized models of tumor progression, AIS and MIA can harbor significant genomic alterations and tumor mutation burden. These observations challenge the notion of accumulating mutation burden during the progression to invasive disease. The finding of high mutation burden in some of these precursor lesions also suggests the intriguing concept of immunotherapeutic options for either treatment or chemoprevention.

Keywords: minimally invasive adenocarcinoma, adenocarcinoma in situ, lung adenocarcinoma precursor lesions

MA24 GENOMIC EVOLUTION, KEAP 3 AND MORE NON-CODING RNA
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MA24.03 BIOLOGIC PROFILING OF PRE-METASTATIC NICHE IN COMPLETELY RESECTED PATHOLOGICAL STAGE I NON-SMALL CELL LUNG CANCER

T. Saito[1], H. Ryota[2], M. Ishida[3], K. Fukumoto[4], H. Matsui[1], Y. Taniguchi[1], H. Yanagimoto[2], K. Tsuta[3], T. Murakawa[1]

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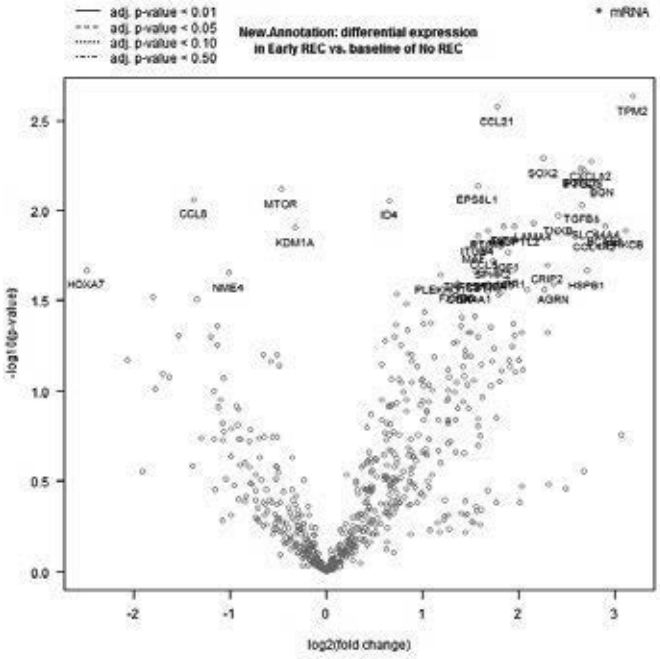
Background: Despite refinement of treatment strategy for non-small cell lung cancer (NSCLC), pathological Stage I NSCLC still develops recurrent disease in approximately 20% of patients even after complete resection. Recently, tumor microenvironment which promotes distant metastasis, or 'pre-metastatic niche', has been indicated to play pertinent roles in postoperative recurrence of cancer. Our aim is to investigate biologic profiles of pre-metastatic niche in pathological Stage I NSCLC. **Method:** Eighteen (12.7%) of 141 patients with pathological Stage IA or IB NSCLC

who underwent R0 lobectomy between Jan. 2008 and Dec. 2013 developed distant metastasis postoperatively. From archived formalin-fixed paraffin-embedded specimens, these 18 cases of postoperative distant metastasis and matched cases were selected for total RNA extraction. To overcome inherent bias in selecting control patients, one-to-one matched pairs were created using propensity score matching of which model included age, sex, smoking history, and pathological stage. The samples with inadequate mRNA quality/ quantity were excluded. Gene expressions were detected by nCounter (NanoString Technologies, WA, USA) with PanCancer Immune Profilling Panel and PanCancer Progression Panel. Detected expressions were then analyzed and compared between the two groups by nCounter Advanced Analysis (version 2.0.115). Genes with unadjusted P-value < 0.01 were regarded as candidates for further investigation **Result:** From preliminary comparative study on 6 paired cases, distant metastasis group showed upregulations of TPM2, CCL21, SOX2, CXCL12, EGFL7, PTGDS, BGN, PS8L1, ID4 and TGFB, whereas it showed downregulations of MTOR and CCL8 compared to recurrence-free group. In LATE-BREAKING ABSTRACT, we will report following results: 1) Complete dataset of the comparative analysis including all pairs with adequate mRNA. 2) Immunohistochemstry and/or in situ hybridization of the candidate genes/proteins on pathological sections.



Conclusion: Biologic profilings of brain metastasis from NSCLC may subsequently help to understand underlying mechanism of postoperative distant metastasis and ultimately lead to novel targeted therapy. Futher details will be added in LATE-BREAKING ABSTRACT.

Keywords: nCounter, distant metastasis, pre-metastatic neche

MA24 GENOMIC EVOLUTION, KEAP 3 AND MORE NON-CODING RNA
WEDNESDAY, SEPTEMBER 26, 2018 - 10:30-12:00

MA24.05 BASELINE SPATIAL HETEROGENEITY OF T790M IN TYROSINE KINASE INHIBITOR NAÏVE EGFR-MUTANT LUNG ADENOCARCINOMAS

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Background: Despite a good initial response, most epidermal growth factor receptor *EGFR*-mutant lung adenocarcinomas develop resistance after treatment with 1st and 2nd generation tyrosine kinase inhibitors (TKIs). Approximately 50-60% of resistance can be attributed to the *EGFR*T790M mutation, which provides a higher affinity ATP binding site that outcompetes TKIs and restore constitutive kinase function. Although classically thought of as *de novo*acquisition, the presence of T790M has been shown to exist in some tumors before TKI-therapy. Obtaining a spatial map of T790M in TKI-naïve tumors can provide insight into development of this type of resistance. **Method:** Eight cases of TKI-naive primary lung adenocarcinoma resections that were later found to be positive for T790M post-treatment with TKI were collected from 2004 to 2012. Initial pre-treatment tumor surgical resections were used for DNA extraction. Two tumor sections per case were divided into equal grid-like regions of approximately 8x8 mm^2. The number of grids ranged from 16 to 32 per case, based on tumor size (0.8 cm to 6.5 cm). Digital droplet polymerase chain reaction was used to genotype the sensitizing EGFR-mutations and T790M mutations at each region. Allelic frequencies (AF) of the mutations were measured. Recurrence free interval, defined as surgical resection date to date of recurrence detection, and total duration of TKI-therapy were extracted from medical records. **Result:** All eight cases of TKI-naïve EGFR-mutant lung adenocarcinomas were positive for T790M at baseline. T790M tumor burden, defined as the mean allelic frequency of T790M, ranged from 0.17% to 40.15% across the tumors. Three main patterns of distribution were observed. In two cases, T790M was present at low level (<1% AF) prevalence throughout the entire tumor. Five cases were characterized by the presence of distinct sub-clonal region, defined as T790M AF high in one or adjacent regions surrounded by regions with low or zero T790M AF. In one case, T790M was the predominant clone with T790M AF closely matching sensitizing EGFR-mutation AF. T790M tumor burden was not associated with either tumor size or recurrence free interval. **Conclusion:** T790M tumor cells exist prior to TKI-therapy in a majority, if not all, EGFR-mutated lung adenocarcinoma that developed T790M mutation as the resistance mechanism to EGFR TKI therapy, rather than by de novo acquisition during TKI-therapy exposure. However, pre-treatment T790M tumor burden did not appear to be associated with recurrence free survival, although this requires more cases for confirmation.

Keywords: Heterogeneity, Resistance, T790M

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MA24.06 LONG NON-CODING RNA EXPRESSION PATTERNS DELINEATE INFILTRATING IMMUNE CELLS IN THE LUNG TUMOUR MICROENVIRONMENT

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Background: The tumour microenvironment is characterized by complex interactions between different cell types, including immune cells that may exhibit pro- or anti-tumour effects. Sequencing and deconvolution techniques present opportunities to identify immune cell composition of bulk tumour data; similarly, these have renewed an interest in the non-coding transcriptome and its regulation of immune- and tumour-biology. Numerous long non-coding RNAs (lncRNAs; >200nt) have emerged as regulators of tumour initiation, progression, and metastasis. Additionally, several immune-related lncRNAs mediate fine-level regulation to balance pro- and anti-inflammatory phenotypes; yet, the landscape of lncRNA expression in human immune cells remains uncharacterized. Thus, delineating these multifaceted regulatory networks is critical to cancer immunology, particularly in immunogenic malignancies such as lung cancer. **Method:** RNA-sequencing data of purified immune-cell subsets ($CD8^+$ T, $CD4^+$ T, B, Monocytes, Neutrophils, and Natural Killer) obtained from flow-sorted healthy peripheral blood samples were probed for lncRNA expression. Sequencing reads were aligned to the hg38 reference genome and quantified to Ensembl v89, yielding 4919 expressed lncRNAs. These immune-associated lncRNAs were correlated with immune cell infiltrate in tumour and paired non-malignant lung adenocarcinoma samples (n=54, The Cancer Genome Atlas) as estimated by the proportion of consistent immune-associated methylation profiles, denoted by leukocytes unmethylation for purity (LUMP) scores. **Result:** We observed that lncRNA expression patterns display a greater degree of cell-type specificity than protein-coding genes in immune cells. In fact, 676 lncRNAs had detectable expression in exclusively one cell type. We uncovered previously-uncharacterized lncRNAs that have expression patterns suggestive of immune-regulatory roles. Compared with lung tumour samples, 19 immune-associated lncRNAs were significantly negatively correlated with LUMP scores (r<-0.400, BH-p<0.0100), 17 of which were also strongly positively correlated with CD45 gene expression (r>0.400, BH-p<0.0100) suggesting expression from immune rather than tumour cells. For instance, the lncRNA *USP30-AS1* is significantly downregulated in tumours (average fold-change=2.96, BH-p=$6.88*10^{-13}$), suggesting its relevance to tumour biology; however, higher transcript expression is correlated with decreased LUMP score (r=-0.685, BH-p=$1.02*10^{-4}$), illustrating its specificity to immune cells. **Conclusion:** Here, we present an atlas of cell-type specific lncRNAs in human immune cells. Our data suggest a functional relevance of lncRNAs to the biology of the tumour microenvironment, and the necessary consideration of

tumour purity when examining non-coding RNA expression in order to avoid conclusions confounded by immune cells in bulk tumour data. Thus, we provide a resource for further elucidation of genomic links between immune and malignant cells, which may aid the development of future prognostic and therapeutic strategies.

Keywords: tumour microenvironment, long non-coding RNA, Infiltrating immune cells

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MA24.07 A NOVEL CIS-ACTING LNCRNA CONTROLS HMGA1 EXPRESSION IN LUNG ADENOCARCINOMA

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Background: High mobility group A1 (HMGA1) chromatin remodeling protein is enriched in several aggressive cancer types, including NSCLC, where mRNA and protein expression are markedly increased. Additionally, high HMGA1 expression has been associated with poor overall survival and chemotherapy resistance. While HMGA1 is deregulated in lung cancer, the mechanisms that mediate its expression are only beginning to emerge. Long non-coding RNAs (lncRNAs), are a class of transcripts have been implicated in the onset of cancer-associated phenotypes in tumourigenesis and metastasis. Recently, an emerging class of lncRNAs - *cis*-acting - has been shown to regulate the expression of neighbouring protein-coding genes, including oncogenes and tumour suppressor genes. Thus, lncRNAs may represent novel actionable therapeutic intervention points in known cancer driving pathways. Here we investigate the role of a *cis*-acting lncRNA, *RP11.513I15.6*, its deregulation in NSCLC, and its relationship with HMGA1. **Method:** LncRNA transcriptomes were deduced from RNA-sequences of 36 microdissected tumour and matched non-malignant tissues. Normalized sequence read counts were used to identify transcripts with significantly deregulated expression (Wilcoxon Signed-Rank Test, BH-p<0.05). Sequencing data obtained from The Cancer Genome Atlas were analyzed to validate these results. SiRNA-mediated knockdown of lncRNA candidates identified in these analyses were performed in a non-malignant lung epithelial cell line (BEAS-2B). Quantitative real-time PCR quantified the effects of lncRNA knockdown on the expression of neighbouring cancer-associated protein-coding genes. **Result:** Our analyses identified *RP11.513I15.6*, an undescribed lncRNA neighbouring *HMGA1*, to be significantly downregulated in adenocarcinoma (>2-fold downregulation in 81.5% of cases). This observation was confirmed in our validation cohort. *HMGA1* expression was found to be anticorrelated with *RP11.513I15.6*, as tumours with downregulated *RP11.513I15.6* displayed significant overexpression of *HMGA1*. This suggested that this lncRNA may be a key negative regulator of *HMGA1*. *In vitro* experiments demonstrated siRNA-mediated inhibition of *RP11.513I15.6* in immortalized lung epithelial cells resulted in a significant increase in the expression of HMGA1 mRNA and protein. Taken together, our results suggest that *RP11.513I15.6* is a novel *cis*-acting lncRNA that negatively regulates HMGA1, and may contribute mechanistically to the maintenance of cancer phenotypes. **Conclusion:** We have discovered a novel, 18-fold downregulated transcript that is anti-correlated with expression of HMGA1, a well established oncogene. *In vitro* studies support the hypothesis that this transcript, *RP11.513I15.6*, is a *cis*-acting lncRNA as siRNA-mediated inhibition led to upregulation of neighbouring HMGA1. Characterizing this oncogene regulatory mechanism will not only further our understanding of cancer biology, but could uncover a novel therapeutic intervention point.

Keywords: genetics, gene regulation, long non-coding RNA

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MA24.09 SYNERGY BETWEEN THE KEAP1/NRF2 AND PI3K PATHWAYS DRIVES NON-SMALL CELL LUNG CANCER WITH AN ALTERED METABOLISM

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Background: The lung is a highly oxidative environment, tolerated through the engagement of tightly controlled stress response pathways. A critical stress response mediator is the transcription factor Nuclear Factor Erythroid-2-Related Factor 2 (NFE2L2/NRF2), which is negatively regulated by Kelch-like ECH-Associated Protein 1 (KEAP1). Alterations in the KEAP1/NRF2 pathway have been identified in 23% of lung adenocarcinomas, suggesting that deregulation of the pathway is a major driver in lung cancer. **Method:** We generated a novel genetically engineered mouse model (GEMM) whereby *Keap1* (*Keap1*$^{f/f}$) and *Pten* (*Pten*$^{f/f}$) were conditionally deleted in the lung, utilising intranasal inhalation of Adenovirus-Cre. The effects on lung pathology were investigated using histopathology, metabolomics and flow cytometry. **Result:** We found that, while loss of *Keap1* alone displayed no abnormalities in the lung, loss of *Keap1* combined with loss of the tumour suppressor *Pten,* promoted malignant transformation. We further monitored tumour progression and immune infiltration in the lung, and metabolite profile changes in the serum of the *Keap1*$^{f/f}$/*Pten*$^{f/f}$ mouse model. Notably, a tumour-specific metabolite signature was identified in the plasma of *Keap1*$^{f/f}$/*Pten*$^{f/f}$ tumour-bearing mice, which indicated that tumourigenesis is associated with metabolic reprogramming. Furthermore, the immune milieu was dramatically changed by *Keap1* and *Pten* deletion, and tumour regression was achieved utilising immune checkpoint inhibition. **Conclusion:** Our study highlights the ability to exploit both metabolic and immune characteristics in the detection and treatment of lung adenocarcinomas harbouring *KEAP1*/*NRF2* pathway alterations.

Keywords: NSCLC, GEMM, KEAP1/NRF2

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MA24.10 INTERROGATING THE METABOLIC EFFECTS OF KEAP1 INACTIVATION IN ADENOCARCINOMA

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Background: The most frequently altered gene in lung adenocarcinoma (ADC) is the *KRAS* oncogene. There are currently no effective treatments to target *KRAS*-mutant ADC. Loss of function in *Kelch-like ECH-associated protein 1* (*KEAP1*) is co-mutated in 18% of *KRAS*-mutant ADC and is mutually exclusive with inactivating mutations in *Tumour protein 53* (*TP53*). KEAP1 is a negative regulator of the transcription factor NRF2, which regulates cellular antioxidant and metabolic pathways. Metabolic dysregulation is considered a hallmark of cancer cells, which utilize anaerobic glycolysis and anabolic glucose metabolism in preference to aerobic oxidative phosphorylation in a phenomenon termed the Warburg effect. **Method:** We interrogated the consequences of *Keap1* loss in *Kras*^{G12D}-induced ADC using conditional genetically engineered mouse models (GEMMs). To examine metabolic features unique to *Keap1*-mutant ADC, GEMMs with *Kras*$^{LSL\text{-}G12D/+}$ alone or with either the *p53*$^{flox/flox}$ allele (*Kras/p53*) or *Keap1*$^{flox/flox}$ allele (*Kras/Keap1*) were investigated. Gene and protein expression of key enzymes involved in glucose metabolism were measured in spontaneous lung tumors. Glycolytic functional assays were performed in live FACS-isolated tumor cells using a novel protocol. **Result:** Major alterations in glycolytic function were identified as unique features of *Keap1* inactivation in lung adenocarcinomas carrying oncogenic activation of *Kras*. Loss of *Keap1* function in *Kras*-mutant ADC therefore created a pro-oncogenic metabolic environment to drive lung tumourigenesis. **Conclusion:** Targeting metabolic dependency in *KRAS*-mutant tumors may provide a unique method of treating this aggressive subset of lung ADC.

Keywords: KEAP1/NRF2, KRAS, NSCLC

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MA24.11 LOSS OF TUMOUR SUPPRESSORS IS ADEQUATE AND SUFFICIENT TO DRIVE LUNG CANCER IN CRISPR/CAS9 MICE.

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Background: In non-small cell lung carcinoma (NSCLC), loss-of-function (LOF) mutations are found in tumour suppressors, highlighting the importance of these genes in the aetiology of lung cancer. The major tumour suppressors (TS) associated with the development of lung cancer are p53, and the kinase LKB1. Unlike oncogenes that have been

successfully exploited therapeutically, LOF alterations in TS are difficult to exploit. The goal of our research is to understand how the loss of TS function allows for metabolic and epigenetic adaptation that favour conditions for tumour growth. **Method:** We developed a CRISPR/Cas9 mouse model of lung cancer representative of tumour suppressors lost in NSCLC. Since LKB1 and p53 are two of the most common LOF tumour suppressors found in NSCLC along with activating mutations in Kras, we used a Cre-dependent Cas9 mouse to create mice that simultaneously lack pulmonary Lkb1 and p53 along with activating $KRas^{G12D}$. Here, we evaluated the development of lung cancers in the context of metabolism and epigenetic marks. **Result:** The metabolic profile of lung tumours harvested from CRISPR/Cas9 mice was significantly different from the mTOR and metabolic profile of lungs harvested from control mice, favouring a switch from glycolysis to mitochondrial metabolism. Epigenetic marks; acetylation and methylation modifications to histones 3 (H3) and H4 were significantly different compared to control mice, indicative of poor prognosis. **Conclusion:** Our study is the first to characterize a new CRISPR/Cas9 mouse model for lung cancer that leverages the loss of two common tumour suppressor proteins associated with lung cancer; Lkb1, and p53. We show that the simultaneous loss of these TS leads to activation of mTOR and pro-survival pathways sustained by metabolic adaptation. Further to this, we observe epigenetic marks that agree with poor prognosis. We conclude from our study that patients with lung cancers that lack expression of LKB1 are likely to respond favourably to interventions that simultaneously target aberrant metabolism with modifiers of tumour epigenetic landscape. Our findings suggest that loss of LKB1 expression serves as a marker for NSCLC.

Keywords: LKB1 and tumour suppressors, CRISPR-Cas9 mice, metabolism and epigenetic tumour landscape

MA25 OLIGOMETASTASIS: DEFINING, TREATING, AND EVALUATING
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MA25.01 EORTC LUNG CANCER GROUP SURVEY TO DEFINE SYNCHRONOUS OLIGOMETASTATIC DISEASE IN NSCLC

A. Levy[1], L. Hendriks[2], T. Berghmans[3], C. Faivre-Finn[4], M. Giaj Levra[5], N. Giaj-Levra[6], B. Hasan[7], N. Girard[8], L. Greillier[9], S. Lantuejoul[10], J. Edwards[11], M. O'Brien[12], M. Reck[13], B. Besse[14], S. Novello[15], A. Dingemans[16]

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Background: Synchronous oligometastasic disease (sOMD) has been described as a separate disease entity; however there is no consensus on what specific criteria constitutes sOMD in NSCLC. A consensus group (CG) was formed aiming to agree on a common sOMD definition (sOMD-d) that could be used in future clinical trials. A European survey was circulated to inform the discussion on sOMD-d. **Method:** An EORTC Lung Cancer Group (LCG) / sOMD-d CG survey containing 31 questions on sOMD-d was distributed between 14/12/17 and 19/02/18 to EORTC LCG, sOMD-d CG, and several European thoracic oncology societies' members. **Result:** 444 responses were analyzed (radiation oncologist: 55% [n=242], pulmonologist: 15% [n=66], medical oncologist: 14% [n=64]; 78% with >5 years' experience in treating NSCLC). Belgium (14%, n=62), Italy (12%, n=55), Germany (11%, n=47), and Netherlands (10%, n=44) contributed most. 81% (n=361) physicians aimed to cure sOMD NSCLC patients and 82% (n=361) included the possibility to treat the patient with radical intent in their sOMD-d. The maximum number of metastases considered in sOMD-d varied: 19%, 42%, 4%, and 17% replied ≤2, 3, 4, and ≥5 metastases, respectively. 79% (n=353) stated that the number of organs involved was important for sOMD-d, and most (80%, n=355) considered that only ≤3 involved organs (excluding primary) should be included in the definition. 317 (71.7%) allowed mediastinal lymph node involvement (MLN) in the sOMD-d, and 22.1% of them counted MLN as a metastatic site. For 195/327 (60%), when N2/N3 disease is included in the sOMD-d, there is no specific issue regarding the MLN volume/location as long as radical treatment is possible. 384 (86%) considered pulmonary metastasis (outside primary tumor: M1a) as metastatic site. Most physicians confirmed sOMD patients with brain MRI (91%, n=403) and PET-CT (98%, n=437). For mediastinum staging, most (64%, n=285) respondents stated that histology/cytology should be obtained when PET-CT shows suspected lymph nodes or in case of a central primary tumor. Pathology proof of metastatic disease was necessary in sOMD for 315 (71%) physicians, and 37% (n=163) acknowledged that histology should be obtained from at least from one metastatic site. Preferred primary outcome parameter in clinical trials of sOMD was overall survival (73%, n=325). **Conclusion:** Although certain consensual answers were obtained (81% aimed to cure and >90% mandated baseline imaging with PET-CT and brain MRI), a number of issues remain unresolved and will require further discussion by a panel of experts to agree on a sOMD-d.

Keywords: Definition, Oligometastase, NSCLC

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MA25.02 SEARCHING FOR A DEFINITION OF SYNCHRONOUS OLIGOMETASTATIC (SOMD)-NSCLC: A CONSENSUS FROM THORACIC ONCOLOGY EXPERTS

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Background: Recent prospective single centre studies reported improved outcomes in patients with sOMD-NSCLC who were treated with radical intent. Since then sOMD has been perceived as a separate disease entity. However, a clear definition of sOMD-NSCLC is lacking. We aimed to develop a definition and diagnostic criteria of sOMD-NSCLC following a consensus process. **Method:** A European multidisciplinary consensus group was established with representatives from different scientific societies. Consensus questions were extracted from a survey, case series and a systematic review. The questions were discussed, and the statement formulated during a consensus meeting in Dublin (23.01.18). **Result: Summary of consensus statement** *Defining sOMD-NSCLC* Definition of sOMD is relevant for patients in whom a radical treatment is technically feasible with acceptable toxicity, taking into account all sites, that may modify the course of the disease leading to a long-term disease control. All sites must be technically and safely treatable. The maximum number of metastases/organs meeting the criteria involved will depend on the possibility of offering a treatment strategy with radical intent, taking into account local control and toxicity. Based on the systematic review, a maximum of 5 metastases and 3 organs is proposed. Diffuse serosal metastases and bone marrow involvement are excluded. Mediastinal lymph node (MLN) involvement should be considered as locoregional disease in the definition of sOMD-NSCLC. MLN involvement is of importance in determining if a radical local treatment of the primary tumour may be applied and the MLN will not be counted as a metastatic site. *Staging of sOMD-NSCLC* PET-CT and brain imaging are considered mandatory. In case of a solitary liver metastasis a dedicated MRI of the liver and for a solitary pleural metastasis, thoracoscopy and biopsies of distant ipsilateral pleural sites are advised. Staging of the mediastinum requires a minimum of a FDG-PET scan, with pathological confirmation preferred if this influences the treatment strategy. Pathological proof is required unless the MDT decides that the risk outweighs the benefit.

Pathology proof is advised for single metastatic location and if it may change the therapeutic strategy, confirmation of the MLN involvement is recommended. **Conclusion:** A multidisciplinary consensus statement on the definition and staging of sOMD-NSCLC was formulated taking into account results of a European survey, a systematic review and case discussion. This statement might be helpful to standardise inclusion criteria in future clinical trials. However, the definition of sOMD may change over time when more prospective data will become available.

Keywords: oligometastatic NSCLC, definition

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MA25.03 DEFINING OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER (NSCLC): AN EVOLVING MULTIDISCIPLINARY EXPERT OPINION

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Background: Synchronous oligometastatic NSCLC definition varies between: 1 metastasis in 1 organ (TNM8), 1-3 metastases (ESMO), ≤3 metastases after systemic treatment with mediastinal nodes (MLN) counting as 1 site (Gomez, Lancet Oncol 2016) to 3-≥5 metastases in ongoing trials. A single definition is however needed to design and compare trials. To assess synchronous oligometastatic NSCLC definitions used by clinical experts in daily practice and its evolution, we redistributed a 2012-case based survey (Dooms et al, presented at WCLC 2013). **Method:** In December 2017, 10 real-life multidisciplinary team (MDT) discussed patients (all good condition, no significant comorbidities, ^{18F}FDG-PET and brain MRI staged, all < 5 metastases, 9/10 ≤ 3 metastases, oncogene-addicted or wildtype NSCLC) were distributed to 33 international NSCLC experts involved in the EORTC oligometastatic NSCLC consensus group, questioning: 1) can you discuss these cases in your MDT?, 2) do these patients have oligometastatic disease? and 3) what is your treatment proposal for the oligometastatic disease patients? Current answers were compared to the previous ones, and the real-life treatment and survival of the patients was added. **Result:** 26/33 experts (24 centers) replied: 8 medical oncologists, 7 pulmonologists, 7 radiation oncologists, 4 thoracic surgeons. 62% discussed the cases in their MDT. 1 case had 100% oligometastatic disease consensus, 3 cases had > 90% consensus, the number of treatment proposals varied between 3 to 8 (Table). Radical treatment was more often offered in case of a single metastasis or N0 status. Compared to 2012 there was a trend towards a more conservative oligometastatic definition and chemotherapy was more often included in the treatment proposal.

Table 1

Case TNM8	oligo-meta-static yes answer % 2012 / 2017	Number of tx proposals 2012 / 2017	Radical tx answers % 2012 / 2017	Real life radi-cal tx intent	real life survival (months) / 5Y survival
EGFR+ T2aN3M1c (3 brain mets)	55 / 38	2 / 5	27 / 23	-	40.1 / -
EGFR+ T4N0M1a (ground glass)	36 / 35	4 / 3	45 / 35	+	65.2 / +
T2aN1M1b (solitary renal)	91 / 96	5 / 5	100 / 92	+	8.3 / -
T1bN3M1b (solitary adrenal)	73 / 58	4 / 5	36 / 54	+	66.1 / +
T2bN1M1c (adrenal + pelvic node)	55 / 50	2 / 5	36 / 46	-	18.6 / -
T2aN0M1c (3 liver mets)	64 / 69	4/ 5	27 / 62	-	51.5 / -
T2aN2M1b (solitary bone)	91 / 92	4 / 5	73 / 85	+	13.4 / -
T3N1M1c (2 brain mets)	91 / 96	3 / 8	73 / 85	+	39.6 / -
T2aN0M1c (1 lung, 1 pancreas)	82 / 69	5 / 4	64 / 50	+	74.0 / +
T1bN0M1b (solitary bone)	100 / 100	3 / 5	82 / 92	+	11.6 / -

Conclusion: Synchronous oligometastatic NSCLC definition was more conservative than in 2012 and linked to radical intent of treatment. Number of organs, MLN status and possibility for radical treatment seem to be components of daily practice synchronous oligometastatic definition.

Keywords: Oligometastatic, Cases, NSCLC

MA25 OLIGOMETASTASIS: DEFINING, TREATING, AND EVALUATING
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MA25.05 CHARACTERISTICS & SURVIVAL OF RESECTED STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC) IN THE MID-SOUTH QUALITY OF SURGICAL RESECTION COHORT

N. Faris[1], Y. Lee[2], M. Smeltzer[2], M. Ray[2], C. Fehnel[1], C. Houston-Harris[1], O. Akinbobola[1], P. Ojeabulu[1], E. Owen[3], R. Eubanks[4], H. Dox[5], D. Talton[6], G. Valaulikar[7], H. Wiggins[8], B. Wolf[9], P. Levy[10], E. Robbins[11], R. Osarogiagbon[12]

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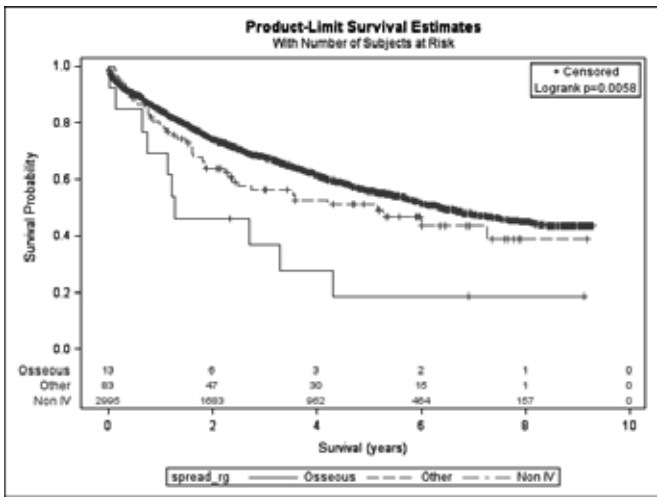
Background: Surgical resection is potentially curative in subsets of oligometastatic NSCLC. We evaluated the characteristics and survival of resected stage IV NSCLC in a population-based cohort. **Method:** Patients were included who had curative-intent resections from 11 hospitals in 4 contiguous Dartmouth Hospital Referral Regions in the mid-Southern USA from 2009-2018. Statistical analyses were performed using univariate and multiple Cox regression models. **Result:** Of 3092 resections, 96 (3.1%) were stage IV: 38 M1a, 54 M1b, and 4 M1c. Of the M1a patients, 1 had a pleural effusion, 37 had a contralateral lung nodule. The most common sites of extrathoracic metastasis were bone (13 (13.5%)), and brain (25 (26%)). Other extrathoracic sites were distant lymph nodes, liver, adrenals, thyroid, pancreas, colon, soft tissue, and esophagus. Stage IV patients had a younger median age (63 vs 67 (p<0.0001)), less Medicare coverage but more Medicaid or Commercial insurance (p=0.0248), fewer comorbid conditions (p=0.0096), higher cT (p<0.0001), and higher-grade tumors (p=0.0002). 58% (22) of M1a patients did not receive treatment to the site of metastatic disease, compared to 72% (39) and 75% (3) of M1b and M1c, respectively (p=0.0086). For patients with bone metastases, median/5 year survival was 1.28 years/0%, compared to 5.16 years/51% for all other metastatic sites and 6.39 years/56% for non-stage IV NSCLC (p=0.0058) (Figure 1). In fully adjusted models, survival for Stage IV patients without bone metastasis did not differ significantly from Stage I-III patients (HR: 1.3, p=0.15). However, Stage IV patients with bone metastasis had significantly worse survival (HR:3.2, p=0.0006).

(See next page)



Conclusion: Bone metastasis connotes a very poor prognosis in patients with oligometastatic NSCLC, but survival of patients with other sites of metastasis was remarkably good in this highly selected group of patients from a population-based multi-institutional cohort.

Keywords: NSCLC, Surgical resection, Oligometastatic disease

MA25.06 RPA ANALYSIS FOR OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER: SMOKING COMBINE T3/4 PATIENTS MAY NOT BE BENEFIT FROM LOCAL CONSOLIDATIVE TREATMENT

J. Zhang, Y. Tang, S. Liu, S. Dong, X. Yang, Y. Wu, W. Zhong

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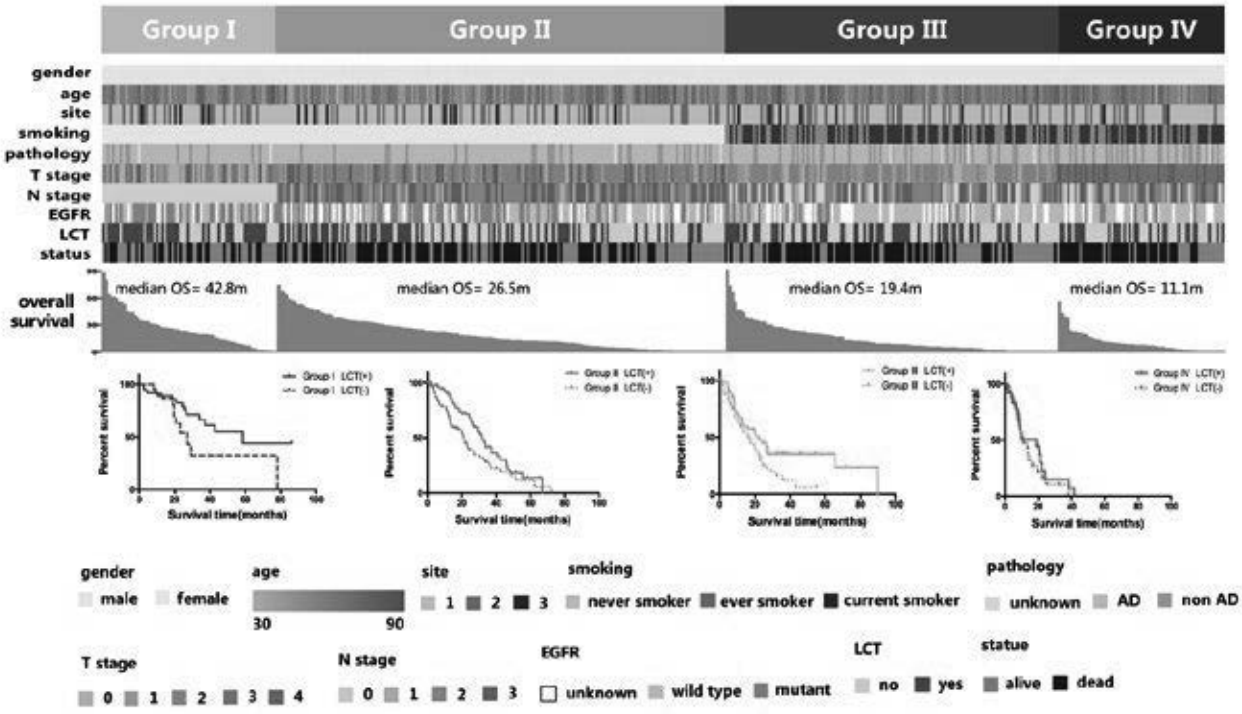
Background: In the literature on oligometastasis, the relative importance of local consolidative treatment (LCT) has been gradually accepted. This study set out to investigate the prognosis heterogeneity and the effect of LCT for oligometastatic non-small cell lung cancer patients. **Method:** We identified 436 patients in Guangdong General Hospital (GGH) from 2009 to 2016 with oligometastatic disease, and the factors predictive of overall survival (OS) were evaluated using Cox regression. Risk stratifications were defined using recursive partitioning analysis (RPA) on training set (2009~2014), which were further confirmed on validation set (2015-2016). And the effect of LCT for different risk groups was further examined by Kaplan-Meier method. **Result:** Factors predictive of OS were: T stage (p=0.001), N stage (p=0.008), metastatic sites (p=0.031) and EGFR status (p=0.043). Prognostic risk RPA model was established, 4 risk groups were identified: Group I, never smokers and N0 disease (3-year OS: 55.6%, median survival time (MST)=42.8m); Group II, never smokers and N+ disease (3-year OS: 32.8%, MST=26.5m); Group III, smokers and T1/T2 disease (3-year OS: 23.3%, MST=19.4m); and Group IV, smokers and T3/T4 disease (3-year OS: 12.5%, MST=11.1m). Among four groups, OS significant differences were observed according to LCT except group IV (p=0.45). **Conclusion:** This retrospective study identified the poor prognostic population (smoking combine T3/4 disease) of oligometastatic non-small cell lung cancer patients, and this population may not be benefit from local consolidative therapy.



Keywords: recursive partitioning analysis, Oligometastasis, local consolidative therapy

MA25.07 EFFECTIVENESS OF SYSTEMIC THERAPY COMBINED WITH THORACIC RADIOTHERAPY FOR PATIENTS WITH OLIGOMETASTATIC NSCLC: A POOLED ANALYSIS

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Background: Local therapy combined with systemic therapy for oligometastases or oligo-recurrence (≤ 5 lesions) in NSCLC has become one of the hottest spots in recent years. At present , there is lack of results from randomised phase III trial in this regard. Therefore, we performed a pooled analysis, aiming to evaluate the effectiveness of the combination of systemic therapy and local thoracic radiotherapy for patients with oligometastatic NSCLC. **Method:** Computerized search of the Pubmed database was performed using the following key words: non-small cell lung cancer, metastasis, stage IV, thoracic radiation. Abstracts were ruled out. In addition, we also reviewed the references listed in the identified articles and included eligible studies for integrity of the literature search. Combination therapeutic modality should include systemic therapy (chemotherapy or targeted therapy) and thoracic radiotherapy. Authors with more than 1 publication involving the same study population were included only once, and the one with most relevant and complete data were included. Literature retrieval was terminated by April 2018. All the analysis was performed in the Stata/SE 12.0. **Result:** A total of 32 articles with full text were retrieved in our initial literature search. After reviewing these articles and corresponding references, 16 studies (9 retrospective studies vs. 7 prospective phase II studies) with a total of 791 oligometastatic NSCLC patients were finally identified as eligible for this analysis. The median progression free survival (PFS) ranged from 6.6 to 16.0 months and median overall survival OS ranged from 10.0 to 27.1 months. Four studies involving 256 patients reported the post-radiotherapy response, resulting in a pooled objective response (CR + PR) rate of 58% (95% CI: 0.41, 0.76). A total of 3 studies involving 168 patients provided comparison data on PFS between systemic therapy alone and systemic therapy plus thoracic radiotherapy, leading to a pooled hazard ratio (HR) of 0.42 (95% CI: 0.28, 0.64) for the combined modality group. **Conclusion:** Consolidative thoracic radiotherapy in addition to systemic therapy may offer significant outcome benefits for oligometastatic NSCLC, leading to a numerically comparable response and survival to locally advanced NSCLC. Results from phase III randomized controlled trials are awaited.

Keywords: oligometastatic non-small cell lung cancer, pooled analysis, thoracic radiotherapy

MA25.09 M1B DISEASE IN THE 8TH EDITION OF IASLC STAGING OF LUNG CANCER: PATTERN OF SINGLE EXTRATHORACIC METASTASIS AND CLINICAL OUTCOM

H. Park, C. Lydon, T. Araki, H. Hatabu, M. Rabin, B. Johnson, M. Nishino

Imaging, Dana Farber Cancer Institute, Boston/MA/US

Background: The 8th edition of IASLC staging of lung cancer has revised M classification and defined M1b disease for single extrathoracic metastasis, which is distinguished from M1c with multiple extrathoracic metastases. We investigated the prevalence of M1b disease in stage IV NSCLC patients (pts), and studied the pattern of single extrathoracic metastasis and its relationship with overall survival (OS). **Method:** 567 pts with stage IV NSCLC (236 males, 331 females, median age: 63) diagnosed in 2008-2012 were reviewed to determine M stage according to the 8th edition of IASLC staging of lung cancer (M1a: separate tumor nodules in a contralateral lobe, pleural/pericardial nodule or effusion; M1b: single extrathoracic metastasis; M1c: multiple extrathoracic metastasis in one or more organs). Clinical characteristics and OS were compared according to M stage. **Result:** Among 567 pts, 57 pts (10%; 95%CI: 7.6-13%) had M1b disease with single extrathoracic metastasis, while 119 pts (21%) had M1a and 391 pts (69%) had M1c disease. Squamous histology was more common in M1b (9/57; 16%) than in M1a (7/119; 6%) and M1c pts (22/391; 6%) (Fisher P=0.03). The median OS of M1b pts was 14.8 months (95%CI: 12.7-24.7 months), compared to 22.7 months (95%CI: 18.5-31.6 months) for M1a and 13.4 months (95%CI: 11.8-15.3 months) for M1c pts (log-rank P < 0.0001). Among 57 M1b pts, brain was the most common site of single metastasis (n=28; 49%), followed by bone (n=16; 28%), adrenal (n=7; 12%), liver (n=3; 5%), muscle (n=2; 4%), and distant node (n=1; 2%). M1b pts with liver metastasis had shorter OS than others (median OS: 8.1 vs. 16.1 months, log-rank P=0.046). Single metastasis in M1b pts were locally treated in 31 pts (54.5%). Brain metastasis was more frequently treated with local treatment than others (26/28, 92.9%vs. 5/29, 17%; p<0.0001). **Conclusion:** M1b disease was noted in 10% of stage IV NSCLC pts. Squamous histology was more common in M1b than in M1a and M1c groups. Brain was the most common site of single metastasis and was often treated locally. Single liver metastasis in M1b disease was associated with shorter OS. The study characterized the unique clinical features of the new category of M1b disease among stage IV NSCLC.

Keywords: Oligometastasis, 8th edition TNM staging, lung cancer

MA25.10 COMPLETE RESPONSE BY PET-CT AFTER RADICAL TREATMENT IN OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER PREDICTS LONGER SURVIVAL

L.A. Cabrera-Miranda[1], F. Barron[2], Z. Zatarain-Barrón[3], L. Ramírez-Tirado[4], M. Salinas Padilla[5], J. Corona-Cruz[6], A. Cardona[7], M. Arguelles[8], F. Maldonado[5], M. Blake[5], E. Jiménez-Fuentes[9], O. Aren[3], O. Arrieta[8]

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Background: Evidence is rapidly accumulating for the use of radical treatment approaches for patients with oligometastatic Non-small cell lung cancer (NSCLC). Several limitations remain, however, to further strengthen the use of radical therapy as opposed to standard maintenance therapy, including a lack of robust markers to predict patient response. In this study, we assessed the utility of reaching a complete response (CR) by PET-CT in patients with oligometastatic disease after radical treatment (NCT02805530). **Method:** We included patients with stage IV NSCLC who presented with ≤5 synchronous, any-site metastases (oligometastatic disease) as assessed by PET-CT. Patients received 4 initial cycles of systemic treatment. Following, patients were evaluated by PET-CT and those with stable disease and partial response received radical treatment to the primary site and metastases (surgery, radiotherapy, chemotherapy plus radiotherapy, radiofrequency and SBRT alone or in any combination). Response to radical treatment was evaluated by PET-CT. Maintenance treatment was permitted. **Result:** 37 patients were included in the analysis. Mean age was 55.7. At diagnosis 43.2% of patients presented with CNS metastases. After 4 cycles of first-line therapy, 100% of patients received treatment to the primary site, while 83.8% also received therapy to metastases. Following radical treatment, 19 (51.4%) patients achieved a CR by PET-CT, while 18 (48.6%) had a partial response (NON-CR). Median PFS was 26.2 months (95%CI 12.2-40.1), and was positively affected by CR by PET-CT (NR vs. 14.3 [95%CI 11.9-16.7]; p<0.001). Median overall survival (OS) was NR. OS was also positively affected by CR by PET-CT (42-month survival: 82.5%±18 for CR vs. 34.4%±28 for NON-CR by PET-CT; p=0.01). **Conclusion:** Patients with oligometastatic NSCLC who undergo radical treatment and reach a CR by PET-CT show a significant improvement in survival outcomes. Our results suggest that CR by PET-CT could serve as a surrogate marker for prolonged survival in this patient subgroup.

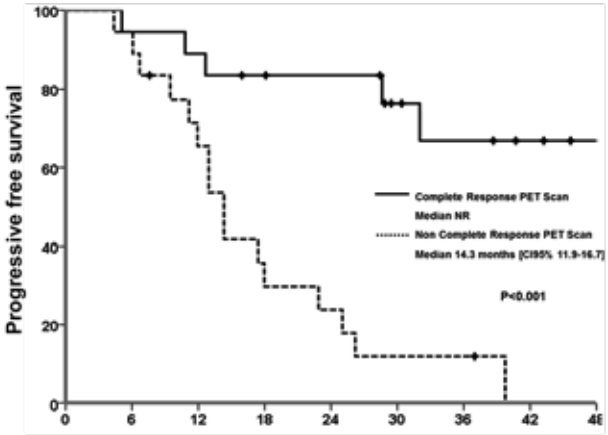

Figure 1A

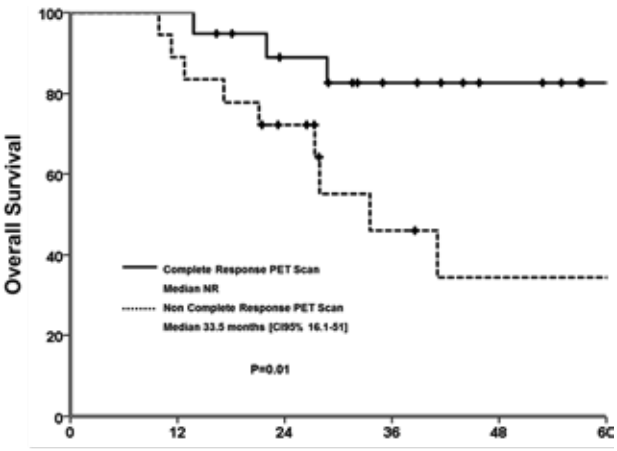

Figure 1B

Keywords: PET-CT, Complete Response, oligometastatic NSCLC

MA25 OLIGOMETASTASIS: DEFINING, TREATING, AND EVALUATING
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MA25.11 CLINICAL AND MOLECULAR PREDICTORS OF OUTCOME IN PATIENTS WITH EGFR MUTANT NSCLC BRAIN METASTASES TREATED WITH RT

F. Moraes[1], J. Weiss[2], M. Moskovitz[3], H. Sorotsky[4], M. Pintilie[2], N. Leighl[4], P. Bradbury[4], G. Liu[4], G. Zadeh[5], M. Doherty[6], A. Kia[7], J. So[8], M. Cabanero[9], T. Pugh[10], V. Sugumar[3], D. Torti[10], M. Tsao[11], J. Torchia[12], D. Shultz[8], F. Shepherd[3], B. Lok[1]

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Background: Brain metastases(BM) develop in ~45% of patients with EGFR mutant(EGFRm) non-small cell lung cancers(NSCLC). There are limited reports on clinical/molecular factors associated with BM outcomes after radiotherapy in EGFRm NSCLC patients. **Method:** We identified patients with EGFRm NSCLC who presented with or developed BM and had their lung tumor resected. Clinical, demographic and TP53 status were collected from medical/pathology records. Whole-Exome Sequencing of the primary tumor was performed. Overall survival(OS) and intracranial progression(IP) were defined from start of BM treatment and correlated with clinical/molecular features. IP was defined from the date of BM treatment until any brain failure, either local(previously present BM) or distant(development of new BM). Categorical and continuous covariates were tested by Fisher exact or Mann-Whitney test, respectively. OS by Kaplan-Meier with groups compared by log-rank. For each model the Harrell Concordance Index(CI) was performed. **Result:** From 41 eligible patients with BM, 9 were excluded due to sequencing quality. Of the 32 remaining patients, 20 (62%) had their BM treated with WBI (15 WBI alone and 5 TKIàWBI), 12 (38%) with TKI±SRS (9 TKI àSRS; 2 TKI alone and 1 SRS alone). Median age at BM was 59.5 years(y). Most of the cohort were female(81%), non-smoker(78%), non-Asian(62%) and 50% presented as stage III or higher at diagnosis. An EGFR exon 19 mutation was present in 72% of patients, 25% had 2 or more EGFRm, 15% with additional driver mutations and 53% with TP53 co-mutation. At a median follow-up of 1.21-y, no clinical/molecular factors(treatment, age, gender, ethnicity, smoking status, stage at presentation, EFGR exon 19 versus 21, number of EGFRm, additional driver mutations, TP53 co-mutation) correlated with survival. There was a trend for longer survival for patients treated with TKI±SRS(median 3.4y) compared to WBRT±TKI(median 1.4y); p=0.08 and for age at BM ≤59.5y(median 2.5y) compared to >59.5y (median 1.4y); p=0.2. Higher risk of IP was observed in younger patients (age as continuous variable) with HR of 0.94(95%CI 0.88-1.0), p=0.04; favoring older patients and remained significant after accounting for treatment modality on multivariate analysis p=0.03. No additional clinical/molecular factors correlated with IP. **Conclusion:** In our study, younger age at BM treatment was associated with higher IP. We also observed a trend for longer OS for younger patients(≤59.5y) and for patients treated with TKI±SRS. Our data suggest that younger patients with EGFR BM should undergo close intracranial follow up and that future studies to define the benefit of brain-directed multimodality treatment are warranted.

Keywords: lung adenocarcinoma, brain metastases, Genomics

MA26 NEW THERAPIES AND EMERGING DATA IN ALK, EGFR AND ROS1
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MA26.01 ACCUMULATION OF CONCOMITANT MUTATIONS INVOLVED IN DRUG RESISTANCE IN THE SEQUENTIAL ALK TKI TREATMENTS OF ALK-POSITIVE NSCLC

S. Lu[1], Y. Yu[1], Y. Ding[2], X. Wu[2], H. Bao[3], Y.W. Shao[2]

[1]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, Shanghai/CN, [2]Translational Medicine Research Institute, Geneseeq Technology Inc., Toronto/CA, [3]Medical Department, Nanjing Geneseeq Technology Inc., Nanjing/CN

Background: ALK tyrosine kinase inhibitors (TKIs), including crizotinib and several next-generation TKIs, have shown promising clinical outcomes for *ALK*-positive lung cancer patients. However, distinct resistant-mechanisms have been suggested for different *ALK* fusion variants in response to various TKIs. The genomic alterations associated with these heterogeneous resistant-mechanisms have not been adequately investigated, especially for patients received sequential ALK TKI treatments. **Method:** The distribution of *ALK* fusion variants in 475 *ALK*-positive lung cancer patients (cohort I) out of 11842 lung cancer patients (4%) tested by next-generation sequencing were analyzed. In addition, mutation profiles of 416 cancer-relevant genes in the post-ALK TKI treatment tumor samples from 52 non-small cell lung cancer (NSCLC) patients (cohort II) who represent the similar distribution of *ALK* fusion variants as in cohort I were analyzed. Thirty-five patients received crizotinib treatment only (crizotinib group), whereas the other 17 patients were treated with multiple lines of ALK TKIs (multi-TKI group), including lorlatinib, alectinib, ceritinib and brigatinib. **Result:** *EML4-ALK* v3 and v1 are the two most common *ALK* fusion variants in both cohorts. In cohort II, 18 different *ALK* activating mutations were found in 17 patients (49%) of the crizotinib group and 10 patients (59%) of the multi-TKI group, although with different mutation patterns. In the multi-TKI group, G1202R was the most frequent *ALK* activating mutation found in 35% of the patients, while L1196M (14%) and G1269A (11%) were more common in the crizotinib cohort. Of note, there was a significant enrichment of concomitant *ALK* activating mutations in the multi-TKI group (p=0.031), as well as a trend of increased number of patients carrying activation of ALK by-pass/downstream pathways (p=0.056) in this group compared with the crizotinib group, resulting in a significantly higher recurrence of dual activation of *ALK* and ALK by-pass/downstream pathways in the multi-TKI group (29%) than that in the crizotinib group (6%) (p=0.031). Patients with concomitant *TP53* mutation had significantly shorter progression free survival (PFS) compared with *TP53* wildtype patients upon crizotinib treatment (median PFS: 8 vs 13 months, HR 1.494, p=0.019) regardless of fusion variant types. **Conclusion:** Significantly higher frequency of concomitant mutations, including concomitant *ALK* activating mutations, and dual activation of ALK and ALK by-pass/downstream pathways, was observed after multiple lines of ALK TKI treatments, indicating the diversity and complexity of resistance-mechanisms in response to next-generation ALK TKIs. Concomitant *TP53* mutation might serve as a prognosis biomarker for worse clinical outcomes treated with crizotinib.

Keywords: Concomitant Mutations, ALK TKIs, drug resistance

MA26 NEW THERAPIES AND EMERGING DATA IN ALK, EGFR AND ROS1
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MA26.02 UPFRONT OR SEQUENTIAL STRATEGY FOR NEW GENERATION ANAPLASTIC LYMPHOMA KINASE (ALK) INHIBITORS: AN ITALIAN RETROSPECTIVE STUDY.

E. Gobbini[1], P. Pizzutilo[2], R. Chiari[3], S. Pilotto[4], C. Dazzi[5], G. Osman[6], P. Bordi[7], L. Ghilardi[8], F.L. Cecere[9], P. Graziano[10], E. Maiello[10], G. Borra[11], O. Martelli[12], V. Gregorc[13], V. Scotti[14], C. Casartelli[15], F. Riccardi[16], P. Rizzo[17], A. Del Conte[18], A. Delmonte[19], C. Bareggi[20], D. Cortinovis[21], C. Sergi[22], A. Rossi[10], G. Rossi[23], E. Bria[4], M. Di Maio[1], S. Novello[1]

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Background: Anaplastic lymphoma kinase (*ALK*) rearrangement confers sensitivity to *ALK* inhibitors (ALKis) in non-small-cell lung cancer (NSCLC). Although several drugs provided an impressive outcome benefit, the most effective sequential strategy is still unknown. **Method:** We retrospectively collected 242 *ALK*-positive advanced NSCLC diagnosed between 2010 and 2018 in 23 Italian institutions (expanded data collection from Gobbini et al. Lung Cancer 2017). 138 patients received exclusively crizotinib as ALKi (not considered for this analysis). 78 patients received crizotinib and a new (second or third) generation ALKis as further treatments (group A). 26 patients performed a new generation ALKi as upfront agent (group B). These groups are larger than those considered in a previous analysis (15 and 8 patients, respectively). **Result:** Study population clinical features and treatments received are summarized in Table 1 (next page).

With a median follow-up of 22.6 months (CI 95% 20.09-25.10), 33 patients had died (32%). In group B, the median progression free survival (PFS) for new generation ALKis administered as first (14.0 months, CI 95% 9.52-18.471), second (12.7 months, CI95% 7.22-18.17) or third-line (12.8 months, CI95% 6.24-19.35) was not statistically different (p= 0.522). The median time from the start of crizotinib to the disease progression after the new generation ALKi sequentially performed (group A) was longer than that one detected in group B for the upfront new generation ALKis (29 vs 14 months, HR 2.47 [CI95% 1.35-4.50], p=0.003). This result was confirmed even considering the time lost between the two treatments in group A. The median overall survival (OS) was not reached. The 12-months OS rate was 97% in group A and 84% in group B. **Conclusion:** New generation ALKis maintain their efficacy regardless of the treatment setting considered. The sequential strategy seems to provide a substantial benefit, but a longer follow-up and larger samples are needed to clarify the survival impact.

Keywords: NSCLC, Sequence, ALK

	Group A Crizotinib followed by new generation ALKis N= 78				Group B Upfront new generation ALKis N=26				
Treatments per line n(%)	**1°**	**2°**	**3°**	**4°**	**1°**	**2°**	**3°**	**4°**	
Crizotinib	28(36)	50(64)	-	-	-	-	2(8)	-	
Alectinib	-	11(14)	18(23)	5(17)	7(27)	-	-	-	
Ceritinib	-	9(12)	23(30)	3(4)	8(31)	8(31)	1(4)	-	
Brigatinib	-	6(8)	6(8)	2(3)	-	2(8)	-	2(8)	
Lorlatinib	-	-	4(5)	5(6)	-	-	1(4)	-	
Chemotherapy	50(64)	2(3)	10(13)	na	11(42)	6(23)	1(4)	Na	
Clinical features n(%)									
Age (range)	58 (27-83)				55 (24-82)				
Male	37(47)				10(38)				p= 0.42
Female	41(53)				16(62)				
Current smoker	8(10)				5(19)				p= 0.23
Never/former smoker	70(90)				21(81)				
ALKi beyond PD	27(34)				4(15)				p= 0.06

MA26 NEW THERAPIES AND EMERGING DATA IN ALK, EGFR AND ROS1
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MA26.03 ACTIVITY OF OSIMERTINIB AND THE SELECTIVE RET INHIBITOR BLU-667 IN AN EGFR-MUTANT PATIENT WITH ACQUIRED RET REARRANGEMENT

Z. Piotrowska[1], H. Isozaki[1], J. Lennerz[1], S. Digumarthy[1], J. Gainor[1], N. Marcoux[1], M. Banwait[1], D. Dias-Santagata[1], A.J. Iafrate[1], M. Mino-Kenudson[1], R. Nagy[2], R. Lanman[2], E. Evans[3], C. Clifford[3], B. Wolf[3], A. Hata[1], L. Sequist[1]

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Background: The spectrum of acquired resistance (AR) to osimertinib is not yet fully characterized. We present a single-center cohort of osimertinib AR biopsies and results of a patient with RET-mediated AR treated with the investigational RET-specific TKI BLU-667 and osimertinib.

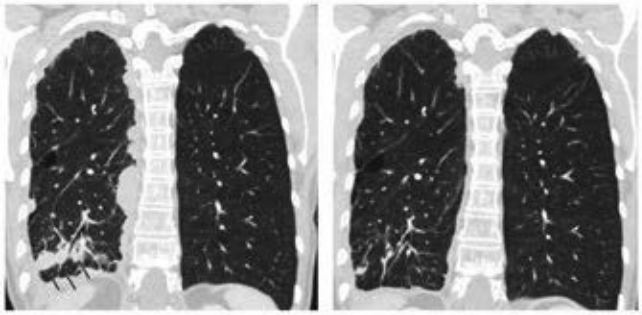
Method: We assayed tissue via SNaPshot or Foundation One next-generation sequencing (NGS) and plasma via Guardant360 NGS under an IRB-approved protocol. *In vitro* studies assessed implications of RET fusions in EGFR-mutant cancers. We treated one patient with osimertinib/BLU-667 using an IRB and FDA-approved compassionate use protocol.

Result: 41 EGFR-mutant patients with AR to osimertinib were assessed histologically and queried by tissue NGS (n=22), plasma NGS (n=9) or both (n=10). Key AR findings: SCLC transformation (2/32 tissue); EGFR C797S (5/32 tissue, 5/19 plasma, all *cis* with T790M); MET amplification (7/32 tissue, 3/19 plasma); BRAF rearrangement (2/32 tissue) and CCDC6-RET rearrangement (1/32 tissue, 1/19 plasma [distinct case]).

CCDC6-RET was expressed in PC9 (EGFR del19) and MGH134 (EGFR L858R/T790M) cells, which maintained MAPK signaling and conferred resistance to osimertinib and afatinib. Inhibition of RET by BLU-667 or cabozantinib resensitized cells expressing CCDC6-RET to EGFR inhibition.

A 60-year-old woman with EGFR del19 progressed on afatinib (T790M+), then osimertinib. Tissue biopsy at osimertinib AR showed acquired CCDC6-RET (T790-wt). She began osimertinib 80mg/BLU-667 200mg daily x2 weeks, then BLU-667 was increased to 300mg daily. Her dyspnea improved within days of initiation. Scans after 8 weeks revealed a marked response with RECIST tumor shrinkage of 78% (Figure). She experienced only grade 1 toxicities of fatigue, leukopenia, hypertension, dry mouth, and elevated transaminases.

Conclusion: RET rearrangements are rare but recurrent in EGFR-mutant patients with AR to osimertinib. *In vivo* models suggest they mediate AR and this patient provides proof-of-concept that combination EGFR+RET inhibition with osimertinib/BLU-667 is a well-tolerated and effective regimen for RET-mediated AR. Further study is ongoing.



MA26.05 COMPREHENSIVE ANALYSIS OF TREATMENT RESPONSE AND PROGRESSION PATTERN IN CHINESE PATIENTS WITH DIFFERENT ALK FUSION-VARIANTS

M. Qiao[1], C. Zhao[1], X. Li[1], T. Jiang[1], F. Wu[1], X. Chen[1], C. Su[1], C. Zhou[2]

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Background: ALK inhibitors and chemotherapy are two major strategies in the treatment of patients with ALK-rearrangements in China. However, the respective treatment response varies and heterogeneous. This study aimed to comprehensively analyze the impact of ALK variants on different treatment response and explore progression pattern respectively.
Method: We retrospectively analyzed a cohort of 135 patients with determined ALK variants and medical record from January 2013 to July 2017 in Shanghai Pulmonary Hospital. **Result:** (See figure 1 below)

The most frequent ALK variant was variant 1 in 62 patients (46%), followed by variant 3a/b in 52 patients (38%) and variant 2 (12%). 69 (51.1%) of patients received chemotherapy, whereas 64 (47.4%) were treated with crizotinib and 2 (1.5%) with alectinib.The similar PFS was observed in patients ALK variant 1 and non-variant 1 regardless of first-line treatment strategy (crizotinib: 15.7 vs. 12.8 months, p=0.53; chemotherapy: 5.7 vs. 8.1 months, p=0.098). However, in the subgroup analysis, patients with ALK variant 1 and baseline brain metastasis had significantly shorter PFS in the first-line setting versus non-variant 1 (4.9 *vs.* 11.3 months, HR=2.96, p<0.01). Additionally, ORR was 21.6% and 50% in variant 1 and non-variant 1 patients with brain metastases, respectively. Moreover, in the analysis of progression pattern, 55 patients with ALK variant 1 and 57 patients with ALK non-variant 1 exhibited PD. As to ALK variant 1, the incidence of CNS relapse in patients treated with crizotinib was significantly higher than patients treated with chemotherapy (39.3% vs. 7.4%, p=0.005). In terms of ALK non-variant 1,the patients treated with chemotherapy had higher incidence of bone progression than patients treated with crizotinib (25% vs. 0%, p=0.021).

Conclusion: Our results firstly indicate the treatment-naïve patients with ALK variant 1 and baseline brain metastasis have inferior response to initial cancer treatment. Different ALK variants have distinct landscape of progression pattern when treated with crizotinib or chemotherapy.

Keywords: Treatment response, ALK variant, progression pattern

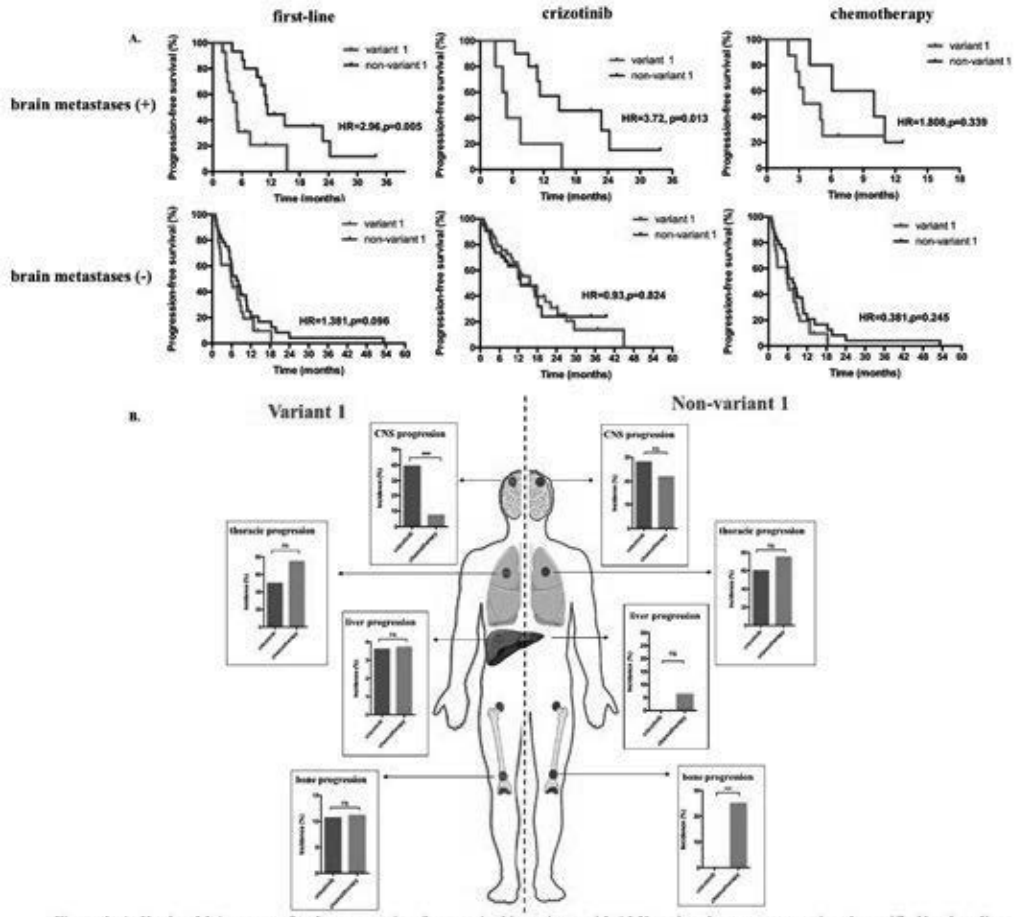

Figure 1. **A.** Kaplan-Meier curves for the progression-free survival in patients with ALK variant 1 versus non-variant 1 stratified by baseline brain metastases status and first-line treatment strategy. **B.** Incidence of different progression patterns in patients with ALK variant 1 versus non-variant1 stratified by treatment strategy.

MA26.06 CRIZOTINIB-TREATED ALK IMMUNOPOSITIVE METASTASIZED NSCLC IS ASSOCIATED WITH AN UNFAVORABLE PROGNOSIS WHEN FISH NEGATIVE

E. Thunnissen[1], B. Lissenberg-Witte[2], M. Van Den Heuvel[3], K. Monkhorst[4], B. Skov[5], J. Sorensen[6], A. Mellemgaard[7], A. Dingemans[8], E. Speel[9], J. De Langen[3], S. Hashemi[10], I. Bahce[10], M. Van Der Drift[11], R. Büttner[12], M. Looijen_Salomon[11], J. Gosney[13], P.E. Postmus[14], S. Samii[15], F. Duplaquet[16], B. Weynand[17], X. Durando[18], F. Penault-Llorca[18], S. Finn[19], B. Oz[20], N. Akyurek[21], J. Wolf[22], L. Bubendorf[23], A. Hiemstra[4], S. Duin[1], I. Marondel[24], W. Timens[25], E. Schuuring[25], P. Pauwels[26], E. Smit[27]

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Background: Metastasized NSCLC with an ALK fusion are sensitive to a range of tyrosine kinase inhibitors. ALK-positive NSCLC has been identified in the pivotal phase III trial with fluorescence in situ hybridization (ALK FISH+). These tumors are also expressing the fusion product (ALK immunohistochemistry (IHC)+). However, discrepant cases occur, including ALK IHC+ FISH-. The aim of this study was to collect ALK IHC+ cases and compare within this group response to crizotinib treatment of ALK FISH+ cases with ALK FISH- cases. **Method:** A prospective multicenter investigator initiated research study was started in Europe. Stage IV ALK IHC+ NSCLC cases treated with crizotinib were collected centrally. Slides were validated centrally for ALK IHC (with 5A4 ETOP and D5F3 Ventana protocol) and ALK FISH (Vysis probes). **Result:** The study started April 1, 2014 and closed in November 2017. Fifteen centers participated. Registration of 3523 ALK IHC tests revealed prevalence of 2.6% ALK IHC+ cases. Local ALK FISH analysis resulted in 46 concordant (ALK IHC+/FISH+) and 18 discordant (ALK IHC+/FISH-) cases. Central validation revealed 37 concordant and 6 discordant cases, 5 of which had follow-up. Validation was hampered by limited amount of tissue in biopsy samples. The time to treatment failure did not differ for concordant nor discordant cases, and neither for local nor validated ALK testing (HR=0.78; 95% CI= 0.27-2.3; p=0.64) and (HR=2.2; 95% CI= 0.72-6.5; p=0.16), respectively). However, overall survival was significantly better for concordant cases than discordant cases after central validation (HR=4.5; 95% CI= 1.2-15.9; p=0.010), but not according to local testing (HR=1.7; 95% CI= 0.45-6.2; p=0.44). **Conclusion:** ALK IHC+ FISH- NSCLC cases are an infrequent finding. We recommend such cases to be validated carefully because our data indicate that ALK IHC+ FISH- cases have a worse survival when treated by crizotinib compared to ALK IHC+ FISH+ cases. This study was funded by an independent research grant by Pfizer

Keywords: survival, ALK validation, crizotinib

MA26.07 ROS1 (SP384) IMMUNOHISTOCHEMISTRY INTER-READER PRECISION BETWEEN 12 PATHOLOGISTS

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Background: ROS1 positive non-small cell lung cancer (NSCLC) patients can be treated with specific tyrosine kinase inhibitors including crizotinib. ROS1 positivity is often clinically detected by fluorescence *in situ* hybridization (FISH), however ROS1 IHC can be used to screen samples prior to FISH confirmation of ROS1 status. The ROS1 (SP384) antibody detects ROS1 with high sensitivity, specificity, and consistency. Consistent interpretation of a ROS1 IHC assay between pathologists is important patient evaluation. Here we present inter-reader precision of 12 pathologists across 60 FFPE cases stained with ROS1 (SP384). **Method:** A retrospective cohort of 60 FFPE NSCLC cases stained with H&E, Rabbit Monoclonal Negative Control Ig, and ROS1 (SP384) were selected to represent positive, negative, and borderline ROS1 IHC status. Twelve practicing lung pathologists independently scored the cases as positive or negative around a cutoff of cytoplasm staining in > 30% tumor cells at a ≥2+ intensity level using Pathotrainer software (Pathomation bvba). Scoring was blinded to other readers and ROS1 status of the cases. Overall percent agreement (OPA), negative percent agreement (NPA), and positive percent agreement (PPA) were calculated in comparison to the group mode. Average overall percent agreement (AOPA), average positive agreement (APA), and average negative agreement (ANA) were calculated pairwise for each reader pair. Following independent assessment, participating pathologists conducted a discordant case review establishing consensus reads for all 60 cases and compared 44 cases to available FISH results. **Result:** OPA of each of the 12 readers to the mode was 96.4% (95% CI 93.9-98.6) with PPA of 96.3% (95% CI 92.7-99.4) and NPA of 96.5% (95% CI 92.8-99.5). Pairwise AOPA between each of the 12 readers was 94.5% (95%CI 91.2-97.7) with APA 94.0% (95% CI 89.5-97.6) and ANA 95.0% (95%CI 91.2-97.9). Consensus IHC scores were concordant with FISH 90.0% (40/44 cases). **Conclusion:** Inter-reader precision around a cutoff of >30% tumor cells with cytoplasmic staining at a ≥2+ intensity level was high in interpreting ROS1 (SP384) in NSCLC samples. Case review highlighted confirmation with FISH in questionable cases and staining patterns to be considered when interpreting ROS1 (SP384) IHC.

Keywords: ros1, crizotinib, Immunohistochemistry

MA26.09 LAZERTINIB, A THIRD GENERATION EGFR-TKI, IN PATIENTS WITH EGFR-TKI-RESISTANT NSCLC: UPDATED RESULTS OF A PHASE I/II STUDY

B.C. Cho[1], J. Han[2], S. Kim[3], K. Lee[4], D. Kim[5], Y. Lee[6], G. Lee[7], J. Lee[8], E.K. Cho[9], J. Kim[10], S.S. Lee[11], Y.J. Min[12], J. Kim[13], S.W. Shin[14], H.R. Kim[1], M.H. Hong[1], J.S. Ahn[15], S. Kang[16], S. Kim[16], S.B. Jang[16], S. Choi[16], M. Ahn[17]

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Background: Lazertinib (YH25448) is a highly mutant-selective, irreversible 3rd-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that can penetrate the blood-brain barrier, and targets the activating EGFR mutations Del19 and L858R, as well as the T790M mutation, while sparing wild type. We report the updated results from a Phase I/II study of lazertinib (NCT03046992) **Method:**

Patients with advanced and metastatic NSCLC who had progressed after treatment with EGFR-TKIs with/without asymptomatic brain metastases (BM) were enrolled in an open-label, multicenter, phase I/II study with dose-escalation and expansion cohorts. Lazertinib was administered once daily at doses between 20 to 320 mg in a 21-day cycle. Patients were assessed for safety, tolerability, pharmacokinetics and efficacy. T790M status was confirmed in the dose-expansion cohorts. **Result:** A total of 115 patients (median age 62 years, female 62%) were enrolled. The dose-escalation cohort included 38 patients administered with 20 to 320 mg across 7 dose levels, and 77 patients in the dose-expansion cohort were administered with 40 to 240 mg across 5 dose levels. No dose-limiting toxicities were observed in the dose-escalation cohort. Systemic exposure increased dose-dependently. Of the evaluable patients (n=110) at data cut-off, the objective response rate (ORR) was 65% (95% confidence interval [CI], 54.9 to 73.4). The ORR for 93 of the T790M+ patients was 69% (95% CI, 58.4 to 78.0). In patients with BM (n=12), the intracranial ORR was 50% (95% CI, 21.1 to 78.9). The most common treatment-emergent adverse events (TEAEs) were pruritus (19%), decreased appetite (17%), rash (14%), and constipation (12%). The most frequently reported TEAEs of grade ≥ 3 were hyponatraemia (2%), nausea (2%) and pneumonia (2%).

ORR in T790M+ patients						
Dose QD	20 mg	40 mg	80 mg	120 mg	160 mg	240 mg
Evaluable patients*, n	2	25	18	22	18	8
ORR, n (%)	2 (100)	17 (68)	11 (61)	17 (77)	11 (61)	6 (75)

* Patients were deemed evaluable for response if they underwent a post-baseline radiological assessment (RECIST 1.1) or were discontinued prior to the post-baseline assessment.

Conclusion: Lazertinib was safe, well-tolerated and exhibited promising systemic and intracranial antitumor activity in EGFR T790M+ NSCLC patients. The dose-expansion cohort as the first and second-line setting has been initiated from April 2018.

Keywords: Lazertinib, T790M, 3rd generation EGFR TKI

MA26 NEW THERAPIES AND EMERGING DATA IN ALK, EGFR AND ROS1
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MA26.10 CNS ACTIVITY OF RAMUCIRUMAB IN COMBINATION WITH OSIMERTINIB IN PATIENTS WITH ADVANCED T790M-POSITIVE EGFR-MUTANT NSCLC

L. Paz-Ares[1], D. Planchard[2], J.C. Yang[3], K. Lee[4], P. Garrido[5], K. Park[6], J. Kim[7], D.H. Lee[8], H. Mao[9], B. Chao[10], H. Yu[11]

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Background: Many patients with NSCLC develop central nervous system (CNS) metastasis. Osimertinib, a novel third-generation *EGFR* tyrosine kinase inhibitor (TKI), has previously demonstrated CNS and systemic efficacy in patients with EGFR-mutant NSCLC. Combination of an *EGFR* TKI with a VEGF/VEGFR2-directed monoclonal antibodies (mAb) have shown promising results in *EGFR*-mutant NSCLC. Ramucirumab, human IgG1 VEGFR2 mAb, was used in combination with osimertinib. Planned exploratory and CNS response analyses aim to examine the safety/efficacy of ramucirumab+osimertinib in patients with CNS metastasis. **Method:** In this ongoing, open-label, multicenter Phase 1 study (NCT02789345), patients with T790M-positive *EGFR*-mutant (Ex19del or L858R) NSCLC who had relapsed after first-line EGFR TKI therapy were enrolled. Patients with asymptomatic and stable CNS metastasis (with/without prior radiotherapy) were eligible. Primary objective of the study was to assess safety and tolerability of ramucirumab+osimertinib. Secondary endpoints include objective response rate (ORR) and disease control rate (DCR). Exploratory endpoints relevant to CNS include CNS ORR and CNS DCR. **Result:** Patients (N=25) were 45-80 years (median 64) with ECOG-PS 0 (n=3) or 1 (n=22) and 10 patients had CNS metastasis at enrollment while 15 never had CNS metastasis. Patients with CNS metastasis could have had prior radiotherapy (n=7) or no radiotherapy (n=3) to the CNS. Median follow-up time was 7.23 months. Fifteen patients remained on study treatment (five with CNS metastasis, ten without). TEAEs of interest (CNS metastasis, no CNS metastasis), such as headache (4/10, 5/15), vomiting (3/10, 4/15), and nausea (2/10, 4/15), were observed with comparable rates in patients with or without CNS metastasis. One patient developed TEAE of cerebral hemorrhage (Grade 1), related to CNS metastasis, but unrelated to study treatment, according to the investigator. Another patient with CNS metastasis developed Grade 5 TRAE of subdural hemorrhage, unrelated to CNS metastasis, ~7 weeks after the last dose of ramucirumab. Only one patient with CNS metastasis had measurable CNS lesions (tumor shrinkage of 24% [SD] as best response). The other nine patients with CNS metastasis had non-measurable CNS lesions, one of whom had a CNS complete response; his systemic best response was SD. The rest of patients had CNS non-CR/non-PD. To date, one patient (1/25) developed CNS progression (due to new CNS lesion); her CNS best response was SD. **Conclusion:** Ramucirumab+osimertinib showed potential antitumor activity in the CNS. Patients with CNS metastasis, with/without prior radiotherapy, appeared to tolerate this combination similarly to patients without CNS metastasis.

Keywords: CNS (brain) metastasis, ramucirumab, Osimertinib

MA26 NEW THERAPIES AND EMERGING DATA IN ALK, EGFR AND ROS1
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MA26.11 EFFECTS OF DOSE MODIFICATIONS ON THE SAFETY AND EFFICACY OF DACOMITINIB FOR EGFR MUTATION-POSITIVE NSCLC

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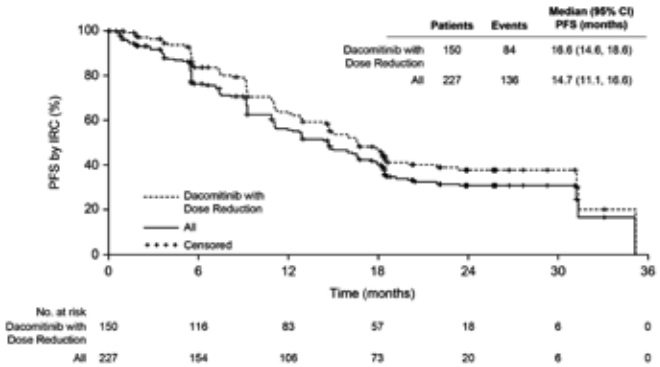
Background: In patients with EGFR mutation-positive advanced stage NSCLC, first-line dacomitinib significantly improved PFS, OS, DoR and time to treatment failure vs gefitinib (ARCHER 1050; NCT01774721).[1,2] Dacomitinib starting dose was 45 mg QD for all patients, with reductions to 30 or 15 mg QD permitted. We explored effects of dacomitinib dose reduction on safety and efficacy in this ongoing study. **Method:** Patients with newly diagnosed stage IIIB/IV or recurrent NSCLC harboring an EGFR mutation (exon 19 del or exon 21 L858R) randomized to dacomitinib received 45 mg PO QD. Study endpoints and protocol-defined dose reduction parameters were previously described.[1] We evaluated reasons for dose reductions, and their effects on incidence and severity of common adverse events (AEs) and key efficacy endpoints (PFS, OS, ORR). Data cutoff dates: 17-Feb-2017 (OS), 29-Jul-2016 (other endpoints). **Result:** Overall, 150 (66.1%) patients dose reduced for AEs (87 and 63 reduced to 30 and 15 mg QD as lowest dose, respectively); most commonly for skin toxicities (62.6%) and diarrhea (14.0%). Median time to each successive dose reduction was ~12 weeks. Incidence and severity of AEs declined following dose reduction, including grade ≥3 diarrhea (11.3% before vs 4.0% after), dermatitis acneiform (15.3% vs 6.7%), stomatitis (3.3% vs 2.7%) and paronychia (7.3% vs 4.7%). PFS was similar in dose-reduced and all dacomitinib-treated patients (Figure). Median OS results were also similar (dose-reduced patients: 36.7 mo [95% CI: 32.6, NR]; all dacomitinib-treated patients: 34.1 mo [95% CI: 29.5, 37.7] as were ORRs (dose-reduced patients: 79.3% [95% CI: 72.0, 85.5]; all dacomitinib-treated patients: 74.9% [95% CI: 68.7, 80.4]).



Conclusion: Efficacy was similar in the dose-reduced patients and the overall study population. Incidence/severity of dacomitinib-related AEs decreased with dose reduction, thereby allowing patients to continue treatment. **References:** Wu, et al. *Lancet Oncol*. 2017. Mok, et al. *J Clin Oncol*. 2018.

Keywords: dose reduction, non-small cell lung cancer, Dacomitinib

MA27 NOVEL DRUGS AND PDX MODELS
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MA27.01 ESTABLISHMENT OF PDX FROM TUMORS CHARACTERIZED BY EGFR MUTATIONS OR ALK FUSION GENES FROM RESECTIONS, BIOPSIES AND PLEURAL FLUIDS

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Background: Patient-derived xenograft (PDX) models allow for cancer tissue expansion, providing an effective method to evaluate tumor biology and mechanisms of response or resistance. Our study aims to establish models in patients enriched for lung adenocarcinoma (LUAD) with *EGFR* mutations or *ALK* fusion genes which respond initially to oral targeted therapy, but typically develop resistance and disease relapse within 2 years. The PDXs will be evaluated for their potential to model therapy outcomes, to determine resistance mechanisms and to evaluate novel therapy strategies to overcome resistance. **Method:** From August 2015 to January 2018, we collected 109 samples from patients with EGFR- or ALK-driven LUAD and from never-smoker LUAD patients with unknown mutation status. Five samples with low tissue viability (i.e. necrotic) or very low tumor content (<100 malignant cells) were excluded. Adequate samples were implanted into the subcutaneous tissue of NOD-SCID mice. At this time, 16 samples have reached the study endpoint (tumor growth $\geq$1.5cm^3) and 60 showed no tumor-growth following implantation (median follow-up: 8m). Results are currently pending for 18 models. **Result:** Samples were collected from surgical resections (31, 36%), CT-guided biopsies (12, 14%), EBUS (19, 22%) and pleural fluid effusions (24, 28%). Most patients were female (51/86, 59%), never smokers (62/85, 73%), and had stage III or IV cancer (55/79, 70%). Mutations in *EGFR* and *ALK* were found in 55/81 (68%) and 12/84 (14%) primary cancers, respectively. Early-passage xenograft engraftment (XG) was observed in only 16 (19%) PDXs, including 9/55 (16%) *EGFR*- and 1/12 (8%) *ALK*-mutant cancers. The phenotype and molecular changes (*EGFR* and *ALK*) were consistent within the PDX model and its corresponding patient sample. Samples collected from surgical-resection specimens showed a trend towards higher engraftment rates (p=0.084). Conversely, the presence of EGFR or ALK mutations showed a trend towards non-engraftment (noXG, p=0.075). Patient smoking status and tumor stage did not influence engraftment rate. To identify reasons for no tumor-growth, we conducted histological analysis in the subcutaneous fat-pads (nodes in the implant sites) of 28 noXG mice. Interestingly, we identified small non-palpable foci of carcinoma in 8 animals (4 *EGFR*+ and 2 *ALK*+). **Conclusion:** Environmental or molecular factors may impair engraftment rates of *EGFR*+ and *ALK*+ LUAD samples in PDX models. Nevertheless, these models recapitulate the primary disease and could be useful for population-based drug-screening studies.

Keywords: lung adenocarcinoma; patient-derived xenograft; TKI

MA27 NOVEL DRUGS AND PDX MODELS
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MA27.02 HYPOFRACTIONATED RADIOTHERAPY NORMALIZES TUMOR VASCULATURE IN NON-SMALL CELL LUNG CANCER XENOGRAFTS THROUGH P-STAT3/HIF-1 ALPHA PATHWAY

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Background: Our study aimed to investigate specific biological effect of hypofractionated radiotherapy (HFRT) on tumor angiogenesis, when compared with conventional radiotherapy (CRT). **Method:** Firstly, models of nude mice as well as dorsal skinfold window chamber (DSWC) bearing H460 and HCC827 (NSCLC cell lines) were established. Tumors suffered irradiation with doses of 0 Gy (control group), 22 Gy delivered into 11 fractions (CRT group) or 12 Gy delivered into 1 fraction (HFRT group). After irradiation, xenograft volumes were recorded every other day. At different time points after irradiation, the vasculature of DSMC was visualized by FITC-Dextran; α-SMA and CD34 immune-histochemical staining was employed to detect the micro-vessel density (MVD) and coverage rates of pericyte on tumor vessels; pimonidazole hydrochloride was used to detect hypoxia; western blotting and RT-PCR were used to detect the expression levels of p-STAT3, HIF-1α, SDF-1 and VEGFA. Then, S3I-201, the STAT3 inhibitor, was used to further verify the mechanism of the effect of HFRT on vascular normalization. **Result:** Compared to CRT groups, the growth suppression effect of HFRT on tumor tissue was enhanced, accompanied by stronger effect on decrease in MVD, vascular normalization and improvement of tumor hypoxia. RT-PCR and western blotting exhibited that HFRT promoted the vascular normalization by activating STAT3/ HIF-1α signaling pathway. **Conclusion:** Compared to CRT, the pathway of p-STAT3/HIF-1α and its downstream angiogenic factors (VEGFA and SDF-1) might play important roles in forming of a window-period of vascular normalization in NSCLC, which contributed to the specific biological effect of HFRT on tumor vasculature.

Keywords: HFRT, angiogenesis, NSCLC

MA27 NOVEL DRUGS AND PDX MODELS
WEDNESDAY, SEPTEMBER 26, 2018 - 13:30-15:00

MA27.03 MULTI-OMIC CHARACTERIZATION OF TKI-TREATED DRUG-TOLERANT CELL POPULATION IN AN EGFR-MUTATED NSCLC PRIMARY-DERIVED XENOGRAFT

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Background: Sixty to eighty percent of advanced stage lung adenocarcinoma patients with epidermal growth factor receptor (*EGFR*) mutated tumors respond to first generation EGFR tyrosine kinase inhibitors (TKIs). However, cure is not yet achievable with any EGFR TKI monotherapy, as patients eventually progress due to acquired resistance. *In vitro* evidence suggests that minor populations of epigenetically modified drug tolerant cells (DTCs) may be important for tumor cells surviving TKI. We hypothesize that molecularly characterizing DTCs *in vivo* and comparing them to the untreated tumor in a patient-derived xenograft (PDX) model may delineate mechanisms of tolerance that closely mimic those occurring in patients. **Method:** DTCs were produced via chronic exposure to erlotinib in a lung adenocarcinoma PDX harbouring an exon 19 deletion. Histological, genomic, transcriptomic (including single-cell RNA-seq), and epigenetic characterizations were performed on DTCs and compared to untreated baseline (BL) tumors. **Result:** Compared to BL, DTCs exhibit decreased levels of proliferation (Ki67 by immunohistochemistry (IHC) and increased expression of senescence/quiescence (p21) and anti-apoptosis (BCL-XL) immunohistochemistry (IHC) markers, while maintaining EGFR pathway signaling (pEGFR, pAKT, pERK, pS6 IHC). Whole exome-sequencing provides evidence that DTCs likely do not represent mutationally distinct subclones from the bulk tumor. Instead, DTCs exhibit a number of differentially expressed genes compared to BL tumors that are involved in cell cycle arrest, senescence/quiescence, differentiation, vesicles, and inflammation. Genes with epigenetic differences (chromatin openness and/or promoter methylation) are involved in similar cellular processes. A minor (<2%) subpopulation of transcriptomically-defined DTC-like cells in the BL tumors are very similar to the DTCs, supporting the hypothesis that DTCs may exist prior to treatment. A number of transcription regulators are found to have differential gene expression and epigenetic regulation as well as DNA-binding motifs found in regions of chromatin uniquely open in DTCs or baseline tumors. These transcription regulators are involved in cell maintenance, proliferation, and differentiation, and may play key roles in promoting DTC phenotype. **Conclusion:** In this specific *EGFR* mutant PDX model sensitive to first generation TKIs, DTC-like cells are found in the BL untreated tumors, and its resultant phenotype after exposure to TKI appears to be involved in cell cycle, differentiation, senescence/quiescence, proliferation and maintenance. PDX models may provide insights into therapeutic strategies to target DTCs, and further improve the survival of *EGFR*-mutated NSCLC patients.

Keywords: Drug-tolerance, epigenetics, Single-cell sequencing

MA27.05 DRUG LOADED MESENCHYMAL STEM CELLS FOR TARGETED LUNG CANCER TREATMENT IN MICE

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Background: Mesenchymal stem cells (MSCs) are cells residing in many tissues of our body. Due to their low immunogenicity, allogeneic MSCs have been used extensively for immune regulation and many other conditions. Over 90% of culture expanded MSCs are entrapped in the lungs after intravenous infusion. Taking this advantage, in this study, we utilized MSCs as a vehicle for targeted delivery of drugs to the lungs to treat lung cancer. **Method:** For enhanced cellular uptake, docetaxel (DTX) was loaded in PLGA-PEG nanoparticles (NPs). Lung cancer was induced in $Kras^{G12D}$ mice, who expressed a form of constitutively activated Kras protein in lung cells upon local administration of cre-advenovirus (AdCre) solution. The size of lung cancer was assessed by PET-CT and tissue analysis. **Result:** The amount of DTX uptake by MSCs at 1, 3, 7, 12, and 24 hours was measured by LC-MS, and the result showed that DTX intake reached peak at 12 hours with ~36 µg in 10^6 MSCs, compared to 15 µg DTX in equal number of fibroblasts, indicating that MSCs had higher NPs-DTX uptake capacity than fibroblasts. To visualize MSCs in vivo, MSCs were labeled with luciferase (Luci). 10^6 MSCs-Luci loaded with NPs-DTX were injected intravenously in mice. In vivo imaging system (IVIS) analysis showed a predominant accumulation of the cells (drug) in the lungs at 24 hours after injection. The effect of MSCs/NPs/DTX in inhibiting lung cancer development was evaluated in $Kras^{G12D}$ mice. Five days after lung cancer induction, the mice received an intravenous injection of 10^6 MSCs loaded with NPs-DTX (~25 µg), NPs-DTX (~200 µg) alone, or PBS every 5 days. 30 days after tumor induction, PET-CT analysis detected large masses in the lungs in PBS treated mice, compared to much smaller masses in MSCs/NPs/DTX-treated or NPs-DTX-treated mice. In consistence, the tumor weight was significantly lower in MSCs/NPs/DTX-treated or NPs-DTX-treated animals than PBS-treated mice, and similar reductions in tumor weight were found in MSCs/NPs/DTX-treated or NPs-DTX-treated mice. **Conclusion:** Thus our data indicate that MSC loaded with DTX can provide targeted therapy for lung cancer to achieve equal cancer inhibition with much lower doses of DTX thus reducing side effects of the drug. As allogeneic MSCs do not cause obvious immune rejection, our study suggests a novel approach for targeted lung cancer therapy.

Keywords: targeted therapy; Mesenchymal Stem Cells; KrasG12D mice

MA27.06 THERAPEUTIC SILENCING OF ONCOGENIC KRAS WITH A MUTANT-SPECIFIC SHORT INTERFERING RNA

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Background: Oncogenic mutations in *RAS*genes are well established drivers of cancer. In particular, lung, pancreatic and colorectal cancers carry high rates of oncogenic mutations in *KRAS*. Promising preclinical strategies with RNA interference (RNAi) have been developed to target oncogenic RAS function, yet a clinically effective anti-RAS therapy remains to be achieved. While genetic knock-down of mutant *KRAS*with RNAi is one promising approach, current methods are not selective and also decrease normal RAS, raising concerns about potential normal tissue toxicity. **Method:** We took a novel in silico approach to develop a library of siRNAs that are theoretically capble of silencing mutant KRAS sequences yet spare the wild-type sequence. We utilized a 3T3 model system to test our library of siRNAS against various human KRAS G12 and G13 mutations compared with the wild-type sequence. Dose titrations were performed to assess the unique affinity of our lead candidate for mutant v. WT. Using a KRAS mutant orthotopic lung model, we assessed in vivo silencing and therapeutic effects following delivery of our lead candidate when packaged into a nanoliposome. **Result:** Here we describe a custom designed short interfering RNA (siRNA) oligonucleotide (KRAS-m) that displays a higher affinity for the most frequent subsets of oncogenic *KRAS*mRNAs than for wild-type *KRAS*mRNA. Using 3T3 cells stably expressing wild-type or various KRAS mutations, we observed that KRAS-m preferentially suppressed expression of G12C, G12D, G12V and G13D missense mutations compared to wild-type KRAS. Additionally, KRAS-m impaired proliferation of lung cancer cells in 2D as well as 3D spheroids embedded in extracellular matrix. In order to optimize *in vivo* stability and minimize toxicity, a 2'O-methylation strategy was utilized and several equipotent modifications were found. To overcome future clinical limitations of delivering siRNA to tumors, we evaluated a lipid nanoparticle platform (LNP) clinically-proved to be safe and highly efficient at delivering systemic RNAi. Biodistribution studies in a syngeneic, orthotopic metastasis model of KRAS (G12D) lung adenocarcinoma revealed substantial uptake of LNP-siRNAs in lung tumors and metastasis. Time-kinetic studies in this model revealed a single delivery of LNP-KRAS-m siRNA significantly silenced KRAS protein expression in tumors for at least 3 days. Compared with LNP-control siRNAs, following two deliveries of LNP-KRAS-m siRNAs model led to significant reductions in disease burden. **Conclusion:** Taken together, our data indicate a novel strategy to target oncogenic *KRAS*-driven lung tumors using a mutant-specific siRNA capable of targeting many of the most common KRAS mutations.

Keywords: KRAS, siRNA, Therapeutic

MA27.07 LUNG ADENOCARCINOMA HARBORING BRAF G469V MUTATION IS UNIQUELY SENSITIVE TO EGFR TYROSINE KINASE INHIBITORS

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Background: BRAF mutations occur in 2-5% of non-small cell lung cancers with ~50% being non-V600E. Previous studies reported that two BRAF G469 mutations, G469V and G469A increase kinase activity and MAPK activation, thus are likely oncogenic. Patients with non-V600E mutations are mostly not sensitive to approved BRAF inhibitors vemurafenib or dabrafenib. We established a lung adenocarcinoma (LUAD) patient derived xenograft (PDX) that is epidermal growth factor receptor (EGFR) wild type and non-amplified, but harbors BRAF G469V mutation, yet is sensitive to gefitinib. We performed functional studies to characterize the oncogenicity and sensitivity of BRAF G469 mutations to EGFR tyrosine kinase inhibitors (TKIs). **Method:** PDX12 was established in NOD-SCID mice from a resected stage IIIA LUAD. The XDC12 cell line was established from PDX12. NCI-H1395 and -H1755 LUAD cell lines with BRAF G469A mutation were obtained from ATCC. BRAF mutant driver activity was characterized by shRNA knockdown of BRAF in LUAD cell lines and the ability of the mutants to promote IL3-independent growth when expressed in Ba/F3 cells. PDX12 responsiveness to TKIs was evaluated by tumor volume shrinkage while cell line sensitivity was quantified using the MTS assay. Drug effects on signaling were assessed by phospho-immunoblotting. Computational modeling was used to predict how the mutations promote BRAF activation and sensitivity to EGFR-TKIs, while purified BRAF proteins were used to validate predictions. **Result:** Knockdown of BRAF by shRNA inhibited growth of all BRAF mutant cell lines, while ectopic BRAF G469V and G469A expression in Ba/F3 cells promoted IL3-independent MAPK activation and growth, supporting both mutations being oncogenic drivers. The XDC12 cell line was sensitive to EGFR-TKIs (gefitinib, erlotinib, afatinib, and osimertinib), but resistant to the BRAF inhibitor dabrafenib, which correlated with inhibition of MAPK phosphorylation. By contrast, H1395 and H1755 cell lines with BRAF G469A mutations were resistant to both the EGFR-TKIs and the BRAF inhibitor. Similarly, only Ba/F3 cells expressing BRAF G469V, but not G469A, were sensitive to EGFR-TKIs. Consistent with the in vitro data and our initial PDX findings with gefitinib, multiple EGFR-TKIs induced tumor shrinkage in PDX12 in vivo. **Conclusion:** BRAF G469V/A mutations are oncogenic drivers but are insensitive to BRAF inhibitors. However, only BRAF G469V, but not G469A mutation, is sensitive to EGFR-TKIs. Thus, two different driver alterations affecting the same BRAF codon can lead to distinct drug sensitivities.

Keywords: BRAF G469V mutation, EGFR-TKIs, patient-derived xenograft model

MA27.09 DUAL INHIBITION OF BCL-XL AND MCL-1 IS REQUIRED TO INDUCE TUMOUR REGRESSION IN LUNG SQUAMOUS CELL CARCINOMAS SENSITIVE TO FGFR INHIBITION

C. Weeden[1], C. Ah-Cann[1], A. Holik[1], D. Merino[2], G. Lessene[1], M. Asselin-Labat[1]

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Background: Fibroblast growth factor receptor 1 (*FGFR1*) gene amplification has been described in 20% of lung squamous cell carcinoma (SqCC), suggesting that FGFR tyrosine kinase inhibitors may constitute a new therapeutic approach for patients carrying this genetic alteration. However, a recently completed clinical trial reported low response rates to FGFR therapy, indicating the need for refined biomarkers. We have recently described that high levels of *FGFR1* RNA expression better predicts response to FGFR inhibitors, yet the treatment results in tumour cell stasis as opposed to cell death. BH3-mimetics are a class of anticancer agents that block the BCL-2 family of pro-survival proteins to induce cell death and were recently approved for clinical use in blood cancers. We therefore hypothesized that combining BH3-mimetics with FGFR-targeted therapy may enhance the killing of SqCC cells. **Method:** We developed patient-derived xenograft models of lung squamous cell carcinoma and evaluated the activity of specific inhibitors of BCL-XL (A1331852), BCL-2 (ABT-199), MCL-1 (S63845) or FGFR (BGJ398) as single agents or in combination in vitro and in vivo. Genetic knockout of BCL-XL was also performed using CRISPR/Cas9. We evaluated compounds synergy in vitro using BLISS assay and in vivo efficacy using mRECIST. **Result:** Here we demonstrate that FGFR therapy primes SqCC for cell death by increasing the expression of the pro-apoptotic protein BIM. We identified a greater reliance of lung SqCC cells on BCL-XL compared to BCL-2 for survival. However, neither BCL-XL nor MCL-1 inhibitor alone gives a survival benefit in combination FGFR therapy *in vivo*. In contrast, triple BCL-XL, MCL-1 and FGFR inhibition resulted in tumour volume regression and prolonged survival *in vivo*, demonstrating the ability of BCL-XL and MCL-1 proteins to compensate for each other in lung SqCC. **Conclusion:** Our work therefore provides a rationale for the simultaneous inhibition of MCL-1, BCL-XL and FGFR1 to maximize therapeutic response in *FGFR1*-expressing lung SqCC.

Keywords: FGFR, Patient-derived xenograft, BH3 mimetic

MA27.10 EGFR-TARGETED THERAPY ALTERS THE TUMOR MICROENVIRONMENT IN EGFR-DRIVEN LUNG TUMORS: RATIONALE FOR COMBINATION THERAPIES

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Background: Non-small cell lung cancer patients harboring EGFR mutations have significant clinical benefit from EGFR-targeted tyrosine kinase inhibitors (TKIs). However, these patients develop resistance eventually. With the promising implementation of immune checkpoint inhibitors targeting the programmed cell death receptor/ligand 1 (PD-1/PD-L1) pathway for the treatment of lung cancer, there is a growing interest in developing combinatorial therapies that could utilize this immuneapproach in the context of targeted therapies. Although many clinical trials have attempted to study combining EHGR-TKIs with PD-1/PD-L1 inhibitors in NSCLC cases, the clinical benefit is still undefined. Therefore, we carry out this study to investigate the immune response of EGFR-TKIs in EGFR-driven lung tumors, aiming to explore factors may influence the efficacy of this combination strategy. **Method:** We investigated the early and long-term antitumor effects of first-generation TKI gefitinib and third-generation TKI osimertinib respectively in mice with $EGFR^{L858R}$ and$EGFR^{19DEL/T790M}$-driven lung tumors.The changes of immune texture in tumors were dynamically tested in different treatment groups by flow cytometry and immunohistochemistry. **Result:** Upon treatment of gefitinib and osimertinib, we saw significant tumor regression in mice with TKI-sensitive $EGFR^{L858R}$ lung adenocarcinoma. However, mice with $EGFR^{19DEL/T790M}$-driven tumors did not respond to gefitinib, but did show a significant tumor response to third-generation TKI osimertinib treatment. Accompanied with obvious tumor shrinkage, we saw a significant increase of infiltrating $CD11b^+$ myeloid cells and $CD3^+$ lymphocytes throughout treatment. We further analyzed subpopulation of $CD11b^+$ myeloid cells and $CD3^+$ lymphocytes. Results showed that EGFR-TKIs may demonstrated anti-tumor activity by raising cytotoxic $CD8^+$ T cells, activating dendritic cells, eradicating $Foxp3^+$ Tregs and inhibiting M2-like polarization at early stage. However, these immune benefits occurred temporarily and gradually disappeared with treatment went on. On the other hands, the proportion of myeloid-derived suppressor cells(MDSCs), particular mononuclear-MDSCs were consistently elevated responding to sensitive EGFR-TKIs treatment. **Conclusion:** Together, results of our study provide novel insights into the immune response to EGFR-TKIs in vivo and provides rationale for potential combinations of EGFR-TKIs and immunotherapies for the treatment of lung carcinomas in the early setting, before the establishment of tumor relapse with long-term EGFR inhibition.And additional therapies aiming to eliminate certain immunosuppressive components should be considered when applying this combination strategy.

Keywords: lung cancer, EGFR-TKI, tumor microenvironment

MA27.11 GENOMIC SEQUENCING AND EDITING REVEALED THE GRM8 SIGNALING PATHWAY AS POTENTIAL THERAPEUTIC TARGETS OF SQUAMOUS CELL LUNG CANCER

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Background: Lung cancer is the leading cause of cancer death worldwide. Squamous cell carcinoma (LUSC) is one subtype of non-small-cell lung cancer (NSCLC), and ranks at the second of lung cancer incidence. Although targeting receptor tyrosine kinases (RTKs) had already brought better clinical outcomes to NSCLC patients carrying corresponding mutations, very few mutated targets had been identified in LUSC subtype, probably because of the lack of mutation hotspot and functional validation of mutated candidate. **Method:** The whole exome (WES) and whole genome (WGS) sequencing and CRISPR-Cas9 genome editing techniques were integrated to explore and validate novel targeting candidates from 11 groups of LUSC primary tumors and corresponding patient-derived xenografts (PDXs). **Result:** The WES data revealed high homologies on the mutation types and signatures among primary tumor and different passages of PDX tumor samples. Nine significant genes carrying single nucleotide variations (SNVs) and three carrying copy number variations (CNVs) were identified as targeting candidates from WES and WGS data based on the mutation frequency and driver gene analysis. The oncogenic or tumor suppressor functions of those 12 candidates were validated through CRISPR-Cas9 loss-of-function system in tumor cells derived from PDX tissues carrying corresponding mutations and in normal bronchial epithelial cell-line. Furthermore, using CRISPRa transcriptionally activating system, one novel candidate, Metabotropic glutamate receptor 8 (GRM8) was elucidated to promote the survival of LUSC tumor cell through inhibiting cAMP pathway and activating MAPK pathway. **Conclusion:** The components of GRM8 signaling pathway could serve as potential targets of squamous cell lung cancer.

Keywords: genome editing, GRM8, lung cancer

POSTER SESSION 1
MONDAY, SEPTEMBER 24, 2018

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-01 ROS1-POSITIVE NON-SMALL CELL LUNG CANCER: REAL-WORLD DATA IN KOREA

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Background: ROS1 rearranged non-small cell lung cancer (NSCLC) is classified as a distinct molecular subset with a therapeutically druggable target. ROS1 rearrangement is most often identified in never-smoker with adenocarcinoma and EGFR and ALK wild type patients. Treatment with tyrosine kinase inhibitors (TKIs) which target the ROS1 kinase domain is considered standard of care for the ROS1-positve NSCLC, by showing a robust and durable response. However, information regarding the clinical characteristics and the outcomes of TKI treatment in the real world remains limited. **Method:** We have identified 103 consecutive cases of ROS1-positive NSCLC from January 2001 to February 2018 by break apart fluorescence in situ hybridization (FISH) (n=84), next-generation sequencing (n=23) or both (n=3). Information on fusion breakpoints was available for 8 patients. Clinical data including patient characteristics, incidence of brain metastasis, and response to chemotherapy or TKI were retrospectively analyzed. **Result:** The median age was 56 years, 58.9% of patients were female, and 75.7% were never smokers. Adenocarcinoma was predominant (98.1%), and 2 cases with pleomorphic carcinoma were identified. Sixty percent of patients had an extra-thorax metastatic lesion, and 22% had intracranial lesion at the initial presentation or at the time of recurrence. Median time to brain metastases was 12.0 months (range 2.1 to 84.1). Majority of the patients received palliative chemotherapy (93.2%), and 7.8% of patients received definite concurrent chemoradiotherapy. Most common fusion partner was CD74 followed by SDC4, EZR, TPM3, TFG, ZCCHC8, SLMAP, and MYO5C, all of which had preserved tyrosine kinase domain of ROS1. There were no clinical correlations between different fusion partners and TKI treatment outcomes. The median overall survival for the study population was 52.1 months (95% confidential interval [CI] 23.6 – not reached). For 90 patients treated with pemetrexed-based chemotherapy, the overall response rate (ORR) and progression-free survival (PFS) was 53.3% and 8.0 months (95% CI 6.4 – 11.7), respectively. The ORR and PFS was 70.7% and 12.7 months (95% CI 8.1 – 21.8) for 50 patients treated with TKI. Brain metastasis was more commonly observed during the TKI treatment (15.5%) than pemetrexed-based chemotherapy (6.7%). **Conclusion:** ROS1-positive NSCLC has distinct clinical characteristics with high and durable response to both TKI and pemetrexed-based chemotherapy. Given its novel characteristics and distinct clinical responses to conventional chemotherapies and TKIs, the treatment strategy for ROS1-positive NSCLC remains to be further developed.

Keywords: ros1, NSCLC, tyrosine kinase inhibitor

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-02 LONG-TERM OUTCOMES WITH FIRST-LINE NIVOLUMAB PLUS IPILIMUMAB IN ADVANCED NSCLC: 3-YEAR FOLLOW-UP FROM CHECKMATE 012

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Background: CheckMate 012 (NCT01454102) is a phase 1 study evaluating several nivolumab monotherapy/combination regimens as first-line treatment for advanced non-small cell lung cancer (NSCLC). CheckMate 012 was the first study to suggest the benefit of nivolumab plus ipilimumab in NSCLC. In the phase 3 study CheckMate 227, nivolumab plus ipilimumab recently demonstrated significantly improved progression-free survival (PFS) as well as more frequent, deeper, and more durable responses versus chemotherapy in patients with chemotherapy-naive advanced NSCLC and high tumor mutational burden (TMB). Here, we provide 2-year follow-up results for nivolumab plus ipilimumab from CheckMate 012. Three-year results, the longest follow-up to date for an immuno-oncology combination in NSCLC, will be presented. **Method:** Eligible patients had recurrent stage IIIb or stage IV chemotherapy-naive NSCLC and Eastern Cooperative Oncology Group performance status 0–1. Patients received nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks (n=38) or every 6 weeks (n=39) until disease progression, unacceptable toxicity, or consent withdrawal; pooled results of these two cohorts are presented. Endpoints included safety/tolerability (primary); objective response rate and PFS (secondary); and overall survival (OS), chemotherapy-free survival (CFS), and efficacy by TMB status (exploratory). **Result:** With 2 years of follow-up, no new safety signals were observed. Thirty-three of 77 patients (43%) achieved objective responses, including six investigator-assessed complete responses (8%), three of which were complete pathological responses. Responses were durable (median duration of response, not reached; range, 1.4+ to 27.9+ months). The 2-year PFS rate was 29%. At the time of database lock, 32 of 34 patients (94%) with OS ≥2 years were alive, with four (12%) remaining on treatment and progression-free; 14 (41%) were off treatment and progression-free without subsequent therapy. Three-year follow-up results to be presented include OS, PFS, and select data on CFS, efficacy by TMB status, and characteristics of long-term survivors. **Conclusion:** With long-term follow-up, nivolumab plus ipilimumab continued to demonstrate durable clinical benefit and a consistent safety profile as first-line treatment for patients with advanced NSCLC.

Keywords: NSCLC, Nivolumab, first-line

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P1.01-03 EFFECT OF PROPHYLACTIC CRANIAL IRRADIATION ON COGNITIVE FUNCTION AND QOL IN NSCLC PATIENTS AT HIGH RISK OF BRAIN METASTASES

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Background: Up to 50% of NSCLC patients develop brain metastases (BM). Prophylactic Cranial Irradiation (PCI) is a potentially useful strategy to prevent this event, although its use remains controversial due to inherent risks. Therefore, actions such as dose adjustment for Whole Brain Radiotherapy (WBRT), or hippocampal-sparing techniques have been explored. We evaluated the impact of PCI on cognitive function and Quality of Life (QoL). **Method:** Within the clinical trial NCT01603849 we evaluated a total of 84 histologically-confirmed NSCLC patients with high risk of developing BM (adenocarcinomas harboring oncodrivers (*EGFR* or *ALK*) and/or carcinoembryonic antigen (CAE) level at diagnosis ≥20 pg/mL). Patients were randomized 1:1, 41 to receive PCI and 43 to observation. Cognitive function (CF) was evaluated before and after treatment and at 6, 9 and 12 months with Mini Mental State Examination (MMSE). Reliable Change Index was used to evaluate the effect on CF. QoL was assessed through the European Organization for Research and Treatment of Cancer (EORTC-QLQ-30). Differences between groups were compared with Mann Whitney U and Friedman test. OS was estimated from the first MRI assessing the absence of BM until death/last follow-up with Kaplan-Meier and compared with Log-Rank test. **Result:** 83.3% of patients presented an *EGFR*-mutation (n=60) or *ALK*-rearrangement (n=6). Median OS was 42.8 vs. 25.9 months among patients with or without PCI (p=0.031). MMSE scores and median score values for global QoL, fatigue and cognitive functioning did not differ among groups or at baseline and follow-up. There were also no differences in percentual change at 1-yr (Table).

Clinical changes (MMSE)		3 months	6 months	9 months	1 yr
		n/N (%)	n/N (%)	n/N (%)	n/N (%)
Without PCI					
	Without Changes	38/43 (88.4)	34/42 (81)	34/42 (81.0)	29/37 (78.4)
	Cognitive Deterioration	0/43 (0)	2/42 (4.8)	0/42 (0)	0/37(0)
	Cognitive Improvement	5/43 (11.6)	6/42 (14.2)	8/42 (19.0)	8/37 (21.6)
With PCI					
	Without Changes	39/41 (95.1)	31/34 (91.2)	31/34 (91.2)	27/31(87.1)
	Cognitive Deterioration	1/41 (2.4)	0/34 (0)	0/34 (0)	1/31(3.2)
	Cognitive Improvement	1/41 (2.4)	3/34 (8.8)	3/34 (8.8)	3/31 (9.7)

		Baseline	3 months	6 months	9 months	1 yr	p-Value (*)	Diff. at 1 yr
		Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)		Median (IQR)
Global QoL	Without PCI	66.7 (50.0 - 83.3)	66.7 (50.0 - 83.3)	66.7 (64.6 - 83.3)	83.3 (66.7 - 85.4)	83.3 (75.0 - 87.5)	<0.001	8.3 (0.0 - 29-2)
	With PCI	66.7 (50.0 - 83.3)	66.7 (50.0 - 83.3)	66.6 (66.7 - 83.3)	83.3 (66.7 - 83.3)	83.3 (75.0 - 83.3)	<0.001	0.0 (0 - 25.0)
p-Value (diff between groups)		0.956	0.786	0.903	0.172	0.595		0.791
Fatigue	Without PCI	22.2 (11.1 - 44.4)	33.3 (22.2 - 44.4)	22.2 (11.1 - 44.4)	22.2 (11.1 - 44.4)	22.2 (11.1 - 33.3)	<0.001	0.0 (-22.2 - 0.0)
	With PCI	22.2 (5.6 -33.3)	33.3 (11.1 - 33.3)	22.2 (8.3 - 33.3)	22.2 (8.3 - 33.3)	22.2 (0.0 - 33.3)	<0.001	0 (0 - 0)
p-Value (diff between groups)		0.493	0.132	0.942	0.931	0.93		0.553
Cognitive	Without PCI	83.3 (66.7 - 100.0)	83.3 (66.7 - 100.0)	83.3 (66.7 - 100.0)	73.3 (83.3 - 100.0)	73.3 (83.3 - 100.0)	0.004	0 (0 - 0)
	With PCI	83.3 (66.7 - 100.0)	83.3 (66.7 - 100.0)	83.3 (66.7 - 100.0)	91.7 (70.8 - 100.0)	83.3 (83.3 - 100.0)	0.017	0.0 (0.0 - 0.0)
p-Value (diff between groups)		0.854	0.983	0.521	0.411	0.757		0.734

Conclusion: PCI was not associated with significant differences in MMSE and QoL scores, furthermore there were no differences when assessing specific subscales (e.g. fatigue and cognitive functioning). These results along with the clinical benefit in OS highlight the benefit of this approach particularly among patients at high risk of developing BM.

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P1.01-04 TREATMENT PATTERNS AND OVERALL SURVIVAL FOLLOWING BIOMARKER TESTING IN REAL-WORLD ADVANCED NSCLC PATIENTS

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Background: Foundation Medicine (FMI) comprehensive genomic profiling and other next-generation sequencing (NGS) tests are gaining importance in routine clinical management of non-small cell lung cancer (NSCLC). They assess multiple genetic alterations that drive sensitivity or resistance to treatment, enabling optimal therapeutic decisions. We evaluated the effect of biomarker testing on treatment patterns and overall survival (OS) in real-world advanced NSCLC (aNSCLC) patients receiving different test types, and in non-tested patients. **Method:** The Flatiron Health (FH) Database comprises patient-level electronic health records from a large network of US cancer clinics. Patients had aNSCLC diagnoses between 01/2013 and 05/2017, ≥2 clinic visits in the FH network, first treatment starting ≤90 days after aNSCLC diagnosis, and biomarker tests before first treatment. Testing data were abstracted for five biomarkers (*EGFR*, *ALK*, *KRAS*, *ROS1*, and PD-L1). Patients were hierarchically categorized into three testing groups: FMI, other NGS, and single-biomarker non-NGS. Biomarker status and patterns in first treatment were described. Cox proportional hazards models were used to compare OS among testing groups and non-tested patients. **Result:** As of 11/30/2017, 355 patients had ≥1 FMI test, 780 had ≥1 other NGS test, and 6,363 had ≥1 non-NGS test prior to first treatment; 5,148 patients were never tested. Table 1 summarizes biomarker status, treatment patterns, and results of multivariate survival models adjusted for baseline demographic and clinical differences among testing groups. Patients with FMI tests were more likely to receive NCCN-recommended targeted treatments. Better OS was observed for FMI, other NGS, and non-NGS compared with non-tested patients.

(See next page)

	FMI		Other NGS		Non-NGS		Non-tested	
	(n = 355)		(n = 780)		(n = 6,363)		(n = 5,148)	
	n	%	n	%	n	%	n	%
Biomarker status[1]								
EGFR mutation	51	14.4	121	15.5	853	13.4	-	-
ALK rearrangement	8	2.3	23	2.9	187	2.9	-	-
ROS1 rearrangement	0	0	3	0.4	33	0.5	-	-
KRAS mutation	94	26.5	189	24.2	415	6.5	-	-
PD-L1-positive	21	5.9	112	14.4	234	3.7	-	-
Patterns in first treatment								
NCCN-recommended targeted therapy[2,3]	77	21.7	129	16.5	1,037	16.3	112	2.2
Non NCCN-recommended targeted therapy[2,4]	2	0.6	3	0.4	11	0.2	40	0.8
NCCN-recommended ICI[2,5]	36	10.1	102	13.1	381	6.0	229	4.4
Non NCCN-recommended ICI[2,6]	2	0.6	0	0	8	0.1	3	0.1
Multivariate Cox proportional hazards model to compare OS, hazard ratio (95% CI)								
All aNSCLC[7]	0.72*	(0.61, 0.85)	0.74*	(0.66, 0.83)	0.78*	(0.74, 0.83)	1.00	(ref)
aNSCLC, non-squamous cell histology[8]	0.69*	(0.61, 0.79)	0.76*	(0.70, 0.80)	0.69*	(0.57, 0.83)	1.00	(ref)
All aNSCLC[9]	0.93	(0.77, 1.13)	1.05	(0.92, 1.21)	1.00	(ref)	-	-
aNSCLC, non-squamous cell histology[10]	0.91	(0.74, 1.13)	1.01	(0.87, 1.17)	1.00	(ref)	-	-
aNSCLC, non-EGFR-mutated, non-ALK-rear-ranged, non-squamous cell histology[11]	0.9	(0.74, 1.10)	0.94	(0.82, 1.08)	1.00	(ref)	-	-

ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; NCCN, National Comprehensive Cancer Network. [1] Denotes biomarker status overall prior to starting first treatment and represents overall status from all test-types. In case of multiple tests, the following hierarchy is used: positive>negative>pending/unsuccessful/indeterminate/unknown. [2] Based on the NSCLC NCCN Guidelines, Version 3. 2018; 02/21/2018. [3] NCCN-recommended targeted therapy implies treatment regimens containing at least one of the following: erlotinib, afatinib, gefitinib, osimertinib, crizotinib, ceritinib, alectinib, brigatinib, dabrafenib+trametinib, cabozantinib, vandetanib, ado-trastuzumab emtansine. [4] Non NCCN-recommended targeted therapy implies treatment regimens containing at least one of the following: necitumumab, cetuximab, panitumumab, vemurafenib, dabrafenib, trametinib, trastuzumab, pertuzumab+trastuzumab, venetoclax. [5] NCCN-recommended ICI implies treatment regimens containing at least one of the following: pembrolizumab, nivolumab, atezolizumab. [6] Non NCCN-recommended ICI implies treatment regimens containing at least one of the following: ipilimumab, avelumab. [7] Adjusted for age, sex, race, clinic type, payer type, smoking history, stage at initial diagnosis, ECOG performance status, histology, and year of advanced diagnosis. [8] Adjusted for age, sex, race, clinic type, payer type, smoking history, stage at initial diagnosis, ECOG performance status, and year of advanced diagnosis.

[9] Adjusted for age, sex, race, clinic type, payer type, smoking history, stage at initial diagnosis, ECOG performance status, histology, year of advanced diagnosis, sample type used for the test, and biomarker status. [10] Adjusted for age, sex, race, clinic type, payer type, smoking history, stage at initial diagnosis, ECOG performance status, year of advanced diagnosis, sample type used for test, and biomarker status. [11] Adjusted for age, sex, race, clinic type, smoking history, stage at initial diagnosis, ECOG performance status, and year of advanced diagnosis.

** Indicates a statistically significant estimate (p<0.05).*

Conclusion: Complexity of real-world aNSCLC biomarker testing and associated treatments creates challenges when comparing OS among testing groups. In the future, as more treatments targeting a wider array of genomic alterations become available and accessible, the utility of NGS-based assays to guide NCCN-recommended treatments with actionable targets and differences in OS may become more apparent.

Keywords: Oncology electronic health record (EHR), advanced non-small cell lung cancer (aNSCLC), next-generation sequencing

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P1.01-05 METFORMIN IN COMBINATION WITH CRIZOTINIB FOR THE TREATMENT OF EML4-ALK+ LUNG CANCER.

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Background: Lung cancer accounts for the highest incidence of cancer mortality worldwide, equating to around 2 million deaths each year. Oncogenic receptor tyrosine kinases (RTK) have been discovered to play a role in cancer progression, and can be the target of novel therapeutics. The anaplastic lymphoma kinase receptor (ALK) is an RTK, and as a result of a chromosomal 2 rearrangement, fuses with echinoderm microtubule associated protein like-4 (EML4) forming the oncogenic EML4-ALK receptor. EML4-ALK contributes to 2-7% of all lung cancer cases and currently the first-line treatment is crizotinib, a tyrosine kinase inhibitor. Although crizotinib produces tumor regression, most patients will develop resistance, constituting a major research problem. Novel strategies are being explored and one such treatment is the anti-hyperglycemic, metformin. Epidemiological studies have shown that metformin reduces the risk of cancer and pre-clinical studies are examining this cytotoxic effect. This work aimed to determine the cytotoxicity and mechanism of a crizotinib/metformin combination *in vitro* in EML4-ALK+ lung cancer.
Method: Crizotinib, metformin and the combination were examined using EML4-ALK+ human lung adenocarcinoma cells (H3122), ALK-/KRAF+ human lung adenocarcinoma cells (A549) and crizotinib-resistant (CR-H3122) cells maintained in crizotinib (0.8 μM). Cytotoxicity was tested using the sulforhodmaine B assay and to assess the validity of this assay the MTT assay was used as a comparison. Western blotting examined changes in ALK, p-ALK, mTOR, p-mTOR. Propidium iodine staining

and flow cytometry examined changes in the cell cycle in H3122 cells. **Result:** Crizotinib exhibits greater potency in H3122 cells compared to the ALK- A549 (IC50's of 0.16 μM vs. 1 μM). Interestingly, the addition of metformin (5 mM) to both cell lines did not change the IC50, however, reduced cell viability by ~30% at lower doses of crizotinib. The MTT assay found the same effect. The IC50 of metformin in H3122 cells was 22 mM, whereas this potency was lost in CR-H3122 cells (only a 50% reduction in cell viability with 50 mM). Mechanistically it was discovered that metformin decreases mTOR phosphorylation, a downstream protein of ALK, but has no effect on p-ALK. Both crizotinib and metformin produced a G1 phase arrest, with the effect being enhanced with the combination. **Conclusion:** Metformin enhances the effect of low dose crizotinib. It appears that metformin acts by targeting the downstream protein, mTOR, and produces a G1 phase arrest, instead of directly inhibiting ALK. The addition of metformin to chemotherapeutics provides a potential treatment for EML4-ALK+ and other lung cancers.

Keywords: crizotinib, metformin, EML4-ALK

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P1.01-06 PLINABULIN, A NOVEL IMMUNO-ONCOLOGY AGENT MITIGATES DOCETAXEL CHEMOTHERAPY -INDUCED-NEUTROPENIA AND -THROMBOCYTOPENIA IN NSCLC PATIENTS.

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Background: Plinabulin (Plin) is a novel non-GCSF small molecule with anti-cancer activity, in development for prevention of Chemotherapy (Chemo)-Induced-Neutropenia (CIN) and under evaluation with induced by Docetaxel (Doc), Adriamycin, Cyclophosphamide, Irinotecan, Gemcitabine, Carboplatin, Abraxane). Plin is administered as a single IV infusion per cycle, and on the same day of Chemo, 30 minutes after Chemo. In contrast to G-CSF, Plin has anti-cancer, immune-enhancing activity due to dendritic cell activation and related T-cell proliferation, and Plin does not cause bone pain. Our randomized phase (Ph) 2 study 101 (NCT00630110) in lung cancer (NSCLC) with Docetaxel (Doc) 75 mg/M^2 +/- Plin established the baseline for Grade 4 neutropenia without Plin. We recently completed the Ph2 portion of the Ph2/3 Study 105 (NCT03102606), comparing Plin with Pegfilgrastim (Peg) for Doc CIN prevention in NSCLC. The 20 mg/m2 Plin dose was equally effective as Peg for CIN, and this dose will be taken into Ph3. The CIN nadir was earlier with Peg, and occurrence of bone pain was higher with Peg vs Plin (33% vs 11%, resp), suggesting a different mechanism of action (MoA). To further understand Plin's MoA, we analyzed hematology results with Plin and Peg treated subjects. **Method:** Ph2 Study 105: NSCLC Pts were randomized to Doc 75 mg/ m^2 day (D)1, and either Peg 6 mg D2 (n=14), or Plin at 5 (n=14),10 (n=13), 20 (n=14) mg/ m^2 D1 (30 minutes after Doc). Blood for central hematology analysis was collected through Cycle 1. Grade (Gr) 4 neutropenia data without Plin (that is Plin 0 mg/ m^2) data was taken from study 101. **Result:** Docetaxel-induced Gr 4 Neutropenia was 14%, 23%, 14%, 33% when Doc was combined with Plin at a dose of 20, 10, 5, 0 mg/ m^2 . At the highest Plin dose of 20 mg/ m^2, Gr 4 Neutropenia frequency (14% for Plin or Peg) and Duration of Grade 4/Severe Neutropenia (DSN; 0.5 days for Plin or Peg) were similar for Plin and Peg, however Gr 4 thrombocytopenia frequency was 50% with Peg and 36% with Plin. All Grade thrombocytopenia was significantly higher (p=0.036) with Peg vs Plin. **Conclusion:** Plin appears to be equally effective as Peg against Doc CIN, however Plin, but not Peg, reduced Doc-induced thrombocytopenia. This is further indication of a difference in MoA for Plin vs Peg.

Keywords: NSCLC, Neutropenia, Thrombocytopenia

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P1.01-07 IMMUNE-RELATED PNEUMONITIS IN NSCLC PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS (ICI): IMPACT OF PREVIOUS THORACIC RADIOTHERAPY

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Background: Pneumonitis is a potentially lethal side effect of immune checkpoint inhibitors (ICI), occurring in 1–5% of patients enrolled in clinical trials. Little is known about the interactions between ICI and previous thoracic radiation. This is the aim of the present study. **Method:** Between December 2012 and November 2017, 318 consecutive non-small cell lung cancer (NSCLC) patients received ICI in our Institution and their charts were retrospectively analyzed. Primary endpoint was to determine whether previous radiotherapy had an effect on pulmonary toxicity. Pulmonary toxicity was retrospectively assessed by Common Terminology Criteria for Adverse Events version 4.0. **Result:** Median follow-up was 32.8 months [95%CI: 5-190]. Median age at the start of ICI was 63 years. 205 patients (64,5%) were males, 103 (32,4%) smokers and 250 (78,6%) with PS ≤1; 206 (64,8%) had adenocarcinoma and 76 (23,9%) squamous; 79 (24,8%) were KRAS mutated, 18 (5,5%) EGFR mutated and 5 (1,6%) ALK positive. PDL1 was ≥ 1% by immunohistochemistry in 86 (27%), negative in 37 (11,6%) and unknown in 196 (61,3%) patients. ICI treatment was median 3rd line (range: 1-12), 89,4% monotherapy PD-(L)1 inhibition. 72 patients (22,6%) received a thoracic RT: 62 out of the 72 RT patients (87,5%) were irradiated with a curative intent. 53 patients (73,6% of the RT patients) received thoracic 3D-conformal RT or intensity modulated RT (normo- or mildly hypofractionated), whereas 9 received SBRT. 16,7% of the RT patients (12/72) showed a G1-4 immune-related pneumonitis (with a G=>3 of 11,1%), whereas for never-irradiated patients the G1-3 rate of immune-related pneumonitis was 2,4% (6/246), with only 1 G3 toxicity observed and no G>4 (t-test, p 0,001). Median interval between the onset of the immune-related pneumonitis and the end of the RT was 22,4 months. **Conclusion:** NSCLC patients treated with ICI may be at higher risk of developing immune-related pneumonitis when previously treated with curative-intent thoracic RT.

Keywords: thoracic radiotherapy, Immune checkpoint inhibitors, immune-related pneumonitis

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P1.01-08 HYPERRESPONSIVE DISEASE: A NEW PATTERN OF RESPONSE IN NSCLC PATIENTS TREATED BY ANTI-PD-1/PD-L1

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Background: Immune-checkpoint inhibitors are standard of care for stage IV non-small cell lung cancer. Pembrolizumab, an anti-PD-1 monoclonal antibody, boosts the host anti-tumor response. Some patients have a better benefit, especially with strongly positive PD-L1 tumors. To our knowledge, hyperresponsive disease has never been reported. **Method:** We present 3 of these cases. **Result:** A 52-year-old woman with lung adenocarcinoma with peritoneal carcinomatosis presented to her community hospital for vomiting and abdominal pain of 3-days duration. She had received first-line chemotherapy (carboplatine-pemetrexed) and after progression, was switched to pembrolizumab, started 10 days ago. PD-L1 expression was 100%. Narcotics and antiemetic medications relieved her severe symptoms, but she required hospitalization for 11 days. She did not receive any corticosteroid medication. Medical team was considering palliative care. Three weeks later, imaging showed an almost complete response. Pembrolizumab was restarted, without any gastrointestinal symptoms, with an ongoing response persisting after 13 cycles. A 73-year-old man with lung adenocarcinoma with bone

metastases was started on first-line pembrolizumab. PD-L1 expression was 100%. Two weeks later, he had severe pelvic pain where a bone metastasis had been previously diagnosed, not treated with radiation therapy. He required a 3-weeks hospitalization, with palliative care for pain control. Imaging showed three weeks later a major regression. He was rechallenged with pembrolizumab without recurrent symptoms, currently receiving his 9th cycle. A 74-year-old man with squamous cell lung cancer with bone and liver metastases was started on first-line pembrolizumab. PD-L1 expression was 95%. Three weeks later, he had severe nausea and vomiting lasting two weeks, not relieved by outpatient antiemetic medications. He was hospitalized for IV medications during 8 days. While hospitalized, imaging showed a major regression of the lung and liver lesions. He even needed corticosteroid medication to decrease his symptoms for 2 weeks. He was rechallenged without recurrent symptoms. No other etiologies were identified for the symptoms of these 3 patients, including immune-related adverse event (especially endocrine and liver tests), radiation therapy, infection, disease progression or medications. We diagnosed hyperresponsive disease on the basis of the severe symptoms, impressive response on the CT scan and rechallenge with the same medication without recurrent symptoms. **Conclusion:** A major response to immune checkpoint inhibitors may mimic a progressive disease. Severe symptoms related to the tumor locations should not systematically be attributed to local progression. Clinicians should suspect the possibility of a hyperresponsive pattern and prescribe imaging to confirm or refute this hypothesis.

Keywords: hyperresponsive disease, Anti-PD-1/PD-L1, NSCLC

P1.01 ADVANCED NSCLC
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P1.01-09 PEMBROLIZUMAB PLUS IPILIMUMAB OR PLACEBO IN 1L METASTATIC NSCLC WITH PD-L1 TUMOR PROPORTION SCORE (TPS) ≥50%: KEYNOTE-598

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Background: Pembrolizumab monotherapy significantly prolonged survival vs chemotherapy in previously untreated, advanced NSCLC with PD-L1 expressed on ≥50% of tumor cells (TPS ≥50%) in KEYNOTE-024. Pembrolizumab with chemotherapy led to higher objective response rates (ORRs) vs chemotherapy alone in a similar population in KEYNOTE-021. KEYNOTE-598 (NCT03302234) will evaluate the effects of combination immunotherapy with pembrolizumab and ipilimumab. **Method:** Eligibility for this randomized, double-blind phase 3 study requires patients be ≥18 years of age and have histologically/cytologically confirmed stage IV metastatic NSCLC, PD-L1 TPS ≥50% per IHC analysis on archival/newly obtained tumor sample, measurable disease per RECIST v1.1, ECOG PS 0/1, absence of *EGFR/ALK* aberration, and no prior systemic therapy. Patients will be randomized 1:1 to up to 35 administrations of pembrolizumab 200 mg Q3W with 18 cycles of either ipilimumab 1 mg/kg or placebo Q6W. Patients may be eligible for 17 and 9 additional administrations of pembrolizumab and ipilimumab/placebo, respectively. Treatment may be discontinued due to disease progression, intolerable toxicity, or consent withdrawal. Randomization is stratified by ECOG PS (0 vs 1), geography (East Asia vs non–East Asia), and histology (squamous vs nonsquamous). Response is assessed every 9 weeks through week 54, then every 12 weeks per RECIST v1.1 by BICR. Treatment-based decisions may utilize modified RECIST v1.1 for immune-based therapy (iRECIST). Site-assessed progression is verified by BICR before treatment discontinuation. AEs are graded per CTCAE v4.0. Primary endpoints are overall survival and progression-free survival. Secondary endpoints are ORR and duration of response by BICR; time to true deterioration in the composite endpoint of cough, pain in chest, and shortness of breath assessed by EORTC QLQ-LC13 and EORTC QLQ-C30; and safety. Approximately 548 patients will be enrolled. Enrollment began on December 18, 2017; as of April 13, 2018, 33 patients have been enrolled. **Result:** "Section not applicable" **Conclusion:** "Section not applicable"

Keywords: pembrolizumab, Ipilimumab, NSCLC

P1.01 ADVANCED NSCLC
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P1.01-10 STAGE III NON-SMALL CELL LUNG CANCER CLINICAL OUTCOMES WITH SURGICAL RESECTION AFTER DEFINITIVE NEOADJUVANT CHEMORADIOTHERAPY

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Background: The role of neoadjuvant CRT followed by surgery (trimodality therapy) continues to evolve in patients with stage III non-small cell lung cancer (NSCLC). To date, limited prospective data exist assessing definitive preoperative radiotherapy doses. We report our clinical experience of high-dose (definitive) radiation-based trimodality therapy. **Method:** Between January 2000 and December 2016, 107 consecutive patients with stage III NSCLC treated with curative intent at our institution with definitive doses of neoadjuvant chemoradiotherapy (CRT) were analyzed. The primary endpoint was overall survival (OS) and secondary endpoint was freedom from recurrence (FFR), analyzed using the Kaplan-Meier method with log-rank testing. Cox regression with forward-model selection was used for the multivariate analyses (MVA). **Result:** The patients had a median age of 58.5 years (range: 38-82) and were predominantly Caucasian (76%) with baseline performance status of 0 (69%). Stage grouping, according to the 7thedition of American Joint Committee on Cancer (AJCC) Lung Cancer Staging criteria, was IIIA: 78.5%, T3/4: 43.9%, N2: 74.8%, N3: 8.4%. CRT was delivered concurrently in 98% of the patients. Median radiation dose was 61.2Gy (range 39.6-69.6Gy); 89% receiving ≥60Gy. Radiation technique was (3D) conformal (71.0%) or intensity-modulated radiotherapy (IMRT) (27.1%). The 30-day and 90-day surgical mortality rates were 4.7% and 7.5%, respectively. At a median follow-up of 30 months (range: 3-186 months), estimated OS and FFR (median/5-year) were 61 months/ 49% and 29 months/ 35%, respectively. On univariate analysis (UVA), age ≥60 (HR, 1.776; 95% CI, 1.084–2.909; P=0.023) and having no health insurance (HR, 3.071; 95% CI, 1.060–8.902; P=0.039; as compared to those with private insurance) predicted for an increased risk of death, while receiving consolidation chemotherapy was associated with improved survival (HR, 0.472; 95% CI, 0.258–0.864; P=0.015). On MVA, age ≥60 was the only characteristic with a continued association with OS (HR, 1.779; 95% CI, 1.056–2.998; P=0.039). On UVA, lack of health insurance was the only predictor of disease recurrence (HR, 6.059; 95% CI, 2.244-16.360; P<0.001). **Conclusion:** In a carefully selected population, full dose neoadjuvant CRT followed by surgery can achieve high OS and FFR even for stage III NSCLC patients, much higher than recent reports of bimodality therapy (RTOG 0617: median OS of 28.7 months and PACIFIC study: median PFS of 16.8 months). Prospective evaluation of high-dose radiation trimodality therapy versus induction chemotherapy alone is warranted.

Keywords: Trimodality, Chemoradiotherapy, Locally advanced non small cell lung cancer

P1.01 ADVANCED NSCLC
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P1.01-11 NAMED PATIENT USE PROGRAM FOR AFATINIB IN ADVANCED NSCLC WITH PROGRESSION ON PRIOR THERAPY: EXPERIENCE FROM ASIAN CENTERS

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Background: A global named patient use (NPU) program for afatinib in patients with advanced/metastatic NSCLC who had progressed during prior therapy was conducted between May 2010 and January 2016 (Cappuzzo F et al, Future Oncol 2018). Here we describe treatment outcomes for patients at Asian centers. **Method:** Eligible patients had progressed after clinical benefit on prior erlotinib/gefitinib and/or had an activating *EGFR/HER2* mutation, had exhausted all other treatments, and were ineligible for afatinib trials. Patients received afatinib (starting dose:30-50 mg/day). Dose modifications were allowed as tolerated. Time to treatment failure (TTF) was calculated from treatment initiation to discontinuation. Adverse event (AE) reporting was mandatory. **Result:** Data were collected from 2242 NSCLC patients across 10 Asian countries. Patients were heavily pretreated, 62% received ≥2 prior chemotherapy lines, and for most, afatinib was 4th-line therapy; almost all had received erlotinib/gefitinib (Table 1). 97% of patients with known tumor status were *EGFR* mutation-positive (m+). Median TTF was 7.6 months overall, and 7.2 months in patients with *EGFR* m+ tumors (Table 1). TTF was >12 months in patients with *EGFR* exon20 insertions and *Her2* mutations. ORR was numerically higher in patients with exon20 insertions and G719X/L861Q/S761I mutations than other subgroups (Table 1). Disease control rate was 78% overall. The most frequently reported AEs were rash and diarrhea; no new/unexpected safety signals were identified.

Table 1. Named patient use (NPU) program for afatinib in advanced/metastatic NSCLC: results from Asian centers

Total number of patients	2242			
Age; years, median	61			
Female/male; %	60/40			
Any prior treatment; n (%)	2223/2242 (99.2)			
Prior erlotinib and/or gefitinib; n (%)	2202/2223 (99.1)			
Prior erlotinib only; n (%)	866/2202 (39)			
Prior gefitinib only; n (%)	927/2202 (42)			
Prior lines of chemotherapy	≥3, 32%; ≥2, 62%; 1, 23%; 0, 15%			
Prior lines of systemic therapy	≥4, 37%; ≥3, 65%; 2, 21%; 1, 14%; 0, 0%			
EGFR m+; n (%)	1240/1281 (97)			
Specified EGFR mutation; n (%)	1101/1240 (89)			
	TTF; months*	n	ORR, %	n
All patients with data available	7.6	1550	24.4	431
EGFR m+	7.2	834	27.7	267
EGFR mutation specified	6.5	740	-	-
Common mutations (Del19 or L858R)	6.4	692	27.4	230
Uncommon mutations (all)	8.0	84	30.3	33
T790M	6.0	34	21.1	19
G719X, L861Q, or S761I	7.8	28	42.9	7
Exon 20 insertion	18.0	25	42.9	7
Her2 m+	12.2	12	14.2	7
p.A775 G776insYVMA	12.4	7	25.0	4

*median m+ve, mutation-positive; ORR, objective response rate; TTF, time to treatment failure **Conclusion:** This analysis from Asian countries in the afatinib NPU program revealed clinically meaningful TTF/ORR in this heavily pre-treated and refractory advanced NSCLC patient population, including activity in common and uncommon *EGFR* mutations. TTF was numerically longer in patients with uncommon mutations (particularly *EGFR* exon20 insertions) and *HER2* mutations than in those with common *EGFR* mutations. The safety profile of afatinib was consistent with non-Asian centers.

Keywords: afatinib, NSCLC

P1.01 ADVANCED NSCLC
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P1.01-12 SWITCH MAINTENANCE PEMBROLIZUMAB IN PATIENTS WITH METASTATIC NON SMALL CELL LUNG CANCER (SWIPE)

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Background: Pembrolizumab is currently indicated for first line use for patients with >50% PD-L1 overexpression and for pretreated patients with >1% PD-L1 expression with metastatic Non Small Cell Lung Cancer (NSCLC). There are currently no data for its use as maintenance treatment. SWIPE is a prospective single arm, one stage Phase II study offering Pembrolizumab as maintenance therapy to non-progressors after first line palliative chemotherapy with NSCLC. (NCT 02705820) **Method:** Standard inclusion and exclusion criteria for checkpoint inhibitors studies apply, however also patients with WHO Performance Status (PS) 2 were allowed and there was no restriction on PD-L1 expression. Treatment consisted of Pembrolizumab 200 mg fixed dose every 3 weeks. Radiological assessement with CT scans every 9 weeks in the first year. The study employs a one stage phase II Fleming's design using Immune Related (IR) Progression Free Survival (PFS) at 1 year as primary endpoint. Using response hypotheses of H0 < 12 % and Ha> 25%, with a significance level α=0.05 and power 0.8, 48 patients are required to be entered into this study. **Result:** Thirty-six (36) patients have been enrolled so far. 29 patients have more than 6 months follow up data, and are the subjects of this analysis. 23 males and 6 female patients. Median age 65 years (range 40-82). PS WHO 0 for 12 patients, WHO 1 for 15 patients and WHO 2 for 2 patients. Histology: adenocarcinoma in 22 patients and squamous in 7 patients. In terms of best radiological response 2 patients had a partial response and 13 patients stable disease. Median IR PFS is 6.8 months (CI 4.0-17.2). The 6 month and 1 year IR PFS rate is 60.7% and 45.8%. Median OS is 11.3 months (CI 7.4-15.2). The 6 month and 1 year OS rate is 65.5% and 48.0% (SPSS version 23). Toxicity was mainly grade 1-2; commonest being fatigue 18 patients (62%), anorexia, arthralgia and cough 10 patients (34%). One patient developed diabetes mellitus (grade 3) as auto-immune toxicity. Three (3) patients developed grade 3 dyspnoea, none of which were related to Pembrolizumab. There was one death during treatment due to sepsis, unlikely to be related to Pembrolizumab. **Conclusion:** Maintenance Pembrolizumab is associated with a clinically meaningful disease control rate of almost 46% at 1 year with manageable toxicity.

Keywords: maintenance, pembrolizumab

P1.01 ADVANCED NSCLC
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P1.01-13 A STUDY OF S-1 PLUS CISPLATIN IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER

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Background: Oral administration of S-1 (Tegafur/Gimeracil/Oteracil potassium fixed combination capsules, 1.0:0.4:1.0 in molar ratio) in combination with cisplatin has been proven non-inferior to the standard-of-care doublet regimen containing docetaxel plus cisplatin in a randomized phase III trial in Japanese patients with advanced non-small-cell lung cancer (NSCLC). The aim of the study was to evaluate the efficacy and safety profiles of oral S-1 plus cisplatin in Taiwanese patients with NSCLC. **Method:** Patients with previously untreated stage IIIB or IV NSCLC were treated with 40 to 60 mg (based on body surface area) of oral S-1 twice daily on days 1–21 plus cisplatin 60 mg/m^2 on day 8 in a 5-week cycle for up to six cycles. **Result:** A total of 55 patients from 5 sites in Taiwan were enrolled and received the study medication. Among the 46 patients who completed at least 2 cycles of treatment and had tumor assessments, disease control rate was achieved at 69.6% (partial response: 19.6%, stable disease: 50.0%), with median overall survival (OS) and progression free survival (PFS) of 15.1 months (95%CI: 11.5, 25.6) and 5.7 months (95%CI: 3.3, 8.4), respectively. Grade ≥ 3 adverse events (AEs) related to study treatment occurred in 11 patients (20.0%). The most commonly observed treatment-related AEs were nausea (41.8%), followed by decreased appetite, anemia and diarrhea. No febrile

neutropenia or treatment-related death were observed in this study. **Conclusion:** The study demonstrated similar efficacy and well-tolerated safety profiles as the previous Phase III study in Japan for patients with advanced NSCLC who received oral S-1 plus cisplatin as the first-line doublet chemotherapy regimen in Taiwan.

Keywords: non-small cell lung cancer, Cisplatin, S-1

P1.01 ADVANCED NSCLC
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P1.01-14 IMMUNOTHERAPY (I) FOR ADVANCED, PRE-TREATED, NON-SQUAMOUS NSCLC (APNS-NSCLC). PRELIMINARY DATA OF A POOLED ANALYSIS

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Background: . To assess the role of I for second line treatment of APNS-NSCLC. **Method:** s. A pooled analysis of the final data of the CA209057, the KEYNOTE-010 and the OAK trial was performed. Overall Survival (OS) was the primary end point of the trial. The outcomes of patients with PD-L1 expression of 1%-49% (PD-L1 1%-49%), PD-L1 expression <1% (PD-L1<1%) or mutated-EGFR (EGFR+) were analyzed comparing any checkpoint inhibitor with standard chemotherapy. An indirect comparison with network meta-analysis was performed between the different checkpoint inhibitors whenever a significant difference was observed in the pooled analysis. Direct and indirect comparisons were performed using a random effect model. **Result:** s. The outcome of 1720 patients was analyzed. 313 patients had been treated with Atezolizumab (A), 292 with Nivolumab (N), 270 with Pembrolizumab (P), and 845 with Docetaxel (D). The preliminary results were detailed in the table. Legend. CI95%: 95% Confidence Interval; *: Pooled Analysis; **: Network Meta-Analysis.

	OS Hazard Ratio	CI95%	
A vs D (PD-L1 1%-49%)	0.571	0.423-0.771	P<0.001
N vs D (PD-L1 1%-49%)	0.62	0.467-0.882	P=0.001
P vs D (PD-L1 1%-49%)	0.76	0.604-0.956	P=0.019
I vs D (PD-L1 1%-49%)*	0.66	0.555-0.786	P<0.001
A vs N (PD-L1 1%-49%)**	0.921	0.609-1.392	P=0.696
A vs P (PD-L1 1%-49%)**	0.751	0.541-1.043	P=0.087
N vs P (PD-L1 1%-49%)**	0.816	0.597-1.116	P=0.491
N vs D (PD-L1<1%)	0.9	0.66-1.214	P=0.491
A vs D (PD-L1<1%)	1.04	0.619-1.747	P=0.882
I vs D (PD-L1<1%)*	0.933	0.72-1.21	P=0.601
P vs D (EGFR+)	0.88	0.453-1.71	P=0.706
N vs D (EGFR+)	1.18	0.693-2.004	P=0.542
I vs S (EGFR+)*	1.052	0.695-1.594	P=0.81

Conclusion: s. Our data seem to confirm the role of I for APNS-NSCLC with PD-L1 1%-49%. On the contrary, not-significant benefits in terms of OS seem to emerge for patients with PD-L1<1% or EGFR+ expression. Likewise, no significant differences seem to emerge from the indirect comparisons between A, N and P for patients with a PD-L1 1%-49% expression. Although all these data need to be analyzed with caution, as expression of indirect comparisons, waiting further conformations from clinical trials they can support clinicians for daily clinical practice.

Keywords: lung canger, Immunotherapy

P1.01 ADVANCED NSCLC
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P1.01-15 ROS1-REARRANGED NON-SMALL CELL LUNG CANCER IS ASSOCIATED WITH HIGH RATE OF VENOUS THROMBOEMBOLISM: ANALYSIS OF THE METROS TRIAL

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Background: Patients with lung cancer are at increased risk for venous thromboembolism (VTE) and 8% to 15% of patients with advanced non-small-cell lung cancer (NSCLC) experience a VTE event during the course of their disease. The incidence of VTE in molecularly defined NSCLC is still unknown. However, emerging data suggests that patients harbouring *ALK*rearrangements are at increased risk of VTE. In light of the high amino-acid sequence and structural homology with ALK protein, we undertook this study to determine the incidence of VTE in patients with *ROS1*-rearranged NSCLC. **Method:** The METROS trial is a multicentre prospective phase II study designed to assess efficacy, safety and tolerability of Crizotinib in pre-treated metastatic NSCLC with *MET*amplification or *MET*exon 14 mutation or *ROS1*rearrangement. *ROS1*-rearranged patients enrolled within cohort A and expansion cohort of the trial were evaluated in this analysis. **Result:** Among 48 patients with ROS1-rearranged lung adenocarcinomas (median [range] age 50 [28-82]); 17 males [35.4%] and 31 females [64.5%]; PS 0-1 [95.8%], 2 [4.2%]; 21 current/former smokers [43.75], 27 never smokers [56.25]) , 20 (41.6%) had at least one VTE event. VTE events consisted in pulmonary embolism (PE) in 11 patients (55%), deep vein thrombosis (DVT) in 11 patients (55%), renal vein thrombosis in 2 patients (10%). Seven patients (35%) had ≥ 1 VTE event. Patients with VTE were more likely to be older than 65 years (P = 0.029). No other associations between clinical characteristics and development of VTE were observed. The occurrence of VTE was not associated with overall survival. **Conclusion:** The incidence of VET is 3- to 5-fold higher in patients harbouring *ROS1*-rearrangment than previously observed for the general NSCLC population. Whether molecular profile of NSCLC should be incorporated into a risk-stratification tool and decision-making algorithm for VTE diagnosis, prophylaxis and treatment remains to be determined prospectively.

Keywords: non-small cell lung cancer, venous thromboembolism, ros1

P1.01 ADVANCED NSCLC
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P1.01-16 FIRST-LINE PEMBROLIZUMAB WITH OR WITHOUT CHEMOTHERAPY IN PD-L1 POSITIVE NSCLC: A NETWORK META-ANALYSIS OF RANDOMIZED TRIALS.

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Background: Pembrolizumab has replaced platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer (NSCLC) with tumor PD-L1 expression >/=50%. Among PD-L1 unselected patients, pembrolizumab + chemotherapy is superior to chemotherapy alone. This network meta-analysis compared pembrolizumab alone with pembrolizumab + chemotherapy in patients with >/=50% PD-L1 positive NSCLC. **Method:** Using the Keynote 024 and 189 (PD-L1 >/=50% subgroup) trials, an indirect network was constructed to compare pembrolizumab and pembrolizumab + chemotherapy through the chemotherapy control arms of each trial. Baseline characteristics and chemotherapy outcomes in both trials were examined for heterogeneity. Overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and adverse events (AEs) including immune-related adverse events (irAE) were extracted from trial results. AE results were unavailable for the PD-L1 >/=50% subgroup of KN189, so overall AE results were used. Comparisons were expressed as hazard ratios (HRs) for survival outcomes, and as risk difference (RD) for ORR and toxicity. **Result:** 507 patients were included: 154 on pembrolizumab, 357 on chemotherapy and 410 on combination. Baseline characteristics of patients in both

trials were similar in age, sex, performance status and smoking history. Both trials also had similar chemotherapy outcomes (PFS 6 vs 5 mos) suggesting similar patient prognosis. Network meta-analysis showed no difference between pembrolizumab + chemotherapy and pembrolizumab alone in OS (HR 0.70, 95%CI 0.38-1.30, p=0.26) or PFS (HR 0.72, 95%CI 0.45-1.16, p=0.18), but combination therapy was associated with higher ORR (+21.5%, 95%CI 4.83-38.2%, p=0.011). Overall and grade 3-5 AE rates were higher with combination treatment compared with pembrolizumab alone, but irAE appeared less common with combination treatment (table). **Conclusion:** Among patients with >/=50% PD-L1 positive NSCLC, pembrolizumab + chemotherapy did not improve OS or PFS compared with pembrolizumab alone, but was associated with higher ORR. Lower rates of irAE with combination therapy are interesting and warrant further study.

Adverse events for Pembrolizumab + Chemotherapy vs Pembrolizumab Alone						
	All Grade Adverse Events			Grade 3-5 Adverse Events		
	Risk Difference (%)	95% CI	p-value	Risk Difference (%)	95% CI	p-value
Any	17.4	8.8, 26.0	<0.001	18.2	4.8, 31.5	0.008
Led to Discontinuation	9.4	1.3, 17.6	0.023	5.7	-1.2, 12.7	0.11
Led to Death	2.1	-2.7, 6.9	0.40	2.1	-2.7, 6.9	0.40
Nausea	37.2	24.7, 49.7	<0.001	2.0	-1.8, 5.8	0.31
Anemia	38.4	26.4, 50.5	<0.001	18.3	9.2, 27.4	<0.001
Fatigue	20.9	8.9, 32.9	<0.001	5.2	0.6, 9.8	0.025
Decreased appetite	14.9	3.5, 26.2	0.01	3.7	0.7, 6.7	0.017
Diarrhea	8.6	-2.0, 19.2	0.11	-0.4	-5.1, 4.4	0.89
Neutropenia	24.9	14.9, 34.9	<0.001	17.3	9.4, 25.1	<0.001
Vomiting	18.3	8.4, 28.3	<0.001	0.8	-2.7, 4.2	0.67
Pyrexia	-0.4	-9.1, 8.3	0.93	NA		
Constipation	10.6	0.7, 20.5	0.036	NA		
Thrombocytopenia	15	7.1, 23.0	<0.001	6.3	0.6, 12.0	0.029
	All Grade Immune-Related Adverse Events			Grade 3-5 Immune-Related Adverse Events		
Any	-13.7	-23.7, -3.74	0.007	-4.6	-11.2, 1.6	0.15
Hypothyroidism	-3.6	-9.4, 2.3	0.23	NA		
Hyperthyroidism	-5.5	-11, 0.1	0.051	NA		
Pneumonitis	-3.2	-8.1, 1.7	0.20	-1.2	-5, 2.5	0.54
Infusion reaction	-1.7	-6.0, 2.5	0.43	NA		
Severe skin reaction	-4.4	-8.4, -4.3	0.03	-0.4	-7.8, -0.1	0.047
Colitis	0.3	-2.3, 2.9	0.84	-0.6	-2.5, 1.4	0.58
Myositis	-1.7	-3.9, 0.5	0.14	NA		
Hypophysitis	0.1	-1.4, 1.6	0.91	NA		
Nephritis	1.1	-0.7, 2.9	0.24	0.8	-0.9, 2.6	0.35

Keywords: advanced NSCLC, immuno-oncology, immune checkpoint inhibitor

P1.01-17 IMMUNE-RELATED ADVERSE EVENTS IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER: SEX DIFFERENCES AND RESPONSE TO THERAPY.

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Background: Sex differences in non-small cell lung cancer (NSCLC) outcomes have been described. Immune-related adverse events (IRAEs) have emerged as a serious clinical problem in the use of immune checkpoint inhibitors (ICI). Risk factors for IRAEs and their association with response to therapy remain controversial. Therefore, we studied sex differences in IRAEs and their association with response to therapy. **Method:** All patients with metastatic NSCLC treated with anti-PD1 and anti-PDL1 therapy at Mayo Clinic Rochester and Florida from 2015 to 2018 were reviewed. Patients receiving treatment at an outside facility or with history autoimmune disorders were excluded. Kaplan-Meier method was used for time-to-event analysis. **Result:** 231 patients were identified, 120 (52%) were women and 111 (48%) were men. Baseline characteristics and ICI distribution were similar among groups (Table 1). Women were more likely to experience IRAEs compared to men (48% vs. 31%, p<0.008). Among patients with IRAEs, women were more likely to be prescribed systemic steroids (63% vs. 41%, p<0.02). Women were more likely to develop pneumonitis (23% vs. 12%, p<0.03) and arthralgia (17% vs. 3%, p<0.04). However, dermatologic toxicities (35% vs. 9%, p<0.002) were more commonly seen in men. In 17% of women the ICI was discontinued due to toxicity (men 7%). Besides sex, no other clinical characteristic was associated with increased IRAEs. Women with IRAEs were more likely to have a radiographic response compared with women without IRAEs (78% vs. 23%, p<0.0001), although this was not observed in men (37% vs. 26%, p>0.22). Better PFS was observed in women with IRAEs (10 months vs. 3.3 months, p<0.0006) compared to women without IRAEs.

	Women % (n)	Men % (n)	p value
PD-L1 expression ≥1%	30 (36)	34 (38)	0.29
Adenocarcinoma	77 (92)	66 (73)	0.02
Bone metastasis	34 (41)	47 (52)	0.05
Brain metastasis	20 (24)	22 (24)	0.76
Liver metastasis	13 (15)	10 (11)	0.53
Prior chemotherapy	74 (89)	85 (94)	0.06
Prior palliative radiation	53 (63)	57 (63)	0.52
IRAEs	48 (57)	31 (34)	0.006
≥3 grade IRAEs	42 (24)	29 (10)	0.22
Received systemic steroids	63 (36)	41 (14)	0.02
Required intravenous steroids	30 (17)	24 (8)	0.47

Conclusion: Women with metastatic NSCLC are more likely to experience IRAEs compared to men. In women, an association between IRAEs and response to therapy was observed. Larger studies are needed to investigate the mechanisms underlying these associations.

Keywords: Immunotherapy, metastatic lung cancer, immune-related adverse events

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-18 IMMUNOSENESCENCE CORRELATES WITH PROGRESSION UPON PD-(L)-1 BLOCKADE (IO) IN ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC) PATIENTS.

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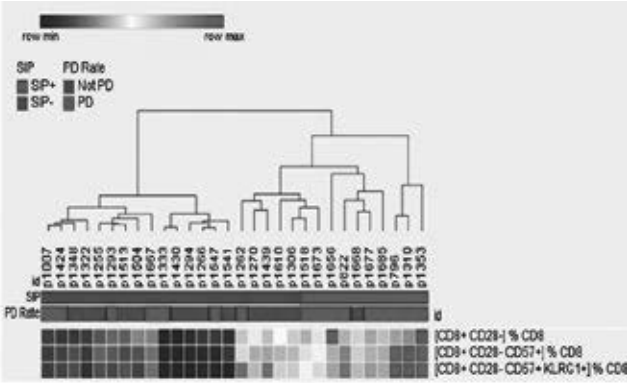
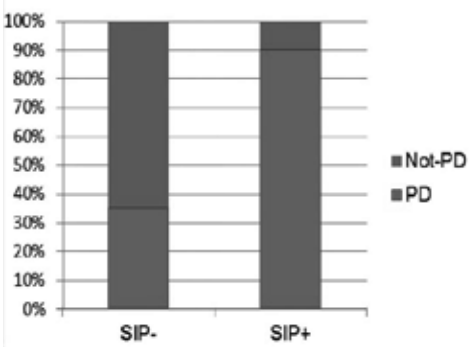
Background: Immunosenescence is a progressive remodeling of immune functions with a multifactorial etiology (i.e. aging, chronic inflammation, cancer). Although a $CD28^{-}CD57^{+}KLRG1^{+}$ phenotype on peripheral T-lymphocytes is a potential hallmark of immunosenescence, the characterization of such phenotype in IO-treated NSCLC patients and the correlation with clinical characteristics and benefit from immunotherapy are unknown. **Method:** A senescent immune phenotype (SIP) defined as a percentage of circulating $CD8^{+}CD28^{-}CD57^{+}KLRG1^{+}$ T-lymphocytes was assessed by flow cytometry (FC) on fresh blood samples from IO-treated aNSCLC patients (03/2017–04/2018). A log-rank maximization method was used to identify a SIP cut-off level and dichotomize patients accordingly. The objective was to correlate SIP with clinical characteristics and RECIST response by univariate logistic regression analysis. **Result:** 39 aNSCLC patients were evaluable for SIP before IO: 38% ≥ 65 years, 87% non-squamous, 38% KRAS mutated, 54% with PD-L1 expression ≥1%, 13% chemotherapy naïve. Among 30 patients evaluable for IO response, 53% had progression (PD), 27% stability (SD), 20% partial response (PR). Median PFS was 1.9 months (95% CI 1.5; 2.5). OS was not calculated due to the short follow-up [6 months (95% CI 4-11)]. SIP (% $CD28^{-}CD57^{+}KLRG1^{+}$) median value on circulating $CD8^{+}$ lymphocytes was 15.26% (min 1.87%, max 56.28%). Overall, 13 (33%) of 39 patients had >22.25% $CD8^{+}$ lymphocytes with a $CD28^{-}CD57^{+}KLRG1^{+}$ phenotype, being classified as SIP^{+}. SIP status did not correlate with age, IO-baseline patients' characteristics or chemotherapy exposure. Among patients evaluable for IO response, only 1 (10%) of 10 SIP^{+} experienced disease control (PR/SD), compared to 13 (65%) of 20 SIP^{-} patients; similarly, PD rate was significantly higher in SIP^{+} compared to SIP^{-} patients (90% vs 35%, p=0.007) (Figure).





SIP+ = [CD8+CD28-CD57+KLRG1+]%CD8 > 22,25

SIP- = [CD8+CD28-CD57+KLRG1+]%CD8 ≤ 22,25

Conclusion: Immunosenescence, monitored by FC measurement of 3 surface molecules on circulating CD8 + lymphocytes, is observed in 33% of aNSCLC patients, is independent of age and correlates with lower IO disease control rate.

Keywords: immunosenescence, advanced non-small cell lung cancer, immunecheckpoints inhibitors

P1.01 ADVANCED NSCLC
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P1.01-19 EFFICACY OF TYROSINE KINASE INHIBITORS IN EGFR MUTATED NON-SMALL CELL LUNG CANCER WITH LEPTOMENINGEAL METASTASES.

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Background: Leptomeningeal dissemination (LM) in patients with non-small cell lung carcinoma (NSCLC) is usually associated with dismal prognosis. However, survival data and optimal management of tyrosine kinase inhibitors (TKI) in EGFR-mutated (EGFRm) patients (pts) are unknown. **Method:** Pts with EGFRm NSCLC with LM treated in 2 institutions were included. Clinical, pathological and radiological data were retrospectively collected. We performed overall survival (OS) analysis from LM diagnosis. We assessed survival, clinical response rate (CRR) and disease control rate (DCR; stable disease > 2 months or clinical response) in patients who received a subsequent TKI after experiencing LM progression with first-line TKI. **Result:** Seventy pts were included between Apr. 2003 and Feb. 2018. Median age was 54 [26-79], 60 (85%) were non-smokers, 51 (73%) female and median number of prior systemic treatments before LM diagnosis was 2 [1-7]. Median OS from LM diagnosis was 7 months (m) [95% CI 6-9], with a 1 year-OS of 29%. Pts received a median of 2 [1-6] lines of subsequent systemic therapy and 19 had additional intrathecal treatment. At first LM progression, 40 pts received subsequent TKI treatment with a median PFS of 3m [95% CI 2-not reached]. DCR and CRR were 73% and 38%, respectively. In patients without T790M mutation (N=36), median OS was 7 months [95% CI 4-7] with 2nd-line erlotinib (N=21) and 3 months [2-17] with 2nd-line afatinib or gefitinib (N=5). Eight patients received high-dose erlotinib as 2nd-line treatment after prior erlotinib with a median OS of 3 months [1-3] and a DCR of 75%. Four patients with T790M mutation received 2nd-line osimertinib with a median OS of 10 months [6-10] and a DCR of 100%. **Conclusion:** Pts with LM from EGFRm NSCLC have prolonged survival with 1st generation TKI. Second-line erlotinib after LM progression is an efficient approach in T790M-negative pts. Erlotinib dose increase is a suitable strategy in erlotinib-refractory T790M-negative pts.

Keywords: Non small-cell lung cancer, EGFR-Tyrosine klinase inhibitors, Leptomeningeal metastases

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-20 PHASE III STUDY COMPARING GEFITINIB (G) TO GEFITINIB COMBINED WITH CARBOPLATIN AND PEMETREXED (GCP) FOR NSCLC WITH EGFR MUTATIONS (NEJ009).

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Background: Although EGFR-TKI alone has been a standard first-line treatment for patients with advanced NSCLC with EGFR mutations, our phase II study (NEJ005) showed promising efficacy of GCP. NEJ009, an open-label, randomized phase III study, was conducted to evaluate the superiority of GCP vs G in progression-free survival (PFS), PFS2, and overall survival (OS). **Method:** Patients with newly diagnosed stage III/IV/recurrent NSCLC harboring EGFR activating mutations (exon 19 deletion or exon 21 L858R) were randomized 1:1 to G 250 mg PO QD or GCP (G 250mg PO QD combined with carboplatin AUC 5 + pemetrexed 500mg/m^2, every 3 weeks). The primary endpoints consisting of PFS, PFS2, and OS were sequentially analyzed according to a preplanned gate-keeping method. Secondary endpoints included objective response rate, safety, and quality of life. **Result:** In Sep 2017, a preplanned required number of events of PFS2 was observed. The ITT population included 344 patients with baseline characteristics fairly well balanced between the arms. Although GCP demonstrated significantly better PFS compared to G, there was no difference in PFS2 between the arms as below. Additional OS analysis (G:101 events vs GCP:83 events) revealed that median survival time of GCP was much longer than that of G (52.2 months vs 38.8 months, HR: 0.695, p=0.013). **Conclusion:** NEJ009 was the first phase III study which evaluated the efficacy of a combination of EGFR-TKI and platinum doublet chemotherapy in untreated advanced NSCLC patients with EGFR mutations. Although GCP regimen failed to demonstrate its superiority in PFS2, it may increase long survivors.

ITT Population	GCP (N=169)	G (N=172)	
	Median (months)	Median (months)	HR
PFS	20.9	11.2	0.493
	[95%CI: 18.0, 24.2]	[95%CI: 9.0, 13.4]	[95%CI: 0.390, 0.623]
			P<0.001
PFS2	20.9	21.1	0.891
	[95%CI: 18.0, 24.2]	[95%CI: 17.9, 24.9]	[95%CI: 0.708, 1.122]
			P=0.806

Keywords: EGFR, gefitinib, phase III

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-21 SAFETY OF DURVALUMAB RETREATMENT IN ADVANCED NSCLC PATIENTS WHO PROGRESSED FOLLOWING INITIAL DISEASE CONTROL IN ATLANTIC

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Background: In ATLANTIC, patients who completed a year of durvalumab (anti-PD-L1) treatment but later progressed off therapy were eligible for retreatment. We evaluated safety in these patients compared with the overall study population. **Method:** ATLANTIC (NCT02087423) was a Phase 2, open-label, single-arm trial in patients with Stage IIIB–IV NSCLC who had received ≥2 prior systemic treatment regimens, including one platinum-based. The study included three independent cohorts. In C1 (*EGFR*+/*ALK*+) and C2 (*EGFR*−/*ALK*−), enrollment was enriched for patients with ≥25% of tumor cells (TC) expressing PD-L1, while patients in C3 (*EGFR*−/*ALK*−) only had PD-L1 TC ≥90%. Patients received durvalumab 10 mg/kg q2w for ≤12 months. Patients who achieved and maintained disease control but then progressed after completing the initial 12-month treatment period were offered retreatment for a maximum of 12 months of further treatment. Safety and tolerability was

a secondary outcome. **Result:** As of November 7, 2017, of 442 patients in the ATLANTIC full analysis set, 102 (23.1%) had completed 12 months of initial treatment and 95 (21.5%) had disease control at the end of initial treatment. A total of 40 patients started retreatment. The median actual duration of exposure to durvalumab was 16.0 weeks (range 1–62; 40.1% of patients on treatment for ≥24 weeks) during initial treatment and 18.1 weeks (range 2–52; 37.5% of patients on retreatment for ≥24 weeks) during retreatment. The table shows safety during initial treatment and retreatment.

	Initial treatment (n=444)	Retreatment phase (n=40)
Cohort,* n (%)		
C1 (EGFR+/ALK+)	111 (25.0)	7 (17.5)
C2 (EGFR−/ALK−)	265 (59.7)	26 (65.0)
C3 (EGFR−/ALK−; TC ≥90%)	68 (15.3)	7 (17.5)
Any TRAE, n (%)	256 (57.7)	19 (47.5)
Grade ≥3 TRAEs	42 (9.5)	6 (15.0)
TRAEs leading to death	0	2 (5.0)†
Serious TRAEs	28 (6.3)	4 (10.0)
TRAEs leading to discontinuation	10 (2.3)	4 (10.0)

Safety analysis set. *A more detailed analysis of exposure and safety by cohort will be presented. †Causes of death were: pneumonitis and respiratory failure; cardiac arrest. TRAE=treatment-related adverse event.

Conclusion: A large proportion of patients (37.5%) maintained retreatment for ≥24 weeks, suggesting that patients who originally completed 12 months of treatment can tolerate sustained retreatment. The tolerability profile of durvalumab upon retreatment was similar to that seen during initial treatment, although there were two treatment-related deaths during the retreatment phase. Retreatment with anti-PD-L1 may be feasible for selected patients with NSCLC who demonstrate original benefit and progress off therapy.

Keywords: durvalumab, programmed cell death ligand-1, Immunotherapy

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-22 EFFECT OF BASAL LYMPHOPENIA ON OUTCOME OF NON SMALL CELL LUNG CANCER PATIENTS TREATED WITH IMMUNOTHERAPY

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Background: The advent of immunotherapy (IO) induced profound change in treatment paradigm of metastatic non small cell lung cancer (mNSCLC). Different agents proved efficacy against the disease, leading to an improvement in patients' (pts) survival. Nonetheless, only a minority of treated pts actually derives a benefit from IO. Some predictive factors, such as PD-L1 and tumor mutation burden, have been identified. Contradictory evidences have shown a potential negative predictive role of basal lymphopenia (BL). We investigated this topic in a retrospective cohort of mNSCLC pts. **Method:** Data about all consecutive mNSCLC pts treated with IO at Istituto Nazionale dei Tumori, Milan, Italy, between 04/2013 and 01/2018 were retrospectively collected. Pts were stratified according to lymphocyte (Lp) count at the first IO administration. BL was considered as a categorical variable, using the Institutional cutoff of 900 Lps/mL. Survival was estimated with Kaplan-Meier method. Log-rank test was used to compare curves. Multivariate analysis was performed with Cox proportional model. **Result:** One hundred fifty pts were analyzed, for a median follow-up of 28.6 mos. IO consisted in an anti-PD1 agent in 64.0% of cases, in an anti-PDL1 agent in 31.3% of cases, in a combination anti-PDL1+anti-CTLA4 in 4.7% of cases. First-line IO was administered in 23 cases, second-line IO in 66 cases, third- or more advanced-line IO in 61 cases. Median progression free survival (PFS) and overall survival (OS) of the global population were 3.2 and 11.2 months (mos), respectively. Thirty pts (20.0%) had any grade BL. These group had a significantly worse PFS (1.9 vs 3.0 mos, p.0010) and OS (4.5 vs 13.5 mos, p<.0001) than the control one. Also disease control rate (DCR) showed a significant difference in favor of non-BL pts (58.3% vs 30.0%, p.0074); response rate had a similar trend (25.0% vs 10.0%), without reaching significance (p.0881). The impact of BL on outcome remained significant after correction for the effects of performance status (p. 0045), which was the only other variable influencing OS. No factors other than BL had an influence on PFS at univariate analyses. **Conclusion:** BL had a detrimental impact on DCR, PFS and OS in our population. Given the limitations of this retrospective analysis, such results deserves confirmation in larger cases series. However, if BL was confirmed as a negative predictive factor for response to IO, it may become part of a multivariable tool to indentify the best treatment option for each pt with mNSCLC.

Keywords: metastatic non small cell lung cancer, Lymphocyte count, Immunotherapy

P1.01 ADVANCED NSCLC
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P1.01-23 HIGH PD-L1 EXPRESSION IS LESS COMMON THAN EXPECTED AMONG ADVANCED NSCLC IN BRAZIL. ARE WE MISSING THE TARGET?

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Background: Immune checkpoint inhibitors improved outcomes of patients with advanced non-small cell carcinoma (NSCLC). In clinical trials 30% of patients had programmed death receptor ligand-1 (PD-L1) expression above 50% and this frequency may vary through different regions of the world. We aim to describe the real world dada on prevalence of PD-L1 expression, EGFR mutation and ALK translocation in Brazil. **Method:** Immunohistochemistry (IHC) for PD-L1, antibody 22C3 PharmDx Dako, was performed in 5 laboratories in Brazil from Aug/2017 through Apr/2018 in cases of advanced NSCLC considered for treatment with immunotherapy. Mutations in EGFR (exons 18 to 21) by Cobas®(Roche), NGS, or other non-specified tests and ALK by IHC (antibodies 5A4 or D5F3) or FISH (Vysis System) were performed in non-squamous cases. All analyses were with SAS (version 9.4). P-values <0.05 were deemed to be statistically significant. **Result:** PD-L1 expression was assessed in 1382 samples of advanced NSCLC. The median age was 67 years, and 55.6% were male. 56.6% had adenocarcinoma, 18.0%, squamous, 20.7%, non-specified NSCLC, 2.5%, other histologies, 1.9%, missing. Of the 1380 cases, 17.4% presented PD-L1 expression ≥50%, 25.4%, 1-49%, and 57.1% <1%. The histological subtype showed association with the expression of PD-L1 (p=0,0431). In adenocarcinoma, 60.7% had no PD-L1 expression, 23.1%, had 1-49%, and 16.1%, ≥50%, while in squamous, 47.3% had no PD-L1 expression, 30.5% had 1-49%, and 22.0%, ≥50%. Among 885 samples with EGFR data, 10.9% were mutated. Both sex and histology showed association with EGFR mutation (p=0.0410 and p<0.0001). Among the men, 9.7% were mutated, while 13,4% of women were mutated. 16.4% of adenocarcinoma and 3.1% of squamous had EGFR mutation. In 855 samples with ALK data, 3.5% were rearranged. ALK rearrangement was associated with sex and age (p=0.0388 and p=0.0088) and was 2.2% in men and 4.8% in women. The group with age <50 had a higher prevalence of ALK rearrangement (8.6%). Among 735 patients without EGFR mutations or ALK rearrangements, 16.8% had PD-L1 ≥50% and 24.0% had 1-49%. **Conclusion:** Our results indicate a lower overall prevalence of PD-L1 expression in advanced NSCLC in Brazil as compared with clinical trial data. Among other potential factors, inadequate sample handling, pre-analytical issues, or epidemiology of the biomarker may impact PD-L1 expression. Prevalence of EGFR mutations and ALK translocations was within the range of prior publications in the country. Further regional and institutional analysis will be presented to better characterize the variations in prevalence of these biomarkers outside clinical trials.

Keywords: lung cancer, PD-L1, immunotherapy

P1.01-24 CLINICAL EFFICACY OF IMMUNOTHERAPY IN METASTATIC NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH PRIOR RADIOTHERAPY

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Background: Pivotal clinical trials (KEYNOTE-001) have demonstrated improved survival in non-small cell lung cancer (NSCLC) patients treated with both radiotherapy (RT) and immunotherapy (IO). The purpose of this study was to document response rates and survival in patients receiving both RT and IO in routine clinical practice. **Method:** All metastatic NSCLC patients treated with Nivolumab or Pembrolizumab between 11/2015 and 10/2017 in one Canadian province were identified. Demographic, tumor, treatment, toxicity, and response data were collected. Fisher's Exact Test and Chi Squared Test were used to assess the relationship between treatment characteristics and outcome. Log Rank Test and Cox Regression were used to assess overall survival (OS) and progression free survival (PFS). **Result:** 271 patients treated with IO were identified of which 202 were treated with previous RT (75%) including 153 treated with chest radiotherapy. Median follow up from initiation of IO was 30.3 (0.3-139.9) weeks. At time of last follow up, 56% of patients had died. There were no statistically significant differences in physician assessed response rates in patients treated with prior radiotherapy (52 vs 58%, p=0.41) or prior chest radiotherapy (52% vs 55%, p=0.71). Median PFS was 11 weeks in patients who received RT and 13.9 weeks in patients who did not (p=0.73). Median OS was 41.3 weeks in the radiotherapy cohort versus 42.9 weeks (p=0.50). On univariate analysis, ECOG (p<0.001) and CCI (p<0.001) were associated with OS while prior chest radiotherapy, prior curative radiotherapy, brain metastases, type of IO, squamous histology, smoking status and age did not. **Conclusion:** There were no statistically significant differences in response rates, PFS or OS in patients receiving IO for mNSCLC treated with or without prior RT.

Keywords: metastatic non small cell lung cancer, Immunotherapy, Radiotherapy

P1.01-25 CARBOPLATIN AND PEMETREXED PLUS BEVACIZUMAB AFTER FAILURE OF FIRST-LINE EGFR-TKI THERAPY FOR NSCLC HARBORING EGFR MUTATION (CJLSG 0908)

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Background: Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is a standard treatment for untreated, advanced non-small cell lung cancer (NSCLC) harboring an activating *EGFR* mutation. Many patients who had disease progression after EGFR-TKI are treated with chemotherapy including a platinum agent, but optimal regimen has not been established. This study was designed to evaluate the efficacy and safety of combination therapy with pemetrexed, carboplatin and bevacizumab after the failure of EGFR-TKI treatment. **Method:** This study was a multicenter, phase II trial. Patients who experienced disease progression after first-line EGFR-TKI treatment for stage IIIB/IV or recurrent non-squamous NSCLC patients with an activating *EGFR* mutation (exon 19 deletions or exon 21 L858R point mutation) were eligible. Patients were treated with pemetrexed (500 mg/m^2), carboplatin (AUC=5), and bevacizumab (15 mg/kg) intravenously on day 1 every 3 weeks. After 4 cycles, patients who had achieved disease control received a maintenance therapy with pemetrexed and bevacizumab every 3 weeks until disease progression or unacceptable toxicity. Response was evaluated by CT scans after every 2 cycles, and toxicity was assessed. Primary endpoint was response rate. Secondary endpoint included disease control rate, progression-free survival, overall survival, and safety. **Result:** Twenty-seven patients were enrolled between March 2011 and April 2015. The median age was 64 years (range: 44-74), and 21 patients were female. All the patients had adenocarcinoma, 17 patients had exon 19 deletion, and 10 had L858R mutation. 9 patients were ex-smoker, and 18 patients were nonsmoker. There were 11 partial responses with an response rate of 41% (95%CI, 22 – 61%). Stable Disease was observed in 16 patients and disease control rate was 100% (95%CI, 87 - 100%). 22 patients (81%) subsequently underwent maintenance therapy. The median progression-free survival was 7.8 months. The median overall survival from enrollment and from the start of first-line EGFR-TKI were 21.6 months and 36.9 months, respectively. Major adverse event was grade 3 and 4 neutropenia in 5 patients (19%), grade 3 hypertension in 3 patients (11%). Grade 3 gastrointestinal hemorrhage occurred in one patient, and grade 1 epistaxis occurred in 6 patients. No treatment-related death was observed. **Conclusion:** The present study reveals that carboplatin and pemetrexed plus bevacizumab therapy is effective and feasible for the patients with NSCLC after the failure of first-line EGFR-TKI.

Keywords: EGFR-TKI, phase II trial, chemotherapy

P1.01-26 SINGLE-CENTRE EXPERIENCE OF CLINICAL OUTCOMES FOR ADVANCED LUNG CANCER PATIENTS IN PHASE I CLINICAL TRIALS.

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Background: Response rates for patients enrolled in early phase clinical trials have historically been reported as 5-10%. An unprecedented number of novel therapeutic options and emerging therapies in lung cancer (LC) have resulted in greater emphasis on early phase clinical trials and molecular stratification. We aimed to evaluate outcomes for patients with LC treated since 2015 with novel agents or combination strategies within an expanding early phase clinical trials unit at The Christie Hospital, Manchester, UK. **Method:** A database of patients consented to phase I clinical trials was interrogated for LC patients recruited over a three-year period. Clinical characteristics including histological sub-type, line of therapy, molecular phenotype, smoking status and ECOG performance status (PS) were collected for each patient. Patient records were reviewed for clinical trial allocation, treatment response, progression-free survival (PFS), and overall survival (OS). **Result:** Over a three-year period to March 2018, 153 lung cancer patients were consented to Phase I clinical trials of Investigational Medicinal Products, of whom 113 (74%) commenced treatment. The median age of patients treated was 64y (range 28-84) with a male predominance (54%). All patients had a PS of 0-1 and 25% were non-smokers. Histological subtypes included non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) and mesothelioma. The overall response rate (RR) by RECIST criteria was 27% across all patients, with a disease control rate of 73%. Median PFS was 6 months, and median OS was 11 months in the entire cohort. Compared with patients with NSCLC, patients with SCLC had worse PFS (7mo vs 3mo, p=0.001) and RR (35% vs 0%). The 28 trials recruiting LC patients in the unit during this period involved therapies targeting EGFR and ROS1, PI3K-mTOR-AKT and RAS-RAF-MEK signalling, DNA repair genes, cell-surface protein overexpression and genes implicated in immune signalling. Novel agents included small molecule inhibitors, monoclonal antibodies, and antibody-drug conjugates, in addition to targeted agents combined with chemotherapy or immune checkpoint inhibitor combinations. Patients had between 0-5 prior lines of therapy with no difference in PFS, OS or RR regardless of prior treatment lines. **Conclusion:** Our data demonstrate clear benefit for lung cancer patient participation in early phase clinical trials. Novel therapeutic agents and evolution of early phase clinical trial design have resulted in promising options for patients with NSCLC, with RR>30% within our unit, regardless of prior treatment status. However, outcomes for SCLC patients lag behind and new therapeutic options are urgently needed.

Keywords: Phase I clinical trials, novel agents, NSCLC

P1.01 ADVANCED NSCLC
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P1.01-27 INFLUENCE OF EGFR-TKIS TREATMENT LINES AND PFS ON THE EMERGENCE OF T790M MUTATION

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Background: For sensitizing EGFR mutation positive lung cancer patients, EGFR-TKIs can be used as the first-line or second-line (after chemotherapy) therapy according to NCCN guideline. However, whether different lines of EGFR-TKIs therapy or different PFS would affect the emergence of T790M, the leading cause of resistance to first and second generation of EGFR-TKIs was unknown. **Method:** We retrospectively analyzed 142 advance NSCLC patients with 93 patients received 1st-line EGFR-TKIs, and 49 patients received 2nd-line EGFR-TKIs after chemotherapy. EGFR sensitizing mutation and T790M mutation was detected simultaneously by hybridization capture-based NGS panel sequencing with tumor biopsy , ctDNA or pleural effusion samples. **Result:** For the patients received 1st-line EGFR-TKIs, 47 carried L858R mutation and 46 carried EX19del mutation; while patients received 2nd-line EGFR-TKIs, 24 carried L858R mutation and 25 carried EX19del mutation. When those patients progressed on TKIs, T790M emerged in 25 of the 47 (53.19%) L858R carriers, and 23 of the 46 (50.00%) EX19del carriers with 1st-line EGFR-TKIs (p=0.76). However, only 6 of the 24 (25.00%) L858R carriers yet 16 of the 25 (64.00%) EX19del carriers with 2nd-line EGFR-TKIs had T790M detected (p=0.006). The incidence of T790M was significant lower in L858R carrier treated with 2nd-line compared with 1st-line EGFR-TKIs (25.00% vs 53.19%, p=0.023), however, there was no difference for EX19del carrier (50.00% vs 64.00%, p=0.26). To further analyzed whether different PFS affected the appearance of T790M, we divided patients into 3 groups as PFS≥13 months (n=48), PFS≤8 months (n=60) and the between (n=34). The incidence of T790M was significantly lower in the PFS≤8 months group compared with the PFS≥13 months (31.67% vs 62.5%, p=0.001). The difference was also significant if only counting the L858R carriers (18.52% vs 59.26%, p=0.002), but not significant in the EX19del carriers (42.42% vs 66.67%, p=0.082). **Conclusion:** 1st-line or 2nd-line EGFR-TKIs generally did not significantly alter the emergence of T790M. But for the L858R mutation carriers, the incidence of T790M is significantly decreased if treated as a 2nd-line EGFR-TKIs therapy. In addition, patients with longer PFS were associated with higher incidence of T790M mutation.

Keywords: T790M, EGFR-TKIs therapy, next generation sequencing (NGS)

P1.01 ADVANCED NSCLC
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P1.01-28 IMPACT OF AFATINIB DOSING ON SAFETY AND EFFICACY REAL-WORLD IN PATIENTS WITH EGFR MUTATION-POSITIVE ADVANCED NSCLC

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Background: Tolerability-guided dose adjustment of afatinib reduced incidence and severity of adverse drug reactions (ADRs) without affecting efficacy in the LUX-Lung (LL) studies in patients with *EGFR* mutation-positive (*EGFR*m+) NSCLC. We evaluated the impact of modifying the recommended starting dose of afatinib (40mg) on efficacy and safety in a real-world setting. **Method:** This non-interventional, observational, multi-country/site study used medical records of TKI-naïve patients with *EGFR*m+ (Del19/L858R) NSCLC treated with first-line afatinib. Primary outcomes were % patients with ADRs by severity, time on treatment (TT), and time to progression (TTP), relative to LL3. Secondary outcomes were % of patients with/reasons for modified starting dose. **Result:** 228 patients from 13 countries were included. Baseline characteristics were generally similar to LL3, but with more Del19 patients (78% vs 49%) and fewer Asian patients (44% vs 72%); 12% had ECOG PS 2–3. 31% of patients received an afatinib starting dose of <40 mg; 20% of patients starting with <40 mg increased their dose during the study. 67% of 40 mg starters underwent dose reductions, with 86% of those occurring in the first 6 months. Dose reductions were more frequent in females, Eastern Asian patients, and those with lower body weight. The main reason for dose modification was ADRs. In <40 mg starters, overall ADR incidence was similar to that in ≥40 mg starters, with fewer G3 (17% vs 25%) and no G4 ADRs. There were no new safety signals, and fewer ≥G3 ADRs and serious adverse events (SAEs) than in LL3 (28% vs 49% and 5% vs 14%, respectively). >60% of patients received medications to treat diarrhea and manage skin AEs. Median TT and TTP were 18.7 months and 20.8 months, respectively, and were not impacted by reduced starting dose or dose modification (19.4/17.7/19.5 and 25.9/20.0/29.0 months for patients who started on ≤30 mg/reduced to <40 mg/remained on ≥40 mg, respectively). The efficacy of afatinib was demonstrated across all patient subgroups analysed (ECOG PS 0/1 vs 2/3, age <75 yrs vs ≥75 yrs, EGFR mutational status); TT and TTP were significantly longer in patients with ECOG PS0/1 versus PS2/3. **Conclusion:** As in pivotal trials, dose adjustments with afatinib in real-world practice reduced the frequency and intensity of ADRs without impacting efficacy. RealGido demonstrated long TT/TTP regardless of afatinib dose adjustment or reduced starting dose, and an acceptable safety profile. The results highlight the benefit of tailoring afatinib dose based on individual patient characteristics and ADRs to optimize outcomes.

Keywords: afatinib, NSCLC

P1.01 ADVANCED NSCLC
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P1.01-29 CRIZOTINIB IN ADVANCED LUNG ADENOCARCINOMA PATIENTS WITH ALK OR ROS-1 REARRANGEMENT: IS IT THE SAME?

B. Han, B. Zhang, J. Xu, Y. Zhang, X. Zhang, T. Chu, S. Wang, R. Qiao, J. Qian, J. Lu, L. Zhang

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Background: Crizotinib is an orally taken tyrosine kinase inhibitor (TKI) targeting both ALK and ROS1 rearrangement, which have defined two different molecular subgroup patients. The aim of the study was to compare the therapeutic efficacy of crizotinib in advanced lung adenocarcinoma patients diagnosed with ALK or ROS1 mutation. **Method:** Patients diagnosed with ALK (Group A) or ROS1 (Group B) mutation were identified from our standardized registration system. The effectiveness of crizotinib in eligible patients was retrospectively analyzed. **Result:** A total of 5348 and 4695 patients were screened and 393 (7.3%, 95% CI, 6.6%-8.0%) and 105 (2.2%, 95% CI, 1.8%-2.7%) positive patients were identified among the two groups, respectively. There were 141 and 32 eligible patients were included for survival analysis. The ORR is 53.0% (95% CI, 43.0%-63.0%) in group A, without statistical significance compared with group B (71%, 95% CI, 51.2%-90.4%, P=0.11). Similar result was also observed in terms of DCR (86%, [95% CI, 79.1%-92.9%] vs. 92.0%, [95%, CI, 80.0%-100.0%], P=0.74). The median PFS in group A was 12.4 months (95% CI, 10.2 -14.7 months), which was statistically worse than patients in group B (18.2 months, 95% CI, 6.3 -29.0 months, P=0.02). The OS was too immature to analyze. **Conclusion:** Patients harboring ROS1 rearrangement derived better prognosis compared with these who had ALK rearrangement when treated with crizotinib.

Keywords: ALK, ros1, crizotinib

P1.01 ADVANCED NSCLC
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P1.01-30 CRIZOTINIB IN ADVANCED NON-ADENOCARCINOMA, NSCLC (NA-NSCLC) PATIENTS WITH ALK REARRANGEMENT: A RETROSPECTIVE STUDY AND LITERATURE REVIEW

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Background: The aim of the study was to investigate the prevalence of anaplastic lymphoma kinase (ALK) rearrangement in non-adenocarcinoma, non-small cell lung cancer (NA-NSCLC) patients and

therapeutic efficacy of crizotinib in these patients. **Method:** From January 2013 to January 2017, NA-NSCLC patients who were diagnosed with ALK rearrangement were screened. The effectiveness of crizotinib in positive patients was retrospectively analyzed. A literature review was performed and eligible cases were analyzed combined with our data. **Result:** A total of 1212 NA-NSCLC patients were screened during the period with 25 positive patients identified (2.1%, 95% CI, 1.3%-2.9%). A statistically higher percentage of female patients (40.0% vs. 10.4%, P< 0.01), non-smoker (72.0% vs.43.2%, P< 0.01), containing adenocarcinoma component (36.0% vs. 7.1%, P< 0.01) and advanced stage (68.0% vs. 45.6%, P=0.03) were observed in ALK positive group. The median PFS of the 9 eligible patients in our institution was 7.0 months (95% CI, 0-15.6 months). We combined our data with the sporadic cases from 10 previous case reports (total n=19) and found that the median PFS was 7.0 months (95% CI, 5.6-8.4 months). **Conclusion:** Our study suggested the opportunity to test ALK rearrangement in NA-NSCLC patients, especially in female, non-smoker and patients containing adenocarcinoma component. Crizotinib provides an option for the treatment of NA-NSCLC patients who diagnosed with ALK rearrangement.

Keywords: Anaplastic lymphoma kinase, crizotinib, non-adenocarcinoma

P1.01 ADVANCED NSCLC
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P1.01-31 WEEKLY REGIMEN OF PAXUS-PM, A NOVEL CREMOPHOR-FREE, WITH CARBOPLATIN IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER IN VIETNAM

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Background: The rationale for developing an alternative paclitaxel formulation concerns Cremophor EL-related side effects, and a novel paclitaxel delivery system might augment its therapeutic efficacy. PAXUS PM (or also known as GENEXOL-PM) is a novel polymeric micelle formulated paclitaxel free of Cremophor. The polymeric micelle formulation is composed of hundreds of low molecular weight, non-toxic, and biodegradable amphiphilic diblock copolymers which include monomethoxy poly (ethylene glycol)-*block*-poly(D,L-lactide). PAXUS-PM is used to breast cancer, non-small cell lung cancer, and ovarian cancer as 3 week regimen. In other words the data of weekly therapy in NSCLC is not published. **Method:** This prospective, single-arm, clinical study was designed to evaluate the efficacy and safety of the combination of Genexol-PM and carboplatin for the treatment of advanced non-small-cell lung cancer (NSCLC). Subjects with nonsmall cell lung cancer who met the inclusion/exclusion criteria underwent the tests required per treatment plans and then received Genexol-PM 100mg/m2 and carboplatin 5 AUC(or 6AUC) on day 1, 8, 15 of every 3-week cycle for a maximum of six cycles as first-line therapy. The study evaluated the objective response rate as primary objective, and other variables including overall survival (OS), progression free survival (PFS), time to tumor progression (TTP), duration of overall response and adverse events. **Result:** Thirty patients were enrolled and analyzed intermittently in this study. The median number of administered cycles was 6. Overall response rate was 76.67% with 2 complete responses (CR) and 21 partial responses (PR). There weren't any patients with progressive disease. The Hematological toxicities were manageable and the major hematological toxic effects were grade 1/2 neutropenia(n=12, 40.0%), grade1 thrombocytopenia(n=1, 3.3%) and grade 1/2 anemia(n=8, 26.7%). There were no grade3/4 adverse events, such as neutropenia and hypersensitivity reactions. The major non-hematologic toxic effects included grade 2 nausea, vomiting and alopecia in all 30 patients. **Conclusion:** Genexol-PM plus carboplatin combination chemotherapy showed excellent antitumor activity. In this study, there was no significant risk of hematologic and non-hematologic adverse events of grade 3/4. Among the paclitaxel formulations developed to allow high doses, there were limitations as an intermediate result, but good efficacy and safety results were obtained in lung cancer. Therefore, the use of CrEL-free, polymeric micelle formulation of paclitaxel allowed administration of higher doses of paclitaxel and showed safe and efficacious results.

P1.01 ADVANCED NSCLC
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P1.01-32 A MULTICENTER, OPEN-LABEL, PHASE II TRIAL OF S-1 PLUS CARBOPLATIN IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS WITH INTERSTITIAL LUNG DISEASE

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Background: The clinical benefit of chemotherapy and the appropriate regimen for non-small-cell lung cancer (NSCLC) patients with interstitial lung disease (ILD) remain unclear. We conducted a phase II study to elucidate the efficacy of S-1 in combination with carboplatin (CBDCA) in NSCLC patients with ILD. **Method:** A total of 33 advanced or recurrent NSCLC patients with ILD were prospectively enrolled in this multicenter, open-label, phase II study (UMIN000011046). Every 4 weeks, CBDCA at a dose of AUC 5 on day 1 and S-1 at a dose of 80 mg/m^2 daily for 14 days were administered. The primary endpoint was the investigator-assessed objective response rate. **Result:** The median age at initiating chemotherapy was 70. Sixteen patients (48.5%) had squamous cell carcinoma histology. With respect to the types of ILD, the usual interstitial pneumonia pattern was dominant (66.7%). The median number of cycles administered was 3, and the overall response rate and disease control rate were 33.3% and 78.8%, respectively. The median progression-free survival, the median survival time and the 1-year survival rate were 4.8 months, 12.8 months and 51.4%, respectively. Acute exacerbation of ILD caused by chemotherapy was noted in 2 patients (6.1%). **Conclusion:** This is the first and largest prospective study designed to evaluate the efficacy of a specific chemotherapeutic regimen as the primary endpoint in patients with advanced NSCLC with ILD. The combination of S-1 with CBDCA may be a treatment option for advanced NSCLC patients with ILD.

Keywords: non-small-cell lung cancer, interstitial lung disease, acute exacerbation

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-33 RANDOMIZED PHASE 2 STUDY COMPARING CBDCA+PTX+BEV AND CDDP+PEM+BEV IN TREATMENT-NAÏVE ADVANCED NON-SQ NSCLC (CLEAR STUDY)

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Background: Bevacizumab (BEV) combined with platinum-based chemotherapy is a standard treatment for advanced non-squamous non-small-cell lung cancer (non-Sq NSCLC). Cisplatin (CDDP) + pemetrexed (PEM) is suggested as the most promising chemotherapy regimen combined with BEV. However, no study has been conducted to evaluate the efficacy and safety of CDDP+PEM+BEV compared with carboplatin (CBDCA) + paclitaxel (PTX) + BEV for advanced non-Sq NSCLC. **Method:** Treatment-naïve patients with advanced or recurrent EGFR/ALK-negative

non-Sq NSCLC from 55 sites across Japan were randomly assigned in a 2:1 ratio to either CDDP+PEM+BEV (4 cycles of CDDP [75 mg/m^2] + PEM [500 mg/m^2] + BEV [15 mg/kg] q3wk, followed by maintenance PEM + BEV q3wk until progression) or CBDCA+PTX+BEV (4 cycles of CBDCA [AUC 6] + PTX [200 mg/m^2] + BEV q3wk, followed by maintenance BEV q3wk until progression). The primary endpoint was progression-free survival (PFS) by central review. The secondary endpoints were PFS by investigators, overall survival (OS), overall response rate (ORR) and safety profile. The target numbers of patients and events were determined to be 210 and 170, respectively, to observe a point estimate of HR for PFS (CDDP+PEM+BEV/CBDCA+PTX+BEV) <0.83 with a high probability (80%) when the true HR was 0.72. **Result:** Between May 2014 and May 2016, 199 patients were randomly assigned to receive CDDP+PEM+BEV (N=132) or CBDCA+PTX+BEV (N=67). The median follow-up duration was 20.6 months. PFS events occurred in 171 patients. The HR for PFS by central review (CDDP+PEM+BEV/CBDCA+PTX+BEV) was 0.825 (95% CI 0.600-1.134, median PFS, 7.6 vs 7.0 months). The median PFS by investigators was longer with CDDP+PEM+BEV than with CBDCA+PTX+BEV (HR 0.634, 95% CI 0.464-0.867, median PFS, 7.4 vs 6.8 months). The median OS was 24.5 months for CDDP+PEM+BEV and 23.6 months for CBDCA+PTX+BEV (HR 0.955, 95% CI 0.620-1.470). The ORR was 57% for CDDP+PEM+BEV and 55% for CBDCA+PTX+BEV. The most common ≥G3 adverse events in both arms (CDDP+PEM+BEV/CBDCA+PTX+BEV) were neutropenia (24%/64%), hyponatraemia (11%/9%) and hypertension (30%/23%). **Conclusion:** CDDP+PEM is the most effective chemotherapy regimen combined with BEV for advanced non-Sq NSCLC.

Keywords: Non-small-cell lung cancer, chemotherapy, bevacizumab

P1.01 ADVANCED NSCLC
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P1.01-34 DOCETAXEL PLUS RAMUCIRUMAB WITH PROPHYLACTIC PEG-G-CSF SUPPORT FOR CHEMO-NAÏVE ELDERLY NSCLC PATIENTS: A PHASE II STUDY (WJOG9416L)

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Background: Docetaxel monotherapy is the standard of care for chemo-naïve Japanese elderly patients with advanced non-small cell lung cancer (NSCLC), according to our results of phase III trial comparing docetaxel and vinorelbine monotherapies (WJTOG9904). In a pivotal phase III study (REVEL), docetaxel plus ramucirumab demonstrated superior response rate (RR) and progression-free survival (PFS) over docetaxel monotherapy in second-line setting for advanced NSCLC. These differences in RR and PFS were translated into overall survival (OS) benefit. This evidence prompted us to investigate docetaxel plus ramucirumab for chemo-naïve elderly patients. However, in a similarly designed Japanese randomized phase II trial (JVCG trial), febrile neutropenia (FN) was observed in 34.2% of docetaxel plus ramucirumab arm. This high incidence of FN is a clinical concern when using docetaxel plus ramucirumab for elderly patients. The ASCO practice guideline recommends primary prophylactic granulocyte-colony stimulating factor (G-CSF) when the risk of FN is 20% or higher. PEGylated-G-CSF (pegfilgrastim) administered once a cycle demonstrated reduction of FN incidence in many types of cancers. Based on the above background, we considered that primary prophylactic PEG-G-CSF would be beneficial for elderly NSCLC patients who received docetaxel plus ramucirumab. **Method:** This is a prospective multicenter, single-arm, phase II study conducted by West Japan Oncology Group (WJOG). Main inclusion criteria includes: chemo-naïve; aged ≥75; histologically or cytologically confirmed NSCLC; ECOG PS 0/1; adequate organ functions; with measurable disease; without contraindication of ramucirumab; written informed consent; and estimated life expectancy of at least 3 months. Intravenous docetaxel (60 mg/m^2, day 1) plus ramucirumab (10 mg/kg, day 1) with subcutaneous PEG-G-CSF (3.6 mg, day 2) every 3 weeks is administered until progression. Continuous docetaxel or ramucirumab monotherapy is permitted when intolerable toxicities occur but clinical benefit is obtained by each drug. The primary endpoint is objective response rate (ORR). Secondary endpoints are PFS, OS, disease control rate, and safety. We assumed that the threshold and expected ORR were 20% and 35%, respectively. Based on this, the number of patients was calculated to be 59 to provide a power of 80% with probability of one-sided type I error being 0.05. Taking ineligible patients into account, the sample size was set at 65. When the study results are promising, we plan to conduct a phase III trial to compare docetaxel plus ramucirumab with PEG-G-CSF support vs. docetaxel monotherapy for chemo-naïve elderly NSCLC patients. Clinical trial information: UMIN000030598. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: docetaxel, ramucirumab, PEG-G-CSF

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-35 TUMOR VOLUME ANALYSIS IN ALK-REARRANGED NSCLC TREATED WITH CRIZOTINIB: IDENTIFYING AN EARLY MARKER FOR CLINICAL OUTCOME

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Background: Targeted inhibition of anaplastic lymphoma kinase (ALK) has been widely used for the treatment of advanced non-small-cell lung cancer (NSCLC) with ALK-rearrangement. We performed tumor volume analysis of ALK-rearranged advanced NSCLC treated with crizotinib to identify an early imaging marker that can predict clinical outcome. **Method:** Forty-two patients with advanced NSCLC harboring ALK-rearrangement (15 men, 27 women; median age: 55.7 years) treated with crizotinib as their first ALK-directed therapy at Dana-Farber Cancer Institute between November 2008 and June 2016. All patients had a follow-up chest CT scan at 8 +/- 3 weeks of therapy and had a dominant measurable lesion in the lung (≥1 cm) on baseline CT. Tumor volume of the dominant lung lesion was measured on baseline CT and follow-up CT at 8 +/- 3 weeks of therapy, using the previously validated technique on the volume analysis software (Vitrea ; Vital Images, Minnetonka, MN). The relationships between the 8-week volume change (%) and overall survival (OS) measured from the 8-week scan date were studied. **Result:** The 8-week tumor volume change ranged from -99.3% to 117.5% (median: -57.7%). Using the 25 percentile of the 8-week volume change of -74%, 11 patients with >74% volume decrease at 8 weeks had a significantly longer OS compared to 31 patients with ≤74% decrease (Median OS: 92.0 months vs. 22.8 months, log-rank p=0.0048). In multivariable analyses using Cox proportional hazards models, the 8-week volume decrease of >74% remained as a significant factor associated with prolonged OS (HR=0.14, 95%CI: 0.03-0.59; Cox p=0.008) after adjusting for other significant variables including tumor stage at presentation (stage IV vs. others, HR=5.6, 95%CI: 1.29-24.3; p=0.02). Of the 31 patients with ≤74% decrease on the 8-week scan, best overall response by RECIST was partial response (PR) in 21 (68%), stable disease in 9 (29%), and progressive disease (PD) in one (3%). None of the 42 patients experienced RECIST-PD prior to the 8-week scan. **Conclusion:** The 8-week tumor volume decrease of >74% on CT is significantly associated with longer OS in patients with ALK-rearranged NSCLC treated with crizotinib. The 8-week tumor volume analysis helps to identify patients who may benefit from alternative therapy in the early course of crizotinib therapy.

Keywords: Non-small-cell lung cancer, Tumor volume, anaplastic lymphoma kinase inhibitor

P1.01-36 THORACIC SURGERY IN NON-SMALL CELL LUNG CANCER WITH EPIDERMAL GROWTH FACTOR RECEPTOR MUTANT AFTER TYROSINE KINASE INHIBITOR THERAPY

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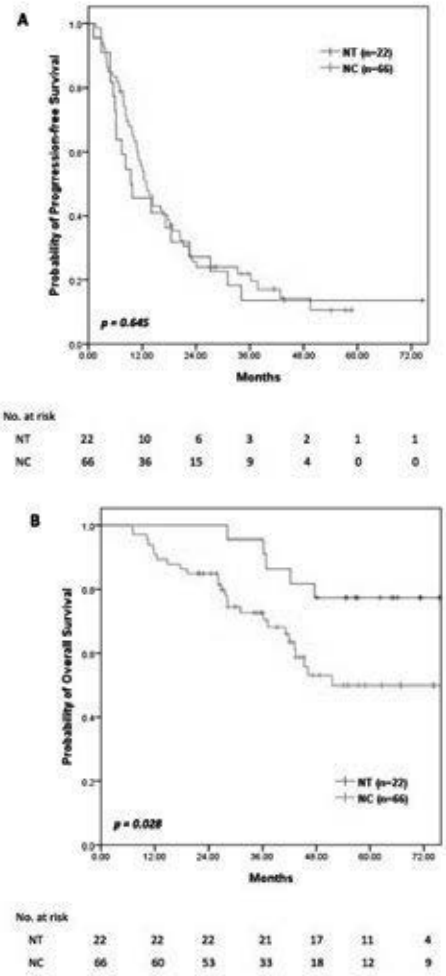
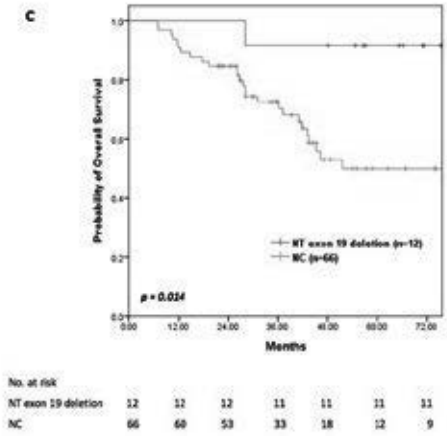
Background: Advanced stage non-small cell lung cancer (NSCLC) patients harboring epidermal growth factor (EGFR) mutation have benefit form treatment with tyrosine kinase inhibitors (TKI). However, the role of multidisciplinary management including neoadjuvant TKI therapy and thoracic surgery is uncertain in advanced stage NSCLC. This retrospective study assessed the impact of the multidisciplinary management in advanced stage EGFR mutation positive NSCLC patients. **Method:** Advanced stage NSCLC patients were retrospectively identified at Department of Surgery, National Taiwan University Hospital from 2006 to 2013 and prospectively observed. Patients with stage IIIA N2 (unresectable), IIIB, and IV EGFR mutation positive NSCLC treated with neoadjuvant TKI without tumor progression followed by thoracic surgery (NT group) were evaluated. Patients with stage IIIA N2 NSCLC treated with cisplatin-based neoadjuvant chemotherapy without tumor progression followed by thoracic surgery (NC group) were also evaluated. Progression-free survival (PFS) and overall survival (OS) were analyzed. **Result:** There were total 88 NSCLC patients in this study. There were 41 men and 47 women. The median age was 58 years. 66 patients were the NC group and 22 patients were the NT group. 60 patients and 20 patients were adenocarcinoma in the NC group and the NT group, respectively. Other patients were squamous cell carcinoma. In the NT group, EGFR status was identified before receiving neoadjuvant TKI therapy. Twelve patients (54.5%) were exon 19 deletion and ten patients were exon 21 L858R mutation. PFS was not significantly different between NC group and NT group (p = 0.645). OS was significantly longer in the NT group than in the NC group (p = 0.028). Exon 19 deletion of the NT group patients had significantly longer OS than the NC group (p = 0.014).





Conclusion: The multidisciplinary management including neoadjuvant TKI therapy and thoracic surgery may possibly have benefit in selected advanced stage NSCLC patients haboring exon 19 deletion.

Keywords: Tyrosine kinase inhibitors, Thoracic Surgery, non-small cell lung cancer

P1.01-37 BPI-9016M, A NOVEL C-MET INHIBITOR, IN PRETREATED ADVANCED SOLID TUMOR: RESULTS FROM A FIRST-IN-HUMAN, PHASE 1, DOSE-ESCALATION STUDY

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Background: BPI-9016M (Betta Pharmaceuticals Co, Ltd, Hangzhou, China) is a potent targeted therapy that inhibits MET and Axl. This first-in-human study is to assess the safety, tolerability, and pharmacokinetics (PK) of BPI-9016M in patients with advanced solid tumor, and to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for the phase Ib/II study. **Method:** Eligible patients were enrolled into sequential dose-escalating cohorts from 100 mg to 1000 mg given orally once per day continually following the conventional 3+3 design. The primary endpoint was safety and tolerability. MTD was defined as the highest dose level resulting in <1 of 3 dose limiting toxicities (DLTs). Blood levels of BPI-9016M were evaluated after single and multiple administration (NCT02478866). **Result:** Twenty patients were enrolled and treated in 6 of 7 predefined dose cohorts (100 mg n=4, 200 mg n=3, 300 mg n=3, 450 mg n=4, 600 mg n=3, 800 mg n=3), dose escalation stopped at 800 mg due to saturation. All had stage IV non-small cell lung cancer (NSCLC) progressed on previous systemic therapy (including previous EGFR TKI in 16 patients). BPI-9016M was well-tolerated in all dose cohorts without DLT. The incidence of overall and grade 3/4 TRAEs was 85% and 45%, respectively. Common TRAEs included elevated ALT (45%), constipation (30%), elevated bilirubin (25%), and oral paresthesia (25%). Tumor response was seen in 1 patients in the 800 mg dose cohort. Systemic exposure to BPI-9016M (maximum plasma concentration and AUC) increased with increasing dose. Mean time to maximum plasma concentration and half-life were 2 to 5.33 hours and 8.09 to 22.3 hours, respectively. Two metabolites (M1, M2-2) were detected. **Conclusion:** BPI-9016M was well tolerated in patients with advanced solid tumor. A phase Ib study is ongoing to investigate the safety and activity of BPI-9016M in patients with c-Met-dysregulated advanced NSCLC (NCT02929290).

Keywords: First-in-human, c-Met, NSCLC

P1.01-38 A PHASE II WITH A LEAD-IN PHASE I STUDY TO EXAMINE SAFETY AND EFFICACY OF HYDROXYCHLOROQUINE AND GEFITINIB IN ADVANCED NSCLC

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Background: Tyrosine kinase inhibitors (TKIs) benefit advanced non-small cell lung cancer (NSCLC) patients that harbor epidermal growth factor receptor (EGFR) mutations, but resistance invariably develops. Preclinical work demonstrated re-sensitization to EGFR-TKIs in cells with acquired resistance, and increased sensitivity of EGFR-mutant cells to erlotinib and hydroxychloroquine (HCQ) combination. We examine the safety and efficacy of HCQ with gefitinib in an Asian cohort of NSCLC patients. **Method:** We enrolled stage IIIB/IV lung adenocarcinomas with sensitizing EGFR mutations. In the early phase of the study, non-smokers with unknown EGFR status were allowed. In the phase I lead-in study (Nov 2008-Jan 2010), maximum tolerable dose (MTD) of HCQ and gefitinib was ascertained via a 3+3 dose escalation schema. In the phase II single-arm study (March 2010-May 2016), all patients were treated with gefitinib 250mg om and MTD (600mg om) of HCQ, and stratified into TKI-naïve and TKI-treated cohorts. In the TKI-treated cohort, patients must have prior response to gefitinib for more than 12 weeks and developed resistance. Primary end point (PEP) in the TKI-naïve cohort was objective response rates (ORR) and progression-free survival (PFS). In the TKI-treated cohort, PEP was ORR, and to determine if combination treatment can re-sensitize acquired resistance to EGFR TKIs. **Result:** 75 patients were treated. EGFR mutations were identified in 77.3%. In the phase I cohort (n=13), MTD of HCQ was 600mg. HCQ-gefitinib combination was well tolerated. Common adverse events were rash and diarrhea, mainly from gefitinib. There was no dose-limiting toxicity. In TKI-naïve cohort (n=37) of the phase II study, ORR was 75.8% (95% CI 57.7-88.9). Median PFS was 9.4 months (95% CI 6.8-12.0). Four patients who were non-evaluable had early toxicities, including pneumonitis and hepatitis flare. In the TKI-treated cohort (n=25), 52% had received 2 or more lines of prior treatment. Disease control rate with TKI re-challenge was 50% (95% CI 21.9-70.9), ORR was 4.2% (95% CI 0.1-21.1). Median PFS was 2.4 months, and median overall survival was 9.9 months (95% CI 5.7-14.0). Three patients achieved a progression-free interval of more than 7 months after re-challenge (7.6; 11.2; 15.9 months). **Conclusion:** Combination of HCQ-gefitinib is safe. In the TKI-naïve cohort, combination treatment did not improve PFS over reported average of 10 months for 1st-generation EGFR TKIs. However, in the TKI-treated cohort, re-responses and disease control to 1st-generation EGFR TKIs were seen, suggesting either a re-treatment effect or disease stabilization with addition of HCQ in acquired EGFR resistance.

Keywords: non-small cell lung cancer, hydroxychloroquine, gefitinib

P1.01-39 COST-EFFECTIVENESS OF CRIZOTINIB VERSUS CHEMOTHERAPY AS FIRST-LINE TREATMENT OF ALK POSITIVE ADVANCED NSCLC -- A REAL WORLD STUDY

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Background: It was reported that crizotinib was a cost-effective alternative compared to pemetrexed plus platinum chemotherapy with the patient assistance program (PAP) in a model-based economic analysis using PROFILE 1014 trial data analysis. However, the cost-effectiveness of crizotinib in the real-world scenario remains unknown, which could be different from RCT results due to continued use of crizotinib beyond progression, anti-angiogenesis drugs combination in clinical practice, and influence from medical insurance (MI) policy change. The aim of study was to assess the cost-effectiveness of crizotinib vs platinum doublet chemotherapy as the first-line treatment for patients with ALK positive NSCLC in the real-world setting. **Method:** Data from 163 advanced ALK positive NSCLC patients were collected from West China Hospital, Sichuan University (Chengdu, China) between Jun 2010 and Oct 2016 with a median follow-up of 27.67 months. The median progression-free survival (m-PFS) as primary clinical outcome was analyzed by Kaplan–Meier method. Direct medical costs were collected from hospital information systems. Since the medical insurance(MI) changed during the study, two situations, including patient's entry period, and follow up period were assessed. Crizotinib, premetrexed, and angiogenesis drugs were not covered by MI in entry period. However, crizotinib and all chemotherapy drugs were MI covered during follow up period. PAP and MI reimbursement referred to local MI policy. Incremental cost-effectiveness ratio(ICER) from perspective of local healthcare systems was calculated with both costs and quality-adjusted life-years (QALYs), as well as the costs discounted at 3% annually. **Result:** Crizotinib improved PFS vs chemotherapy in ALK positive patients. (median PFS 19. 67 m vs. 5.47 m, P < 0.001). Moreover, crizotinib obtained ICER of $36,285.39 before the end of 2016, when crizotinib, pemetrexed and anti-angiogenesis drugs were not MI covered. This is more than Willingness to pay(WTP) threshold (3-times of GDP per capita in mainland China or Sichuan Province). However, ICER was $7,321.16 which is less than WTP when crizotinib and all chemotherapy drugs were covered by MI from the end of 2016. Sensitivity analysis demonstrated a 99.7% probability for crizotinib to be more cost-effective than chemotherapy, when crizotinib and all anti-cancer drugs were MI covered. In addition, one-way sensitivity analysis for reimbursement ratio of crizotinib indicated that cost-effective tendency for crizotinib increased as reimbursement ratio increased. **Conclusion:** Our real-world analysis suggests crizotinib could be an effective, and cost-effective first-line treatment for ALK positive advanced NSCLC compared to chemotherapy with the MI coverage currently in Chengdu, China.

Keywords: cost-effectiveness, ALK-positive, real-world

P1.01-40 RANDOMIZED PHASE II STUDY OF DOCETAXEL PLUS BEVACIZUMAB OR PEMETREXED PLUS BEVACIZUMAB FOR ELDERLY PTS WITH UNTREATED ADVANCED NSCLC: TORG1323

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Background: The addition of bevacizumab (B) to platinum doublets prolongs the survival for non-squamous NSCLC. The role of monotherapy with B is unclear for elderly non-squamous NSCLC pts. **Method:** Pts were pathologically diagnosed untreated elderly (≥75 years old) non-squamous NSCLC, who were stage IIIB, IV, or recurrent disease, and PS 0-1. EGFR mutation or ALK rearranged pts were allowed after receiving each tyrosine kinase inhibitor. Pts were randomized 1:1 to receiving either docetaxel (D) or pemetrexed (P) with B. The primary endpoint was progression-free survival (PFS) assessed by independent review committee. B was administered 15 mg/kg, D was 50 mg/m^2, or P was 500 mg/m^2 every 3 weeks until disease progression or unacceptable toxicity based on our previous studies. Selection design was adopted for this study. The planned sample size was 120 pts to yield 80% power to select an optimal regimen correctly and PB is chosen for the further evaluation if the point estimate of hazard ratio (HR) for PFS was ≤1.20. **Result:** Enrollment was terminated in early at the end of March 2017 because of slow accrual. Total 103 pts (DB/PB= 51/52 pts) were enrolled and 99 pts (49/50 pts) were full analysis set. Patient characteristics were well balanced between two arms. Median age was 78 (range: 75-88) in DB and 79 (75-94) in PB. EGFR mutation+/ALK translocation+/wild type/unknown= 13/0/34/2 in DB and 13/2/33/2 in PB. Total 77 events occurred at data cut-off, which corresponded to 77.7% power. The median PFS of DB and PB were 6.1 months and 4.6 months (HR 1.03, 95%C.I. 0.66-1.61: p=0.901). The response rates were 43% and 40% (p=0.840), respectively. The incident of ≥Grade 3 leukopenia (69% vs. 27%, p<0.001), neutropenia (86% vs. 44%, p<0.001) and fatigue (10% vs. 0%, p=0.027) were higher in DB. However, the frequency of febrile neutropenia was not different (16% vs.12%, p=0.578). One patient in PB was died of rupture of abdominal aortic aneurysm. **Conclusion:** PB is less toxic and the efficacy is comparable between two arms for elderly (≥75 years old) advanced non-squamous NSCLC. PB is a candidate for the further evaluation. Clinical Trial information: UMIN000012786.

Keywords: bevacizumab plus pemetrexed, bevacizumab plus docetaxel, elderly

P1.01-41 A PHASE 2 STUDY OF DS-8201A IN HER2-OVEREXPRESSING OR -MUTATED ADVANCED NON-SMALL-CELL LUNG CANCER

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Background: Approximately 30% of non-small-cell lung cancers (NSCLC) are human epidermal growth factor receptor 2 (HER2)-overexpressing (immunohistochemistry [IHC] 2+ or 3+) and approximately 2% have HER2-activating mutations. Although HER2 is considered a potential target for NSCLC, no HER2-targeted therapies are approved for the treatment of NSCLC. DS-8201a is a novel HER2-targeted antibody-drug conjugate with a humanized HER2 antibody attached to a topoisomerase I inhibitor payload (DXd) by a cleavable peptide-based linker, and with a high drug-to-antibody ratio of 7 to 8. In preliminary results from the ongoing phase 1, DS8201-A-J101 trial, DS-8201a (5.6 and 6.4 mg/kg) had a confirmed objective response rate (ORR) of 20.0% (1/5) in HER2-expressing NSCLC (Tsurutani et al, ESMO 2017). In addition to NSCLC, DS-8201a also showed substantial antitumor activity with a manageable safety profile in multiple other HER2-expressing tumors such as breast, gastric, and colorectal cancers. **Method:** This multicenter, open-label, 2-cohort, phase 2 study will assess the efficacy and safety of DS-8201a in subjects with HER2-overexpressing or -mutated unresectable and/or metastatic nonsquamous NSCLC that is relapsed/refractory to standard treatment or for which no standard treatment is available (NCT03505710). Overall, approximately 80 subjects will be enrolled; 40 subjects in each of 2 cohorts (cohort 1: HER2-overexpressing [IHC 3+ or IHC 2+]; cohort 2: HER2-mutated including exon 20 insertions and single-nucleotide variants in kinase, transmembrane, and extracellular domains [eg, L755S, V659E, S310F]). To be eligible for inclusion in cohort 1, HER2-overexpression must be assessed and confirmed by central testing based on archival samples. To be eligible for inclusion in cohort 2, any HER2-activating mutation must be documented based on archival tumor samples analyzed by Clinical Laboratory Improvement Amendment-certified laboratory or equivalent. All enrolled subjects will receive a 6.4 mg/kg dose of DS-8201a once every 3 weeks; study treatment will be continued until progressive disease or unacceptable toxicity. The primary endpoint is ORR based on RECIST version 1.1 (percentage of complete and partial response) by an independent radiologic facility. Secondary efficacy endpoints include progression-free survival, duration of response, disease control rate, and overall survival. Safety assessments include serious and treatment-emergent adverse events, physical examinations, vital signs, and clinical laboratory parameters. The study will enroll subjects in North America, Europe, and Japan. Recruitment began in May, 2018. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: HER2, Antibody-drug conjugate, NSCLC

P1.01-42 REAL-WORLD EVALUATION OF TOLERABILITY IN OLDER ADULT PATIENTS (≥75 YEARS OLD) WITH EGFR-MUTATED NSCLC

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Background: NSCLC patients carrying EGFR mutations are diagnosed across a wide age distribution. Although EGFR tyrosine kinase inhibitors (TKIs) are generally well tolerated, there remains a paucity of real-world data on toxicity and health utility scores (HUS) in older patients. **Method:** A longitudinal observational study evaluated health-related quality of life (HRQoL) using HUS through the EQ-5D questionnaire, and common EGFR-TKI toxicities using PRO-CTCAE in NSCLC outpatients carrying EGFR mutations. Patients were classified into two groups: older (≥75 years) and younger (<75 years). Patient characteristics and outcomes were extracted from chart review; patients were classified as having stable or progressive disease according to imaging findings. HUS and PRO-CTCAE results were compared descriptively. **Result:** Of 240 patients and 774 encounters, 52 patients (22%; comprising 157 encounters) were aged ≥ 75 years. Gender and race were similarly distributed in both age groups: 63% of older patients and 70% of younger (<75 years) were female; 56% of older patients and 53% of younger patients were Asian. Use of gefitinib in older patients was much higher than other drugs: among 147 patients who received gefitinib, 27% (40 patients) were older, compared to 15% (5/33) for osimertinib and 15% (3/20) for erlotinib. Of patients receiving afatinib (n=11) and chemotherapy (n=32), none were ≥ 75 years. The following table describes HUS and PRO-CTCAE results by treatment and age group for stable patients.

	Older Adults (≥75 years)			Younger Adults (<75 years)		
	N	HUS, mean (SD)	PRO-CT-CAE*, median [IQR]	N	HUS, mean (SD)	PRO-CT-CAE*, median [IQR]
Stable on gefitinib	34	0.83 (0.20)	4.5 [0,16]	77	0.80 (0.15)	4 [0,15]
Stable on osimerti-nib	5	0.80 (0.23)	13.5 [0,17]	22	0.87 (0.12)	0 [0,13.5]
Stable on erlotinib	3	0.82 (0.08)	0 [0,9]	11	0.80 (0.14)	0 [0,16]

*Higher PRO-CTCAE indicates more severe toxicities/symptoms.

Conclusion: In a real-world evaluation, patients 75 years or older comprised almost a quarter of all patients with EGFR-mutant advanced NSCLC. Afatinib and chemotherapy were not used at all in this population. Gefitinib was used most commonly, with similar toxicities and health utilities between older and younger patients. Osimertinib and erlotinib were used too infrequently in this study for conclusive age comparisons.

Keywords: older adults, quality of life, Epidermal growth factor receptor

P1.01-43 NEXT-GENERATION SEQUENCING IN THE EXPLORATION OF GENETIC HETEROGENEITY FOR LUNG ADENOCARCINOMA PATIENTS WITH EGFR ACTIVATING MUTATIONS

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Background: Increasing evidence leads to a ratiocination that genetic heterogeneity of the lung adenocarcinoma patients with sensitive EGFR mutations may impact clinical responses and outcomes to EGFR-TKIs. **Method:** We performed targeted NGS with a gene panel covering 416 cancer-related genes to profile genetic characteristics of 69 lung adenocarcinoma patients with activating EGFR mutations and assessed the contribution of targeted NGS to exploration of genetic heterogeneity of such cohort. **Result:** We detected total 200 actionable genetic alterations (mean 2.9 variations per patient, range: 1-7 variations) in tumor DNA and 140 actionable genetic alterations (mean 2.0 variations per patient, range: 0-5 variations) in matched plasma ctDNA, respectively. The concurrent genes with the highest mutation rate were *TP53* (observed in 72.5% patients), other uncommon *EGFR* mutations (observed in 21.7% patients), *EGFR* amplification (observed in 20.3% patients), *RB1* (observed in 10.1% patients), *PIK3CA* (observed in 7.2% patients), and *MYC* (observed in 5.8% patients). NGS provides EGFR mutation detection in plasma with a test sensitivity of 88.2% and specificity of 100.0%. Novel mutations potentially related to primary drug resistance were identified including: *CDC73*, *SMAD4*, and *CTNNB1* missense mutations; *RB1*, *ARID1A*, *ARID2*, *DNMT3A*, *STK11*, and *ATR* frameshift indel; *CDKN2B-PATA31D1*, *NFKBIA-OR11H12* fusion gene; PRKCI, CCNE1, MCL1, ARAF copy number gain; RB1 loss. The pathways analysis showed that unique pathways in the primary resistant cohort included: 1) immune related pathways: Toll-like receptor signaling pathway, T cell receptor signaling pathway; 2) epithelial-mesenchymal transition (EMT) related pathways: TGF-beta signaling pathway; 3) downstream pathway of EGFR: PIK3CA/AKT/mTOR signaling pathway; 4) cell function related pathways: Mismatch repair pathway, AMPK signaling pathway, TNF signaling pathway, Notch signaling pathway, and Transcriptional misregulation in cancer. **Conclusion:** In conclusion,

we note the complexity and heterogeneity of activating *EGFR*-mutant lung adenocarcinoma that may confer primary resistance to EGFR TKI using NGS platform. This study highlights the advantage of the NGS than traditional methods on testing *EGFR* mutations, enabling further refinement in sub-classification for the improved personalization of lung cancer treatment.

Keywords: primary resistant mechanism, activating EGFR mutation, Genetic heterogeneity

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-44 OUTCOME OF UNCOMMON EGFR MUTATION POSITIVE NEWLY DIAGNOSED ADVANCED NSCLC PATIENTS: A SINGLE-CENTRE RETROSPECTIVE ANALYSIS.

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Background: The significance of uncommon EGFR mutations in newly diagnosed advanced NSCLC patients is incompletely known. We aimed to analyze the demographic profile, outcome and treatment attributes of these patients. **Method:** We retrospectively surveyed 5738 advanced NSCLC patients who underwent EGFR testing in our centre from 2013 to 2017 by in-house primer probes on real time PCR platform. Descriptive data was accumulated from electronic medical records. Survival plot was calculated from Kaplan Meir and compared between groups using Log Rank test. **Result:** Out of 1260 EGFR mutation positive patients, 83 (6.58%) had uncommon mutations in isolation or in various combinations. Uncommon mutations were more frequent in men than in women (59% vs.41%), in never smokers than in smokers (65.1 % vs. 20.5%) and in adenocarcinomas than non -adenocarcinomas (96.4% vs. 3.6%). Overall Exon18G719X, Exon20insertion, Exon20T790M, Exon20S768I , Exon21(L858R/L861Q) were present in 9.6%, 19.3%, 12%, 3.6% and 3 .6% patients respectively . Dual mutation positivity was found in 50.6% patients. One patient (out of 83) had triple mutations: Exon18G719X, Exon20S768I and Exon21L858R. On classifying patients as per TKI sensitivity, it was found that TKI sensitive single and dual mutations were found in 15.7 % and 4.8% respectively .TKI insensitive single mutations were found in 31.3% and a combination of TKI sensitive and insensitive mutations was found in 48.2 % patients. The median duration of follow up was 13 months. Five patients were lost to follow up. Overall 50.6% patients received oral TKI and 34.9% received chemotherapy as first line therapy. Response to first line therapy could be assessed in 54 patients, out of whom 28 had partial response, 14 had stable disease and 12 had progression. Median progression free survival (PFS) on first line therapy was 8.3 months (CI 5.3-12.9). Median overall survival of patients who received TKI during the course of their disease was 20.2months (CI 11.4 -28.9). Median overall survival of the entire cohort was 15.8 months (CI 10.1-21.5). Among all uncommon mutations, patients with dual mutations did better, with a median overall survival time of 22.6 months (CI 8.2-37.0, P=0.005) . It was observed that TKI Sensitive/ TKI Insensitive Dual mutations had a superior overall survival of 28.2 months (CI 15.2-41.2,P=0.042) as compared to TKI Sensitive (single or dual) and TKI Insensitive single uncommon EGFR mutations. **Conclusion:** Uncommon EGFR mutations constitute a distinct heterogeneous group, hence it is imperative to understand each subgroup more to define optimal treatment.

Keywords: advanced NSCLC, Uncommon EGFR

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-45 CRIZOTINIB EFFICACY IN ALK-POSITIVE ADVANCED STAGE NON-SMALL CELL LUNG CANCER PATIENTS: A REAL-WORLD EXPERIENCE FROM TURKEY

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Background: ALK mutation is observed in 4% of patients diagnosed with NSCLC. The present study aimed to evaluate the efficacy of crizotinib, an ALK inhibitor, and clinical characteristics of ALK-positive NSCLC patients. **Method:** In this multicenter, retrospective study, data of ALK-positive advanced stage NSCLC patients who received crizotinib were retrieved from hospital records. **Result:** Data of 353 ALK-positive metastatic NSCLC patients receiving crizotinib in any treatment line were analyzed. The mean age of the patients was 53.2±12.6 years [median, 53 years (21-85 years)] and 193 (54.7%) patients were male. Age at diagnosis was significantly higher in males than in females (54.8±11.8 years and 51.3±13.2 years, respectively; p=0.044). The rate of patients who never smoked was 50.1%. The most common histological subtype was adenocarcinoma (96%). The frequency of brain metastasis at the time of diagnosis was 23.4%. The most common initial symptoms were cough (56%) and dyspnea (53%). Initial ECOG score was 0 or 1 in 80% of the patients. Crizotinib had been used in 37% of the patients in the 1st-line treatment, in 45% of the patients in the 2nd-line treatment, and in 18% of the patients in the ≥3rd-line treatment. **Table 1.** Response rates of the patients

		Treatment line			
	Overall N (%)	1 N (%)	2 N (%)	3 N (%)	Other N (%)
Complete response	28 (7.9)	9 (7.3)	14 (8.9)	4 (9.8)	1 (5.6)
Partial response	217 (61.5)	78 (62.9)	103 (65.2)	25 (61.0)	10 (55.6)
Stable disease	50 (14.2)	18 (14.5)	21 (13.3)	7 (17.1)	4 (22.2)
Progressive disease	67 (13.3)	19 (15.3)	20 (12.7)	5 (12.2)	3 (16.7)
Undefined	11 (3.1)				
ORR	245 (69.4)	87 (70.2)	117 (74.1)	29 (70.8)	11 (61.2)
DCR	295 (83.6)	105 (84.7)	138 (87.4)	36 (87.1)	7 (83.4)
Undefined	11 (3.1)				

ORR was 69.4% and DCR was 83.6% (Table 1). ORR and DCR in the patients received crizotinib were 70.2% and 84.7% in the 1st-line treatment, respectively and were 74.1% and 87.4% in the 2nd-line treatment, respectively. The frequency of brain metastasis was 40.2% at 12 months. Of these patients, the median PFS and OS were 11.3 and 28.0 months, respectively. The most common side effects were fatigue, visual disturbances, nausea, abdominal discomfort, and pretibial edema. **Conclusion:** Clinical characteristics of ALK-positive patients and crizotinib efficacy are consistent with studies. Response rates and survival outcomes are similar regardless of treatment lines. Crizotinib is safely used in these patients.

Keywords: NSCLC, ALK inhibitor, crizotinib

P1.01-46 CIRCULATING TUMOR DNA ANALYSIS FOR PREDICTING RESPONSE TO OSIMERTINIB AND DISEASE PROGRESSION IN EGFR-MUTANT NON-SMALL-CELL LUNG CANCER

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Background: Circulating tumor DNA (ctDNA) has emerged as a promising non-invasive modality to detect biomarkers associated with a broad array of malignancies, including lung cancer. We aimed to assess whether ctDNA could be used to predict response to EGFR-tyrosine kinase inhibitor (EGFR-TKI) therapy and disease progression. **Method:** Plasma samples were serially collected at every clinic visit from patients with metastatic EGFR-mutant non-small-cell lung cancer (NSCLC) enrolled in a clinical trial of osimertinib treatment, local ablative therapy (LAT) upon progression, followed by osimertinib re-challenge (NCT02759835). Patients with no prior EGFR-TKI treatment or patients with T790M-positive NSCLC after EGFR-TKI treatment receive osimertinib. Upon progression, patients with ≤5 progressing sites undergo LAT and resume osimertinib. ctDNA was detected using droplet-digital PCR *EGFR* mutation detection assays. The changes in ctDNA mutant allele levels were correlated with response to treatment and tumor progression. To identify additional genetic changes that may be related to osimertinib resistance, an enhanced Tagged-Amplicon Sequencing NGS assay (InVisionSeq™) was utilized which covers SNVs, InDels and amplifications in 36 genes commonly mutated and therapeutically actionable in NSCLC. **Result:** 353 samples from 17 patients were analyzed. At baseline, EGFR mutations were detected in 15 (88%) patients. One patient with overall low metastatic tumor burden and another patient with most tumor burden in the brain did not have detectable ctDNA at baseline. For patients treated with osimertinib before first progression, 12 (86%) achieved a partial response (PR) and 2 (14%) had stable disease (SD) as their best response. ctDNA decreased after initiation of osimertinib in these patients with 7 (50%) patients having no detectable ctDNA within 28 days. In those with ongoing PR (n=5) and prolonged stable disease (n=1), ctDNA remains undetectable (n=5) or low (n=1). Among 7 patients who had first progression, 5 (71%) patients had an increase in corresponding mutant *EGFR* allele in ctDNA 2-4 months before radiographic progression. While exploration of osimertinib resistance mechanisms by InVisionSeq™ is ongoing, early results demonstrate that allele frequencies of mutations in genes, including *EGFR*, *PIK3CA*, and *TP53* closely reflected response and resistance to osimertinib. *MET* and *EGFR* amplification, as well as emergence of *EGFR* C797S mutant were identified as key resistance mechanisms by ctDNA analysis. Full details on all patients will be presented at the meeting. **Conclusion:** Quantitative assessment of plasma ctDNA is a relatively non-invasive tool to monitor the therapeutic response to treatment with EGFR-TKI and for early detection of resistance mechanisms for clinical decision making.

Keywords: EGFR-mutant NSCLC, osimertinib, Circulating Tumor DNA

P1.01-47 PHASE I/II TRIAL OF DASATINIB AND OSIMERTINIB IN PATIENTS WITH ADVANCED EGFR-MUTANT NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: The presence of epidermal growth factor receptor (EGFR) mutations is associated with sensitivity to EGFR tyrosine kinase inhibitors (EGFR-TKIs), but a subset of patients (pts) do not respond to EGFR-TKIs or have very short duration of response, suggesting intrinsic resistance. Moreover, acquired resistance to EGFR-TKIs is inevitable for most patients. We showed that overexpression of Cripto-1, a member of the EGF–CFC family, contributes to the development of intrinsic resistance to EGFR-TKIs through the activation of the Src pathway and that the combination of EGFR-TKI therapy and Src inhibition works synergistically in preclinical models. **Method:** This was an open-label, phase I/II trial of osimertinib and dasatinib, a multi-kinase inhibitor with activity against Src, in EGFR-TKI treatment-naïve pts with advanced EGFR-mutant NSCLC (NCT02954523). Pts with pleural or pericardial effusions at study entry were excluded. The primary endpoint of the phase I part was to establish a safe and tolerable phase II dose of osimertinib and dasatinib. Dose escalation included 2 dose levels (dose level 1: osimertinib 80 mg QD, dasatinib 50 mg BID, dose level 2: osimertinib 80 mg QD, dasatinib 70 mg BID). In addition, 2 dose levels below the starting dose level could be explored if dose reductions were necessary. **Result:** 7 pts (4 at dose level 1, 3 at dose level 2) were enrolled to date. None of them had dose limiting toxicities (DLTs), but given frequent dose reductions and toxicities beyond the DLT period at dose level 2, dose level 1 is being further assessed (up to 6 pts at dose level 1). The most common treatment-related adverse events (TRAEs) included pleural effusion (n=6), AST elevation (n=5), ALT elevation (n=5), rash (n=5), and diarrhea (n=4), most of which were grade 1 or 2. 3/2/1 pts had grade 1/2/3 pleural effusion, respectively. 4 pts had grade 3 TRAEs, which included pleural effusion, fatigue, neutropenia, anemia, and headaches. No grade 4 or 5 toxicities were observed. Among 6 evaluable pts, 4 confirmed partial response (PR)/1 unconfirmed PR/1 stable disease were observed. Responses were durable with all the PRs ongoing. **Conclusion:** The combination of dasatinib and osimertinib showed no new safety signals and demonstrated evidence of anticancer activity. Treatment-related toxicities were manageable with dasatinib dose reductions and supportive measures. The safety and efficacy of dasatinib and osimertinib will continue to be explored.

Keywords: EGFR-mutant NSCLC, osimertinib, dasatinib

P1.01-48 NAB-PACLITAXEL PLUS GEMCITABINE IN ADVANCED NSCLC AFTER PLATINUM-BASED CHEMOTHERAPY: FINAL RESULTS AND CAVEOLIN-1 EXPRESSION

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Background: Nab-Paclitaxel (PTX) plus gemcitabine significantly improved overall survival, progression-free survival, and response rate in patients with metastatic pancreatic adenocarcinoma. Anti-tumor synergy between nab-PTX and gemcitabine was recently demonstrated in mouse model. Combination treatment increases intra-tumoral gemcitabine levels attributable to a decrease in the primary gemcitabine metabolizing enzyme, cytidine deaminase. Higher caveolin-1 expression in tumor-associated stroma was associated with improved overall survival and response rate in patients with advanced non-small-cell lung cancer (NSCLC) treated with nab-PTX. Based on these data, we planned to assess the efficacy and safety of combination with nab-PTX plus gemcitabine in patients with NSCLC previously treated with platinum-based chemotherapy. **Method:** Patients with advanced NSCLC with progressive disease to platinum-based chemotherapy, ECOG performance status (PS) 0 or 1, and adequate kidney, liver and bone marrow function were eligible. Treatment consisted of nab-PTX (100 mg/m^2) plus gemcitabine (1000 mg/m^2) on days 1 and 8 of each 3-week cycle until progression disease or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Archived tumor blocks, if available, were collected for caveolin-1 expression analysis using immunohistochemistry. **Result:** Of the 28 patients enrolled, 28 were evaluable for response and toxicity. The median age was 68 years (range 47-79), 23 males and 5 females. Histology subtypes were: adenocarcinoma 19 patients, squamous cell carcinoma 9 patients. Seventeen patients had ECOG PS 1 and 11 patients had PS 0. Twenty-four patients were 2nd line and 4 patients were 3rd line. The median number of cycles administered was 4 (range 1-10). The overall response rate was 17.9%. The disease control rate was 67.9%. The median progression-free survival was 3.1 months (95% confidence interval [CI] = 1.6-4.1). The median overall survival was 11.7 months (95% CI = 8.0-19.3). Five patients (17.9%) had grade 4 neutropenia, 4 patients (14.3%) had grade 3 anemia, 3 patients (10.7%) had grade 3 thrombocytopenia. However, no patients developed febrile neutropenia. Remarkable non-hematologic toxicity was interstitial pneumonia with grade 3 in 4 patients (14.3%), neuropathy with grade 3 in 2 patients (7.1%) and infections with grade 3 in 2 patients (7.1%). Caveolin-1 expression analysis will be presented at the meeting. **Conclusion:** The efficacy of nab-Paclitaxel in combination with gemcitabine in advanced second or third-line NSCLC patients was limited and the high onset of interstitial pneumonia was unacceptable.

Keywords: nab-paclitaxel plus gemcitabine, caveolin-1 expression, Non-small-cell lung cancer

P1.01-49 IRAE, POSSIBLE PREDICTIVE MARKERS FOR IMMUNE CHECKPOINT INHIBITORS

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Background: Although an immune-related adverse event (irAE) in immune checkpoint inhibitors (ICIs) is a major cause of discontinuation of ICIs, few reports have examined detailed clinical background in clinical practice. **Method:** Sixty-one patients with non-small cell lung cancer who underwent treatment with ICIs (nivolumab or pembrolizumab) at the Saga University Medical School Hospital from December 2015 to January 2018 were included. Clinical background, therapeutic effect, and progression free survival (PFS) were retrospectively examined between AE discontinuation group (AEg) and progressive disease (PD) discontinuation group (PDg). **Result:** Of the 41 patients receiving nivolumab, nine cases (22.5%) were discontinued due to AE and 22 cases (55.0%) were PD. Of 21 patients receiving pembrolizumab, nine cases (42.9%) were discontinued due to AE and 8 cases (38.1%) were PD. There was no significant difference between nivolumab and pembrolizumab in the discontinuation rate due to AE (p=0.14). When comparing the clinical background between the AEg and the PDg, the response rate was 50.0% in the AEg and 6.7% in the PDg, which was significantly higher in the AEg (p=0.001). The median PFS was significantly longer in the AEg, 301 days (95% CI: 193-336) in the AEg and 60 days (95% CI: 74-178) in the PDg (Log-Rank, p=0.009). Among irAE, the incidence of interstitial lung disease (ILD) was 3/49 (6.1%) in cases without interstitial pneumonia (IP) or radiation pneumonitis as the underlying diseases, whereas it was significantly higher at 6/12 (50.0%) in cases with those underlying diseases (p=0.001). Among nine patients who developed ILD, grade3 or more was 2 cases, of which 1 case was grade5. **Conclusion:** Discontinuation due to AE during treatment of ICIs may be a predictive marker of good response to ICIs and favorable outcome since anti-cancer effect continued even after discontinuation. However, the presence of IP or radiation pneumonitis as the underlying disease is a risk factor for the onset of ILD, so it is necessary to carefully consider the indication for treatment of ICIs.

Keywords: immune checkpoint inhibitor, predictive marker, immune-related adverse event (irAE)

P1.01-50 REAL WORLD EXPERIENCE OF NIVOLUMAB IN PATIENTS WITH METASTATIC NONSMALL CELL LUNG CANCER (MNSCLC)

D. Ksienski[1], E. Wai[2], M. Lesperance[3], N. Croteau[3], L. Fiorino[1], Z. Poonja[1], G. Geller[1], D. Fenton[1], E. Brooks[1], D. Glick[2]

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Background: Immune related adverse events (irAE) from immunotherapy in metastatic melanoma have been correlated with efficacy; this association is less clear in mNSCLC. We aimed to evaluate the correlation between irAE and clinical efficacy of Nivolumab (N) in mNSCLC. **Method:** All mNSCLC patients (pts) treated with N between 11/2015 to 10/2017 at BC Cancer were identified. Demographic, tumor, treatment details, and frequency and grade (Gr, CTCAE v4.0) of irAE, were collected from chart review. Kaplan-Meier curves of overall survival (OS) from initiation of N based on the development of irAE and utilizing a 6-week landmark analysis were evaluated using the log-rank test. **Result:** Characteristics of cohort (n=230): median age 64y (range 39-82), primary histology: non-squamous (74%), brain metastases rate: 13%, ECOG PS>1: 31% at start of N, and median Charlson Comorbidity Index (CCI) 6, and 72% of pts had received 1 prior line of systemic therapy. 100 pts (44%) experienced 143 separate irAE of Gr 1(64), Gr 2(54), Gr 3(12), Gr 4(9), and Gr 5(4). Three treatment related deaths were due to pneumonitis, hepatitis and colitis. 48 pts (21%) required treatment interruption due to irAE, of whom 28 discontinued N completely. With a median follow-up of 7.0 months (range: 0.07-30), 136 pts died and median OS from initiation of N was 9.2 months (95% CI 7.8-12.9). Median OS was 12.9 months and 8.6 months for patients requiring treatment interruption due to irAE or not, respectively. For landmark analysis, 15 pts were excluded as they died within 6 weeks from initiation of N. Using 6-week landmark analysis, there was no significant difference in OS amongst pts who developed any irAE (median 8.1 months, 95% CI: 6.1-not reached) compared to those who did not (median 10.8 months, 95% CI: 8.6-14.5; log rank test p=0.567). Development of colitis was associated with a lower median OS (4.4 months, 95% CI: 3.8-not reached) versus pts who did not (10.8 months, 95% CI: 8.6-14.5; p=0.0103). Thyroid changes (p=0.473), dermatitis (p=0.29), pneumonitis (p=0.318), hepatitis (p=0.135), and arthralgias (p=0.465) were not associated with different OS compared to those without irAE. **Conclusion:** Despite 31% of pts having PS>1 and a high CCI, N was well tolerated. In the studied cohort, development of any irAE was not associated with improved survival. The finding of worse survival amongst pts with colitis requires further study.

Keywords: immune related adverse events, Nivolumab

P1.01-51 REAL WORLD EXPERIENCE OF PEMBROLIZUMAB IN PATIENTS WITH METASTATIC NONSMALL CELL LUNG CANCER (MNSCLC)

D. Ksienski[1], E. Wai[2], M. Lesperance[3], N. Croteau[3], L. Fiorino[1], Z. Poonja[1], D. Fenton[1], G. Geller[1], E. Brooks[1], D. Glick[2]

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Background: Immune related adverse events (irAE) from immunotherapy in metastatic melanoma correlate with efficacy; this association is less clear in mNSCLC. We aimed to evaluate the correlation between irAE and clinical efficacy of pembrolizumab (P) in mNSCLC. **Method:** All mNSCLC patients (pts) treated with P between 11/2015 to 10/2017 at BC Cancer were identified. Demographic, tumor, treatment details, and frequency and grade (Gr, CTCAE v4.0) of irAE, were collected from chart review. Kaplan-Meier curves of overall survival (OS) from initiation of P based on the development of irAE and utilizing a 6-week landmark analysis were evaluated with the log-rank test. **Result:** Characteristics of cohort of 41 pts were: median age 68y (range 50-81), females 49%, non-squamous histology 81%, PD-L1 status <1%/1-49%/>50%/unknown 0/12%/83%/5%, brain metastases rate 15%, and liver metastases rate 12%. ECOG PS>1 at start of IO 32% and median Charlson Comorbidity Index (CCI) 4. P was delivered to 42% in first line setting. With a median of follow-up of 6.6 months (range: 0.7-32.3), 17 pts (41%) had died and 16 (39%) were still receiving drug. 16 pts (39%) experienced a total of 24 irAE; Gr of irAE 1/2/3/4/5: 10/12/1/1/0. The most common irAE were arthralgias (5pts), pneumonitis (4pts), and dermatitis (4pts). Treatment was temporarily held in 4pts (10%) due to irAE and permanently discontinued in 3 pts (7%). Median OS from initiation of P was 22.6 months (range: 10.6-not reached, NR). On univariate analysis, male gender (HR=3.36, 95% CI: 1.08-10.48) and ECOG>1 (HR=3.24, 95% CI: 1.13-9.35) correlated with worse OS. Median OS amongst pts requiring treatment interruption due to irAE was NR and for those treated continuously was 14.0 months. 1 pt was excluded from landmark analysis as they died within 6 week from initiation of P. Using 6 week landmark analysis, there was no significant difference in OS amongst pts who developed any irAE (median NR, 95% CI: 4.8 months-NR) compared to those who did not (14.0 months, 95% CI: 10.6-NR, log rank test p=0.84). Thyroid changes (p=0.411) and dermatitis (p=0.951) were not associated with differences in OS compared to those without irAE. **Conclusion:** Despite 32% of pts having PS>1 and a high CCI, the incidence of serious irAE was low. The impact of gender on response to P requires more study. Development of irAEs was not correlated with improved survival.

Keywords: pembrolizumab, immune related adverse events

P1.01-52 BR-34- RANDOMIZED TRIAL OF DURVALUMAB & TREMELIMUMAB +/- PLATINUM CHEMOTHERAPY IN PATIENTS WITH METASTATIC SQUAMOUS OR NON-SQUAMOUS NSCLC

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Background: Immunotherapy improves survival of patients with non-small cell lung cancer (NSCLC). Current clinical trials are studying

various combinations of PD-1/PD-L1 inhibitors and CTLA-4 agents with or without chemotherapy, to enhance treatment efficacy. This trial will determine the effects of adding platinum chemotherapy to combination of check point blockade with durvalumab and tremelimumab in the first line treatment of advanced non-small cell lung cancer. **Method:** BR-34 is a CCTG led randomized proof-of-concept trial of durvalumab and tremelimumab, with or without platinum-based chemotherapy in patients with metastatic squamous or non-squamous NSCLC. Patients who have histologically confirmed Stage IV NSCLC and wild type EGFR and ALK, PDL-1 unselected, with measurable disease by RECIST 1.1, and available tissue for biomarker testing are eligible and are stratified by stage, histology and smoking status. Primary end point is overall survival. Secondary end points include progression free survival at 1 year, overall response rate, quality of life, cost effectiveness and correlative studies on tissue and blood (including PD-L1, tumour mutation burden and cell-free DNA) with outcomes and response, and PFS by iRECIST (exploratory). In total 300 patients will be recruited from Canada, Australia and Italy. Arm A will receive 4 cycles of fixed doses of tremelimumab (T) 75 mg plus durvalumab (D) 1500 mg every 28 days IV, followed by durvalumab (D) maintenance and Arm B will receive standard platinum-doublet chemotherapy in combination with T+D every 21 days for 4 cycles, followed by maintenance D (with pemetrexed for those with non-squamous histology), until progression. **Result:** BR-34 was initiated in February 2017 in Canada and total 150 patients have been randomized as of April 2018, including 137 from Canada and 13 from Australia. 28 sites are open to accrual in Canada, 15 in Australia the trial will soon be opened in Italy. **Conclusion:** At the current rate of accrual, the CCTG BR-34 trial should be fully accrued by Q1 2019. This is the first randomized trial of combination checkpoint blockade +/- platinum-doublet chemotherapy in advanced non-small cell lung cancer. Acknowledgements: BR-34 is an academic, co-operative group trial led by Canadian Cancer Trials Group (CCTG) in collaboration with ALTG and NHMRC Clinical Trials Centre, with support from AstraZeneca and Canadian cancer society. NCT03057106

Keywords: BR-34, Immunotherapy combination

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-53 BONE METASTASES AND EFFICACY OF IMMUNOTHERAPY IN PATIENTS WITH PRETREATED ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: Approximately 40% of NSCLC patients develop bone metastases (BoM). Bone has active functions in regulating immune system. To date, no trial evaluated the role of BoM in modulating response to immunotherapy. Aim of the present study was to investigate whether presence of BoM impact on immunotherapy efficacy. **Method:** Two different cohorts of pretreated NSCLC patients (cohort A: Non-squamous; cohort B: Squamous) were evaluated for nivolumab efficacy in terms of objective response rate (ORR), progression free survival (PFS), and overall survival (OS) according to presence or absence of BoM. All patients received nivolumab at standard dose of 3 mg/kg every 2 weeks within the Italian Expanded Access Program. **Result:** Cohort A accounted for 1588 patients with non-squamous NSCLC: 626 (39%) with (BoM+) and 962 (61%) without BoM (BoM-). Cohort B accounted for 370 patients with squamous histology: 102 BoM+ (32%) and 251 BoM- (68%). In Cohort A, BoM+ had a significantly lower ORR (12% versus 34%; $p < 0.0001$), shorter PFS (2.0 versus 4.0 months, $p < 0.0001$) and shorter OS (7.4 versus 15.3 months, $p <0.0001$). In cohort B, BoM+ had significantly lower ORR (15% versus 22%; $p < 0.04$), shorter PFS (2.7 versus 5.4 months, $p <0.0001$) and shorter OS (5.0 versus 10.9 months, $p <0.0001$). Presence of BoM negatively affected outcome irrespective of PS (OS cohort A: PS-0 BoM+ 12.0 versus 20.9 months in PS-0 BoM-, $p<0.0001$; OS cohort B: PS-0 BoM+ 5.8 versus 16.4 months in PS-0 BoM-, $p<0.0001$). Multivariate analysis confirmed that presence of BoM independently associated with higher risk of death with HR 1.64 and HR 1.78, for Cohort A and B, respectively. **Conclusion:** Our results, the first assessing BoM in patients treated with immunotherapy, suggested that BoM predict lower efficacy of immunotherapy. BoM should be included as stratification factor in clinical trials.

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-54 A PHASE I/IB STUDY OF BINIMETINIB (MEK162), A MEK INHIBITOR PLUS CARBOPLATIN/PEMETREXED IN NON-SQUAMOUS NSCLC

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Background: MEK remains an important potential target in RAS/RAF dependent tumours. Binimetinib (MEK16) is a highly selective oral inhibitor of MEK1/2, which has shown activity in melanoma and other cancers. Data from preclinical models suggest greater activity with intermittent versus continuous dosing of MEK inhibitors when added to chemotherapy. This dose escalation study combines intermittent binimetinib with pemetrexed plus carboplatin in chemotherapy naive patients with advanced non-squamous NSCLC. **Method:** A standard 3+3 dose-escalation design was used with planned dose expansion at RP2D (N=30) in genotypically defined cohorts (*KRAS G12C* mutant (mt), non-*G12C* mt and wild type). The primary endpoint was to define the RP2D of binimetinib using an intermittent dosing schedule in combination with standard doses of pemetrexed and carboplatin. Secondary objectives included safety, pharmacokinetics (PK), response and exploring potential biomarkers of response or toxicity. Binimetinib (30-45 mg BID) was commenced on day 1 cycle 1 for 5 days followed by a 48-hour washout period. If well tolerated, pemetrexed/carboplatin (500 mg/m^2/AUC 5 mg*min/mL) were added on day 8 cycle 1 and binimetinib resumed from days 8-26 with a 48 hour drug washout before cycle 2. For subsequent cycles, pemetrexed/carboplatin were administered on day 1, binimetinib on days 1-19 every 21 days. Key eligibility criteria included ECOG performance status 0-1, adequate organ function, measureable disease by RECIST and no active CNS metastasis. Patients with *EGFR/ALK* mt lung cancer were permitted in the dose escalation phase after progression on standard TKI therapy. **Result:** Between 03/2017 and 04/2018, 11 patients have been enrolled in 2 dose escalation cohorts (4 *KRAS* mt, 4 *EGFR* mt including 1 ex20ins). Six patients were treatment-naive, 3 received prior EGFR TKI and 2 prior pembrolizumab. To date, 7 have experienced grade 3 adverse events (AEs) deemed at least possibly related to binimetinib (anemia, neutropenia, abdominal pain, diarrhea, nausea, vomiting, fatigue, transaminitis). No grade 4/5 AEs have been seen. Related AEs seen in >20% of patients include: rash, mucositis, diarrhea, fatigue, transient visual changes, nausea, edema, neutropenia and vomiting. Antitumour activity was seen at each dose level of binimetinib. Final data on toxicity, response, PK and confirmation of RP2D will be presented at the meeting. **Conclusion:** The addition of binimetinib to pemetrexed/carboplatin appears to have manageable toxicity with evidence of activity in non-squamous NSCLC. Dose expansion in genotypically defined cohorts will continue and a cohort combining binimetinib with pembrolizumab is planned.

Keywords: MEK inhibitor; KRAS; binimetinib

P1.01-55 UNIQUE GENETIC PROFILES FROM CEREBROSPINAL FLUID COULD PREDICT SURVIVAL OF EGFR-MUTANT NSCLC WITH LEPTOMENINGEAL METASTASES

Y. Li[1], B. Jiang[1], M. Zheng[1], H. Tu[1], J.-. Yang[1], X. Zhang[1], J. Ye[2], Q. Zhou[1], W. Zhong[1], C. Zhang[1], S. Chuai[3], Y. Wu[4]

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Background: Leptomeningeal metastases (LM) are more frequent in NSCLC with *EGFR* mutations; and cerebrospinal fluid (CSF) could reveal the unique genetic profiles of LM in our previous studies, but whether they could predict the overall survival (OS) of LM remains unknown. **Method:** *EGFR*-mutant NSCLC patients with LM were enrolled, and clinical data and genetic profiles detected by Next-generation sequencing were collected. We further drew nomogram with endpoint of OS after LM, then performed index of concordance (C-index) and survival analysis to evaluate predictive role. **Result:** In total, 61 patients were enrolled and all with genetic profiles from CSF. Patents with high copy number variations (CNVs) or harboring CDK6, TP53 exon5 or FGF19 in CSF demonstrated significant poorer OS than those without (Fig. 1). Cox regression analysis indicated CNVs, CDK6, CDKN2A, TP53, MET and NTRK1 as prognostic factors and further selected for nomogram (Fig. 2). C-index of nomogram was 0.743, indicating the moderate predictive effect. In the calibration curves, we scored the patients based on the model, using bisection and trisection methods to divide into low and high points groups; and low, medium and high points groups (Fig. 3), and significant difference were found in both the survival analyses (NA versus 7.47months, $P<0.01$) and (NA, 10.33 versus 4.43 months, $P<0.01$) respectively. Patients who received Osimertinib after LM seemed to have longer OS than those who did not (14.5 months versus 7.7 months) but without significant difference($P=0.10$); however interestingly, in those with EGFR T790M negative who took Osimertinib after LM by themselves obtained survival benefit than those who did not(NA

Conclusion: Unique genetic profiles from CSF could well predict OS of LM. High CNVs, CDK6, TP53 exon5 or FGF19 in CSF in CSF may be related to poor prognosis of LM.

Keywords: Leptomeningeal metastases, Cerebrospinal fluid, Nomogram

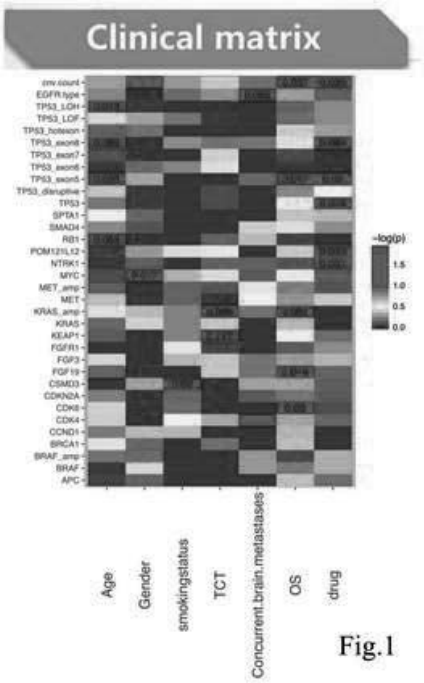

Fig.1

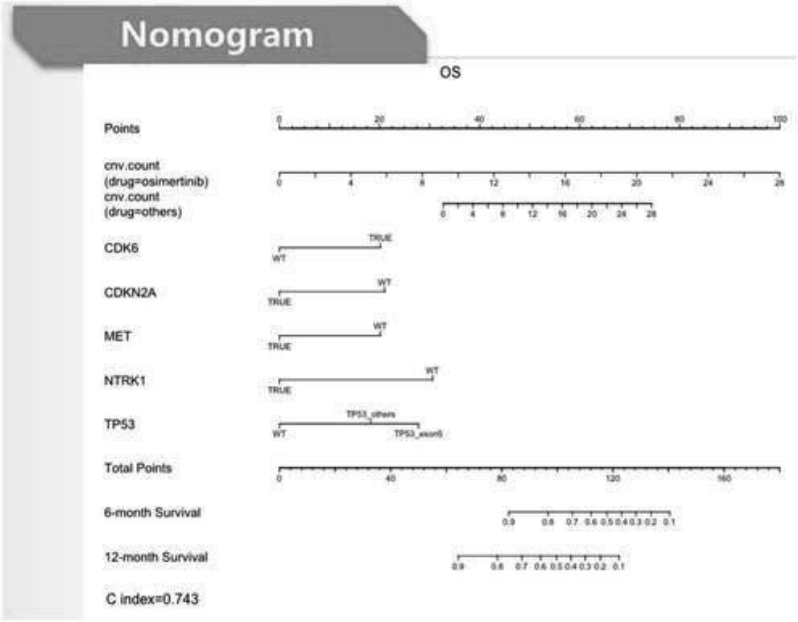

Fig.2

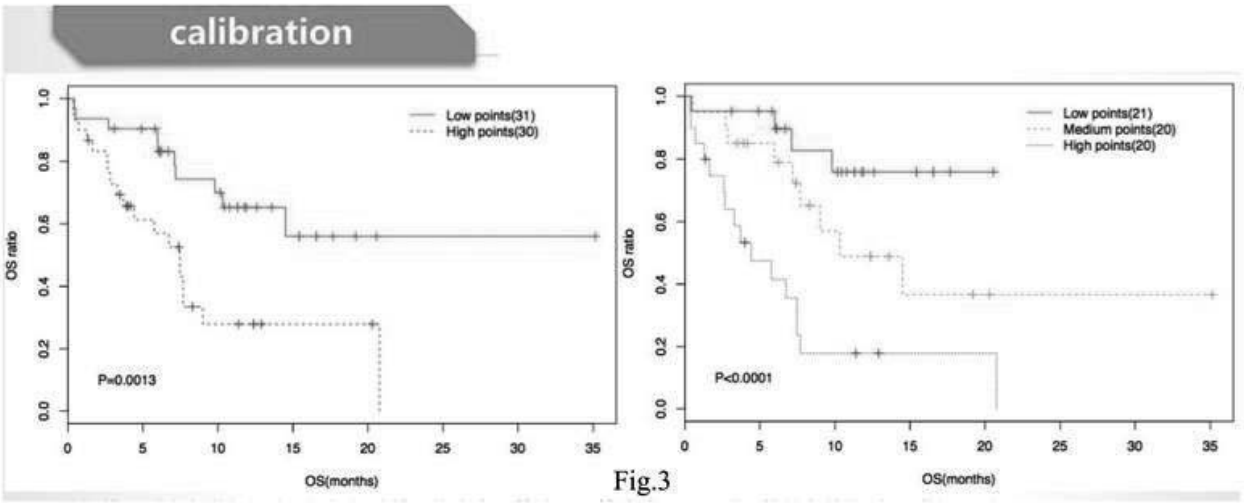

Fig.3

P1.01-56 CONCURRENT MUTATIONS IN CHINESE LUNG CANCER PATIENTS CARRYING HER2 GENOMIC ABERRATIONS

J. Zhao[1], Y. Li[2], X. Dong[3], X. Ai[4], Y. Chen[5], G. Lin[6], X. Zhang[7], W. Wang[8], C. Xu[5], R. Chen[2], X. Xia[2]

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Background: Although human epidermal growth factor receptor 2 (HER2, ERBB2) genomic aberration has been identified as therapeutic targets, clinical trials of HER2-directed therapies have disappointing results in lung cancer. We hypothesize that the concurrent alterations might be one of the reasons, thus the aim of this study was to describe frequent concurrent alterations in Chinese lung cancer patients harboring HER2 mutations. **Method:** A total of 147 cancer patients with HER2 mutations were enrolled in the study. Tumor biopsy, ctDNA and pleural effusion samples were collected for detection alterations using hybridization capture based next-generation sequencing (NGS), which enables the simultaneous detection of single-nucleotide variants, insertions/deletions, rearrangements, and copy-number alterations of at least 59 genes (59-1021). **Result:** Sixty-two of 147 patients with HER2 genomic aberrations were diagnosed as lung cancer. The HER2 gene was amplified in 11 (18%) patients, whereas HER2 mutations were detected in 48 patients, co-occurrence of HER2 amplification and mutations were in 3 patients. Thirty of the 62 patients (48.39%) had concurrent actionable mutations across 18 genes, which involved in RTK-PIK3CA-mTOR signaling pathways, cell-cycle pathway, DNA repair pathway, RAS-RAF-MAPK pathway and some others (details in table). Moreover, 7 patients had more than 2 concurrent mutations besides HER2 mutation/amplification. Table 1. concurrent genetic alterations in HER2-altered lung cancer patients

Signaling pathway	Concurrent actionable mutations	Number of patients
RTK-PIK3CA-mTOR	EGFR	11
	PIK3CA	4
	STK11	2
	FBXW7	1
	TSC1	1
	FLCN	1
	C11orf30	1
Cell-cycle	CDKN2A	5
	CCND1	2
	RB1	1
DNA repair	BRCA2	1
	ATM	1
RAS-RAF-MAPK	BRAF	1
	KRAS	1
Others	MDM2	2
	JAK2	2
	SMARCA4	2
	PTCH1	1

Conclusion: Concurrent of actionable genetic alterations in HER2-altered Chinese lung cancer patients was common. The complex molecular profiles elucidate the importance of comprehensive analysis of genetic mutations when considering anti-HER2 targeted therapy.

Keywords: HER2-mutant LC, concurrent gene alterations, next generation sequencing (NGS)

P1.01 ADVANCED NSCLC
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P1.01-57 THE ROLE OF EGFR MUTATION AS A PROGNOSTIC FACTOR IN SURVIVAL AFTER DIAGNOSIS OF BRAIN METASTASIS IN NSCLC: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The brain is a common site for metastasis in non-small-cell lung cancer (NSCLC), causing poor prognosis and reducing quality of life. This meta-analysis was designed to evaluate the relationship between the mutational status of the epidermal growth factor receptor (EGFR) and overall survival (OS) in NSCLC patients with brain metastases. **Method:** Electronic searches were performed in PubMed, EmBase, and the Cochrane Library to identify studies evaluating the association of EGFR mutation with OS in NSCLC patients with brain metastases through September 2017. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to calculate the summary results using random-effects models. Sensitivity, subgroup, and publication bias tests were also conducted. **Result:** This meta-analysis identified 18 studies involving 4,373 NSCLC patients with brain metastases. The summary results indicated that mutated EGFR associated with significantly improved OS compared with wild type EGFR (HR: 0.73; 95%CI: 0.54-0.99; $P = 0.045$). Subgroup analyses suggested that this relationship persisted in studies conducted in Eastern countries (HR: 0.59; $P = 0.021$), in studies with retrospective design (HR: 0.70; $P = 0.004$), with sample size ≥ 500 (HR: 0.52; $P = 0.001$), mean age of patients ≥ 65.0 years (HR: 0.59; $P = 0.043$), percentage male < 50.0% (HR: 0.60; $P = 0.002$), percentage of patients receiving tyrosine kinase inhibitor ≥ 30.0% (HR: 0.60; $P < 0.001$), and in studies with higher quality (HR: 0.67; $P = 0.007$). Finally, although significant publication bias was observed using the Egger test ($P = 0.008$), the results were not changed after adjustment using the trim and fill method (HR: 0.73; 95%CI: 0.54-0.99; $P = 0.045$). **Conclusion:** This meta-analysis suggests that EGFR mutation is an important predictive factor linked to improved OS for NSCLC patients with brain metastases. It can serve as a useful index in the prognostic assessment of NSCLC patients with brain metastases.

Keywords: lung cancer, EGFR, Brain metastasis

P1.01 ADVANCED NSCLC
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P1.01-58 VARIANTS DISTRIBUTION AND HETEROGENEITY OF OUTCOMES TO CRIZOTINIB IN ALK-REARRANGED CHINESE NON-SMALL CELL LUNG CANCERS

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Background: *ALK*-rearranged NSCLC is a unique molecular subgroup with high sensitivity to ALK inhibitors. Crizotinib, a FDA-approved tyrosine kinase inhibitor for *ALK*-rearranged NSCLCs, showed remarkable response in *ALK*-positive NSCLC. However, the magnitude and duration of clinical responses to crizotinib among different *ALK* variants are found to be heterogeneous, and studies about the clinical outcomes showed contradict conclusions. **Method:** We collected sequencing information from 110 *ALK*-positive Chinese NSCLC patients, whose tissue or plasma biopsies were sequenced in a CLIA-certified genomic profiling laboratory. Sequencing results were reviewed with the intent of studying *ALK* rearrangement distribution and clinical outcomes to crizotinib. **Result:** A total of 134 *ALK* rearrangements were identified in this cohort, with 39 unique rearrangements. *EML4* was the most common *ALK* rearrangement partner, with variant 3 (v3) as the most frequent variants (42.7%) of *EML4-ALK* fusion, accounting for 71.6% (96/134) of all the rearrangements in 87.3% (96/110) patients. For *EML4-ALK* positive patients after crizotinib treatment (n=96), survival analysis revealed that patients with *EML4-ALK* only displayed favorable PFS (10.0 vs 7.2 months, p=0.037) and OS (36.0 vs 20.0 months, p=0.037) than those combined with other fusions. *In vitro* data reported that variant v3 and

v5 was structurally stable and less sensitive to *ALK* inhibitors due to the lack of TAPE domain. In this study, patients harboring v3 and v5 displayed significantly inferior OS than those with other variants (31 vs 37.6 months, p=0.010). For all the *ALK*-rearranged patients (n=110), no significant difference was observed between the survival of *EML4-ALK* and non-*EML4-ALK* (PFS, 9.4 vs 14.5 months, p=0.61; OS, 35.1 vs 35.5 months, p=0.58), below and above 40-years (PFS, 7.3 vs 11.3 months, p=0.23; OS, 25.4 vs 35.5 months, p=0.69). **Conclusion:** This study demonstrated the distribution pattern of *ALK* rearrangements in Chinese NSCLCs, and illustrated the clinical outcomes of *ALK*-positive patients in different sub-groups. We hope this study could improve basic knowledge of *ALK* rearrangement and might be helpful for clinicians in choosing patients for appropriate medical treatment. Moreover, these findings advocate for more comprehensive *ALK* genomic profiling and validation of current results of clinical outcomes in large populations.

Keywords: ALK, crizotinib, NSCLC

P1.01 ADVANCED NSCLC
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P1.01-59 A BETTER REAL WORLD PRACTICE FOR ROS1 POSITIVE NSCLC PATIENTS, DRIVEN BY THE TARGETED NEXT GENERATION SEQUENCING(NGS) AND THE TARGETED TKI

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Background: Methodologically, Targeted NGS had been shown comparable to classical testing methods in testing sensitivity and specificity in several driver genetic aberrations. However, Data of standard TKI treatment outcome in NGS identified ROS1-positive NSCLC was rare, especially in TKI confirmatory clinical trials, thus it is practical and necessary to evaluate it in the real world. **Method:** We carried out a real word retrospective study in our center. From September 2015 to December 2017, NSCLC in-patients with targeted NGS testing (Burning Rock Dx; 8 genes or 56 genes panel) results were included in our study. Data of NGS multiple genes testing, crizotinib efficacy and potential clinical and genetic influential factors, and safety were analyzed. **Result:** 1104 NSCLC patients with targeted NGS testing (Burning Rock Dx; 8 genes or 56 genes panel) results were included in our study. All testing was based on tumor biopsy and adenocarcinoma is the domain histology. The occurrence rate of ROS1 rearrangement was 1.5 %(N=17). Seven phenotypes of ROS1 rearrangement were detected and the most common one was CD74-ROS1, which accounted for 45% (9 of 20). Furthermore, three patients were found carrying two different ROS1 rearrangements. 41% (7 of 17) patients were discovered with other concomitant mutations: including TP53 &PIK3CA mutation(n=1), TP53&CDKN2A mutation(n=1), TP53 & BRCA2 mutation(n=1), PIK3CA &ALK missense mutation (p.R311H) (n=1), MET amplification(n=1) ,TP53 mutation(n=1), ERBB2 mutation(n=1), Among all NSCLC patients with ROS1 rearrangement, 13 patients were diagnosed at stage IV and 12 patients received crizotinib treatment. The average follow-up period since crizotinib initiation was 12.7 months (range from 1.5 to 28 months). The ORR and DCR of crizotinib were 75% and 83% (9 PR, 1 SD and 2 NA) respectively. The median progression-free survival (mPFS) of crizotinib treatment was 14 months. Of influential factors analysis, it was shown that NSCLC patients with exclusive ROS1 rearrangement had a longer PFS than those carrying concomitant mutations (mPFS 15.5months vs 8.5months; p=0.0213) and there was no significance impact on PFS considering brain metastasis, crizotinib treatment lines or rearrangement subtypes. No grade 3 and 4 adverse events were observed in this retrospective study. **Conclusion:** Crizotinib is highly effective and tolerant in NGS identified ROS1 rearrangement advanced NSCLC in real-word clinical practice and the data is consistent with that in the previous clinical trials applying IHC/FISH/RT-PCR as ROS1 companion diagnosis. NSCLC patients with exclusive ROS1 rearrangement had better PFS under Crizotinib treatment compared to those with concomitant mutations.

Keywords: next-generation sequence, ros1 rearrangement, crizotinib

P1.01 ADVANCED NSCLC
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P1.01-60 PREVENTING AND TREATING BRAIN METASTASES WITH THREE FIRST-LINE EGFR-TKI IN PATIENTS WITH EGFR MUTATION ADVANCED NSCLC

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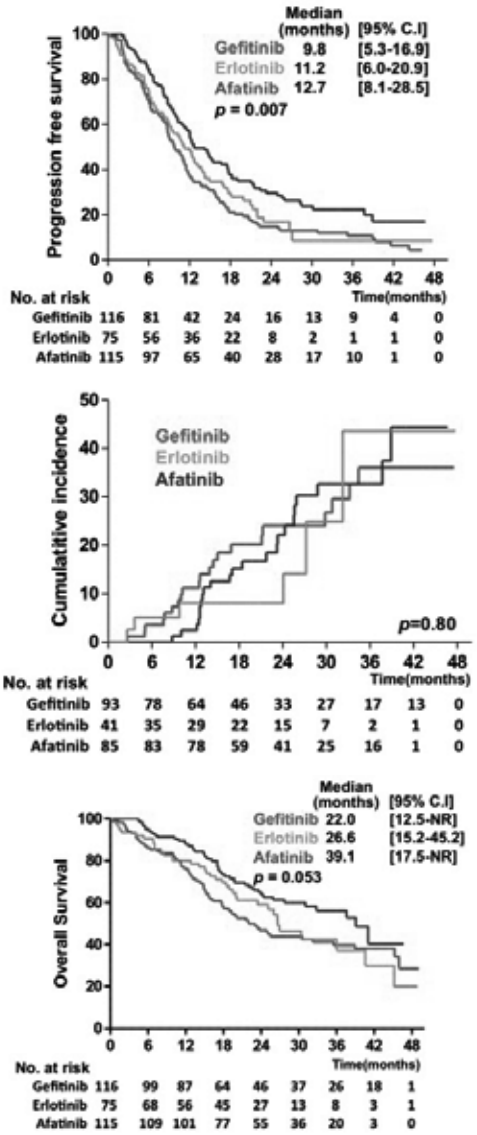
Background: Brain metastases (BM) are common in advanced non-small cell lung cancer (NSCLC), and the prognosis is poor with few therapeutic options. This retrospective study evaluated the efficacy of three epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) in preventing and treating BM in patients with EGFR mutation-positive advanced NSCLC. **Method:** All patients with EGFR mutation-positive advanced NSCLC who visited a tertiary referral center from December 1, 2013, to November 30, 2017, were analyzed retrospectively. These patients received gefitinib, erlotinib, or afatinib until disease progression, death, or intolerable adverse events. The cumulative incidence of subsequent BM and the progression-free survival (PFS) and overall survival (OS) of both the BM patients and non-BM patients were estimated by the Kaplan-Meier method and compared using the log-rank test. We performed Cox proportional hazards regression for the predictors of subsequent BM and determinants of PFS and OS. **Result:** A total of 306 patients with newly diagnosed or recurrent NSCLC were enrolled. Among these patients, 116, 75, and 115 received first-line gefitinib, erlotinib, and afatinib, respectively. The patients who received afatinib had a better PFS (12.7 versus 9.8 months, p=0.001) and OS (39.1 versus 22.0 months, p=0.035) than those who received gefitinib. The cumulative incidences of subsequent BM were similar among the patients who received different TKIs (p=0.80). Patients with initial BM were associated with a shorter PFS (p < 0.001) and OS (p=0.015) than those without BM. Among the initial BM patients, there were no differences in median PFS (p=0.34) and median OS (p=0.46) in the three EGFR-TKI groups.



Conclusion: Our data suggested afatinib provided significant benefits in terms of PFS and OS as well as preventing subsequent BM compared to gefitinib, in addition to providing the same effectiveness in treating BM as gefitinib

Keywords: Brain metastasis, tyrosine kinase inhibitor, EGFR mutation

P1.01-61 CLINICAL CHARACTERIZATION OF ERBB2 EXON 20 INSERTIONS AND HETEROGENEITY OF OUTCOMES TO AFATINIB IN CHINESE LUNG CANCERS

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Background: *Human epidermal growth factor 2* (*HER2, ERBB2*) gene alterations have been identified as oncogenic drivers in 2-5% of lung cancers. *ERBB2* In-frame insertions in exon 20 (20ins) lead to constitutive activation of receptor and downstream pathways. However, response heterogeneity of different exon 20 insertions to ERBB2 inhibitor afatinib exists. *In vitro* and structural modeling results suggested that Glycine778 may facilitate inhibitor binding to ERBB2. In this study, our aim was to improve our understanding of clinical characteristics in *ERBB2*-mutated Chinese lung cancer and investigate the clinical outcomes of specific *ERBB2* exon 20 insertions in response to afatinib. **Method:** We reviewed 7520 lung cancer patients whose tissue or plasma biopsies were sequenced in a CLIA-certified sequencing laboratory between 2015 to 2018. Clinical records of 19 patients (18 adenocarcinomas and 1 squamous cell carcinoma) with several different *ERBB2* 20ins after afatinib treatment were collected for clinical outcomes evaluation. **Result:** *ERBB2* 20ins were identified in 2.27% (171/7,520) in this Chinese lung cancer cohort. It occurred with a high proportion in females with adenocarcinoma histology. 11.7% (20/171) *ERBB2* 20ins-positive patients harbored concomitant *ERBB2* amplification. Y772_A775dup (119/171, 69.6%) was the most frequently occurred 20ins subtype, followed by G778_P780dup (18/171, 10.5%). For the 19 patients treated with afatinib, they had a median PFS of 4.5 months and median OS of 11.5 months. The overall response rate in this cohort was 15.8% (3/19) and disease control rate was 68.4% (13/19). Next, we interrogated the clinical outcomes of specific 20ins subtype responding to afatinib. We found that patients harboring G778_P780dup (G778) achieved longer median PFS (10 vs 3.3 months, p=0.32) and median OS (19.7 vs 7 months, p=0.16) than non-G778 patients, consisting with *in vitro* results. Although statistical significance was not achieved due to limited number of G778_P780dup patients, this result warranted further investigation into this phenomenon. Moreover, to the best of our knowledge, we identified the first case of a lung squamous cell carcinoma patient harboring *ERBB2* 20ins from this cohort. He displayed favorable response to afatinib and achieved partial response with significant tumor shrinkage. **Conclusion:** We interrogated the characteristics of *ERBB2* exon 20 insertions in a large cohort from single ethnicity. It demonstrated the response heterogeneity to afatinib among different *ERBB2* exon 20 insertion subtypes. It highlighted the importance to correlate drug efficacy with specific *ERBB2* exon 20 insertion variants in clinical application.

Keywords: ERBB2, afatinib, heterogeneity

P1.01-62 THE THIRD GENERATION IRREVERSIBLE EGFR INHIBITOR HS-10296 IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: The epidermal growth factor receptor (EGFR) T790M mutation is the most common mechanism of drug resistance to EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC) patients with sensitizing EGFR mutations. The third generation irreversible EGFR inhibitor HS-10296 has been shown to be safe and effective against both EGFR TKI-sensitizing and T790M resistance mutations in preclinical studies. **Method:** A Phase I, open-label, multi-center clinical trial was conducted in patients with locally advanced or distant metastatic NSCLC who have progressed following prior therapy with EGFR TKIs. The study was consisted of dose-escalation cohorts (55, 110, 220 and 260 mg) and dose-expansion cohorts (55, 110 and 220 mg) with once daily oral administration of HS-10296. In each expansion cohort, tumor biopsies were collected for central determination of EGFR T790M status. Patients were assessed for safety, tolerability, pharmacokinetics and efficacy of HS-10296. **Result:** A total of 117 patients (median age 60) received at least one dose of HS-10296 across multiple sites in China (43 patients), Taiwan (69 patients) and the United States (5 patients). Maximum tolerated dose (MTD) has not been reached in this study. The most common adverse events were grade1/2 rash, pyrexia, upper respiratory tract infection, constipation, diarrhoea and blood creatine phosphokinase elevation. Drug-related serious adverse events were anemia (0.8%), blood creatinine elevation (0.8%), anemiarhabdomyolysis (0.8%) and blood creatine phosphokinase elevation (0.8%) occurred mainly in the cohorts with higher doses at 220 mg or 260 mg, respectively. These data demonstrated favorable tolerability and safety of HS-10296 in patients enrolled. The pharmacokinetics of HS-10296 was dose proportional and the plasma half-life was 30.7~37.5 hours. Among 82 evaluable patients (18 in escalation cohorts and 64 in expansion cohorts) with the EGFR T790M mutation, the overall objective response rate (ORR) was 52.4% (43/82; 95% CI, 41.6 to 63.3), while disease control rate (DCR) was 91.5% (75/82; 95% CI, 85.4 to 97.5). 110mg cohort showed better DCR (97.2% VS. 86.1%) than 55mg cohort. Phase II study is ongoing with the dose at 110 mg. **Conclusion:** HS-10296 has the potential to provide clinical benefit to locally advanced or distant metastatic NSCLC patients with EGFR T790M mutation who had disease progression following prior therapy with EGFR TKIs. (The study was sponsored by Jiangsu Hansoh Pharmaceutical Co., Ltd.; ClinicalTrials.gov number, NCT02981108)

Keywords: T790M, epidermal growth factor receptor (EGFR), lung adenocarcinoma

P1.01-63 CORRELATION BETWEEN IMMUNE-RELATED ADVERSE EVENTS AND EFFICACY OF IMMUNE-CHECKPOINT INHIBITORS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Immune-checkpoint inhibitors (ICIs) are a standard treatment in advanced non-small cell lung cancer (NSCLC). However, ICIs can induce immune-related adverse events (irAEs) that may compromise treatment continuation. Here we report our experience in patients with NSCLC, the incidence of irAEs and its correlation with efficacy. **Method:** We have retrospectively analyzed 101 patients with advanced NSCLC receiving ICIs in our institution from March 2014 to January 2018. IrAEs were graded following CTCAE v4.0. Kaplan Meier and log-rank tests were used to evaluate progression-free (PFS) and overall survival (OS). Analyses were performed using SPSS v24 package. **Result:** Median age was 66.4 [37-85] years, 74.3% were male. 33 (32.7%) patients presented squamous and 68 (67.3%) non-squamous histology. Most frequent ICIs were nivolumab (50%), pembrolizumab (31%) and atezolizumab (16%), used as monotherapy (79.2%) or in combination with chemotherapy (20.8%). 37.6% patients were treated with ICIs in first line setting, while

62.4% in second or beyond. Median duration of treatment was 2.7 [0.6-26.2] months. 61 (60.4%) patients developed 106 irAEs, with a mean of 1.02 [0-4] irAEs per patient. Most frequent irAEs were rash (24.5%), pruritus (22.6%), diarrhea (21%), arthritis (8.5%), hypothyroidism (7.6%), hyperthyroidism (2.9%), hepatitis (2.9%) and pneumonitis (2%). 8 (7.5%) patients experienced grades (G) 3-4 irAEs: 1 G3 pneumonitis, 4 G3 diarrhea, 1 G3 mucositis, 1 G3 nephritis and 1 G3 hemolytic anemia. One treatment-related death due to pneumonitis was reported. Patients receiving ICIs in second line or beyond experienced significantly less irAEs (54.1%) than those treated in first line (73.7%), *p* 0.04. 47 (46.5%) patients received systemic corticosteroids during immunotherapy, 29.8% for irAEs management. 11 patients (10.9%) discontinued treatment due to irAEs. At the time of data analysis, 86.8% of irAEs had improved. With a median follow-up of 8.9 [0.6-48.2] months, median OS was superior in patients experiencing irAEs: not reached (NR) *vs* 7.8 [95%CI, 5.2-10.5] months (*p* 0.001). Similarly, PFS was significantly longer: 6.2 [95%CI, 2.3-10.1] *vs* 2.7 [95%CI, 1.8-3.5] months (*p* <0.0001). OS was higher in patients who did not receive steroids during ICIs therapy: NR *vs* 9.9 [95%CI, 6.8-13.0] months (*p* 0.024). No association was found between efficacy and the use of antibiotics in the 3 months before first ICIs injection or during treatment. **Conclusion:** In our series, the presence of irAEs in patients with advanced NSCLC treated with ICIs was associated with efficacy in terms of PFS and OS. A negative correlation between usage of systemic corticosteroids and outcomes was found.

Keywords: non-small cell lung cancer, immune-checkpoint inhibitors, immune-related adverse events

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P1.01-64 IMPACT OF STK11 CO-MUTATION ON OUTCOMES FOLLOWING IMMUNOTHERAPY AMONG PATIENTS WITH TP53 AND KRAS MUTATED STAGE IV NSCLC

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Background: Mutations in LKB1/*STK11* may predict a poor response to immunotherapy in NSCLC. We previously showed that pretreatment neutrophil-to-lymphocyte ratio (NLR) ≥5 predicted a poor response to immunotherapy in NSCLC. We evaluated the impact of *STK11* mutation (MT) alone, and co-existing MTs in *KRAS* and *TP53* on outcomes in patients (pts) treated with immunotherapy at the University of Pennsylvania. The role of NLR was also evaluated. **Method:** Patients with metastatic NSCLC that underwent NGS and who received 2nd-line immunotherapy were identified (2/2013 – 12/2016). Patient demographics, tumor characteristics, and outcomes were analyzed from the electronic medical record. Chi-square and the Wilcoxon Rank-Sum test were used to assess correlation between NLR and MT status. Median overall survival (mOS) and median progression free survival (mPFS) times are estimated from Kaplan-Meier curves. A Cox proportional hazard model (HR) was used to assess the effect of mutation status on survival outcomes. **Result:** 110 pts were included with the following MT status: 5 *STK11*, 16 *KRAS*, 29 *TP53*, 13 *KRAS/TP53*, 7 *KRAS/STK11*, 9 *TP53/STK11*, 7 *KRAS/TP53/STK11*, 24 no *STK11*, *KRAS* or *TP53* MT. In univariate and multivariable analyses, *STK11* MT was not independently associated with mPFS or mOS after immunotherapy. Among pts with *TP53* MT, the presence of a *STK11* MT was associated with improved mPFS (4.3 vs. 2 mo, HR 0.416, p=0 .035, (95% CI 0.18 –0.94)) and statistically similar mOS (13.1 vs 6.8 mo, HR 0.43, p=0.09 (95%CI 0.16–1.14)) compared with *STK11* wild type (WT). Conversely, among pts with *KRAS* MT, the presence of a *STK11* MT was associated with similar mPFS (2.2 vs 2.8 mo, HR 1.64, p=0.247 (95% CI 0.7–3.8)) and mOS (3.5 vs 7.7 mo, HR 2.3, p=0.09 (0.16–1.14)) compared with *STK11* WT. NLR did not correlate with MT status. After stratifying for NLR (<5 and ≥5), the effect of *STK11* MT on mOS in the *TP53* MT group was amplified in pts with NLR<5 (n=46, HR 0.05, p=0.021, 95% CI 0.004-0.63) compared to *TP53* MT with *STK11* WT (HR 4.3, p=0.036 (95% CI 1.1-16.9)). **Conclusion:** STK11 mutation status alone does not correlate with pre-treatment NLR and is not independently associated with survival outcomes after immunotherapy. PFS following immunotherapy is improved in patients with co-existing *TP53* and *STK11* MT compared to *STK11* WT. An OS benefit after immunotherapy is amplified in patients with NLR<5, *TP53* MT, and *STK11* co-MT. * Authors Marmarelis and Bange contributed equally

Keywords: Immunotherapy, STK11, TP53

P1.01 ADVANCED NSCLC
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P1.01-65 PII OF PEMETREXED OR PEMETREXED PLUS BEVACIZUMAB FOR PREVIOUSLY UNTREATED ELDERLY (>=75) NON-SQUAMOUS NSCLC (LOGIK1201)

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Background: Pemetrexed (P) provided equivalent or more efficacy to docetaxel with fewer side effects against NSqNSCLC and subset analysis revealed elderly patients receiving P had a longer time to progression and OS than those treated with docetaxel (JCO 22:1589, 2004). Bevacizumab (B), antibody binding with VEGF, is expected additional effect to chemotherapy for patients with NSqNSCLC. To evaluate the efficacy and safety, we conducted randomized phase II study of P and P/B for elderly patients with NSqNSCLC. **Method:** Eligibility criterias were: NSqNSCLC, no prior therapy, stage IIIB, IV, postoperative recurrence, age ≥75 years, PS 0-1, adequate bone marrow function. Patients were randomly assigned in a 1:1 ratio to P or P/B. Primary endpoint was PFS. Secondary were RR, OS, toxicity and cost-effect. Stratified log-rank test was used. Assuming PFS of median 3.3 (P) and 7.4 (P/B) months, significance level bilateral 20%, power ≥80%, estimated required number was 32 and target sample size was set 40. **Result:** *Forty-one patients from 12 institutions were enrolled between 8/31/2012 and 6/30/2016 and 40 patients (P 20, P/B 20) were assessable. Patients' characteristics were as follows: male/female = 23/17; median age (range) = 78 (75-83); stage IIIB/IV/postOp = 1/30/9; PS 0/1 = 11/29; all adenocarcinoma. The median PFSs (95%CI) were 5.4 (3.0-7.4) and 5.5 (3.6-9.9) months, respectively, and there is no significant difference (p=0.66). RR was significantly higher in P/B (15% vs. 55%, p=0.0146) and there was no significant difference in OS (median 16.0 vs. 16.4 months, p=0.58). G3/4 leukopenia, neutropenia, thrombocytopenia and fatigue (%) were 10, 20, 5, 25 and 30, 55, 5, 45, respectively. Costs were higher in P/B (median 1,522,008 vs. 3,368,428 JPY, p=0.01). No treatment-related deaths occurred.* **Conclusion:** P showed similar PFS and OS with favorable toxicity and low cost compare with P/B in elderly (>=75) patients with NSqNSCLC.

Keywords: elderly NSqNSCLC, randomized phase II study, pemetrexed and bevacizumab

P1.01 ADVANCED NSCLC
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P1.01-66 RANDOMIZED PHASE II EVALUATING EGFR-TKI ASSOCIATED WITH ANTI-ESTROGEN IN WOMEN WITH NON-SQUAMOUS ADVANCED STAGE NSCLC: IFCT-1003 LADIE TRIAL.

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Background: The incidence of lung cancer is increasing dramatically in women with recent findings as the preferential involvement of the EGFR pathway and the potential impact of hormonal factors in women. Preclinical data have shown that the combination of an EGFR-TKI with

an anti-estrogen could overcome resistance to EGFR-TKI. **Method:** IFCT-1003 LADIE Trial was a 2x2 arms parallel open-label randomized phase II trial. PS 0-2 post-menopausal women with advanced stage lung adenocarcinoma were treated with gefitinib (G 250 mg/day) vs. G + fulvestrant 500 mg / month with a supplementary dose at day 15 (G+F) in the EGFR mutated group (EGFR+) in 1st or 2nd line setting or with erlotinib (E 150 mg/day) vs. E + fulvestrant (E+F) in the EGFR wild-type group (EGFR WT) in 2nd or 3rd line setting until progression or unacceptable toxicity. Primary objective was progression-free survival (PFS) at 3 and 9 months for EGFR WT and EGFR+ patients, respectively. **Result:** From 02/2012 to 03/2017, 204 pts (G 104, G+F 100) and 175 (E 87, E+F 88) were enrolled in the EGFR+ and EGFR WT cohorts respectively. The median number of fulvestrant injections was 10 in the G+F group and 3 in the E+F group. The tolerance was correct (grade 3/4: 24.2% in the G+F group *vs* 21.3% in the G group, 16.0% in the E+F group *vs* 13.8% in the E group) and no treatment-related death. In the EGFR+ cohort, the primary endpoint was reached as 54 pts in the G+F group were non-progressive at 9 months. Nevertheless, addition of F to G was not associated with significant better PFS (9.9 *vs* 10.1 months) or OS (22.1 *vs* 29.9 months). In the EGFR WT cohort, the primary endpoint was not reached as 29 patients were non-progressive at 3 months. Here also, addition of F to E was not associated with better outcome (PFS 1.8 *vs* 2.0 and OS 10.0 *vs* 7.3 months). No PFS difference was observed in the subgroup of patients with positive staining for REα. **Conclusion:** Addition of fulvestrant to EGFR-TKI is feasible and is associated with good PFS in the EGFR mutated group. Nevertheless, the lack of benefit associated with the combination of fulvestrant to EGFR-TKI does not support its future development in a phase 3 trial in women with NSCLC.

Keywords: fulvestrant, EGFR-TKI, NSCLC

P1.01 ADVANCED NSCLC
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P1.01-67 CLINICAL RELEVANCE OF ALK/ROS1 RESISTANCE MUTATIONS AND OTHER ACQUIRED MUTATIONS DETECTED BY LIQUID BIOPSY IN ADVANCED NSCLC PATIENTS

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Background: Liquid biopsies (LB) for circulating tumor DNA (ctDNA) can be a tool for somatic mutation detectionin NSCLC patients. However, the applicability and clinical relevance of *ALK*/*ROS1* and other acquired mutation detected by LB is poorly described. We evaluated *ALK*/*ROS1* and other acquired mutations detected by *ctDNA* in a large cohort of *ALK*/*ROS1*+ NSCLC patients described to date. **Method:** Advanced *ALK*/*ROS1*+ NSCLC patients were prospectively enrolled from October 15 to April 2018 in 9 French institutions. ctDNA anlaysis was performed using ctDNA using InVisionFirst™ (36-gene panel) for *ALK* (*EML4* variants v1, v2, v3), *ROS1* (*CD74, SLC34A2, SDC4 and EZR)* fusions, and other somatic mutations. **Result:** 120 patients were included: 96 *ALK*, 24 *ROS1*. The median prior tyrosine kinase inhibitors (TKI) received was 2 (0-4). Blood samples (n=402) were collected: tyrosine kinase inhibitors (TKI)-naive (n=30), during (n=257) or at progression (PD) under TKI (n=73. Prior treated patients received at least 1 TKI (1-6). Preliminary results are available for the first 54 patients; *ALK/ROS1* status was confirmed by *ALK* IHC (39), FISH (56) and RNAseq (2). *ALK* mutations were detected in 36% of blood samples at PD to TKI (12/33): 8% (1/13) post-crizotinib and 55% (11/20) post next-generation TKI *(F1174/F1174V/D1203N/R1192P/G1202R (6)/F1174L+G1202/G1202R+F1174L+C1156Y)*. Complex *ALK* mutations were observed in 2/12 samples (17%) post next-generation TKI (*G1202R+F1174L+C1156Y/F1174L+G1202R*). Other *acquired* mutations were found in 36% (12/33) of samples at PD: *TP53* (10), *NFE2L2* (4), *PTEN* (2), *PI3KCA* (1), *CDKN2A* (1). Complex *ALK* mut.+ *non-ALK* mut. were found in 6/33 (18%) samples, 1 post crizotinib (*G1269A+R1264K+L1196Q+F1164L+C1156Y+NFE2L2(4)*), and 5 samples post next-gen TKI *(G1202R+PTEN/G1202R+TP53/F1174L+G1202R+TP53/TP53(2)+D1203N/TP53+R1192P)*. Non-*ALK* mut. were exclusive and could explain TKI resistance in 6/33 (18%) samples. **Conclusion:** Routine liquid biopsies can assess the heterogeneity of the TKI resistance, detecting *ALK* resistance and other acquired mutations in pretreated advanced *ALK & ROS1* NSCLC patients. This could have an impact on clinical outcomes. The association of *ALK* mut. and complex *ALK* mut. +/- other acquired mut. with clinical outcomes will be presented at the congress.

Keywords: Liquid biopsy, ALK, ROS1, resistance, mutation

P1.01 ADVANCED NSCLC
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P1.01-68 CORRELATION OF THE LUNG IMMUNE PROGNOSTIC INDEX (LIPI) AND PDL1 STATUS WITH OUTCOMES FOR IMMUNE CHECKPOINT INHIBITORS IN ADVANCED NSCLC PATIENTS

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Background: Baseline LIPI, based on derived NLR (neutrophils/[leucocytes-neutrophils]) and lactate dehydrogenase (LDH) was associated with outcomes for immune checkpoint inhibitors in advanced NSCLC patients. We assessed the correlation between LIPI and PDL1 for ICI outcomes in NSCLC. **Method:** Baseline dNLR and LDH and clinical data were retrospectively collected in advanced NSCLC patients, treated with PD1/PDL1 +/- CTLA4 inhibitors from Nov. 2012 to Mar. 2018, in a multicentric cohort (N=794) from 11 centers. LIPI stratified 3 groups: good (dNLR<3+LDH<upper limit of normal (ULN), intermediate (dNLR>3 or LDH>ULN), poor risk (dNLR>3+LDH>ULN). PDL1 positivity was defined as ≥ 1% tumor cells expression by immunohistochemistry. **Result:** 476 patients (60%) were male, 693 (87%) smokers, 695 (88%) had PS ≤1, with median age 65; 576 (73%) had *non*squamous histology. PDL1 was ≥ 1% in 195 (70%) patients, negative in 82 (30%), and unknown in 517. The median of prior lines was 1 (0-11). The median PFS and OS were 4 months (m) [95% CI 4-5] and 12 m [10-15]. dNLR was>3 in 276 (35%) and LDH>ULN in 290 (37%) patients. LIPI stratified 349 patients as good (44%), 323 (41%) as intermediate and 121 (15%) as poor LIPI risk groups. LIPI was an independent factor for OS (table) and PFS (HR 2.58; CI 1.3-5.2, *P*=0.02). ≥ 1% PDL1 and ≥ 50% PDL1 were not correlated with OS and PFS. Median OS for good, intermediate, and poor LIPI risk groups were 21 m [17-23], 11 m [9-14] and 4 m [2-6], respectively (*P*=<0.0001). Median PFS for good, intermediate, and poor risk was 5 m [5-7], 4 m [3-5], and 2 m [1-3], respectively (*P*=0.0005). No differences were observed in LIPI groups according to the PDL1 expression.

Multivariate analysis for OS	HR	95% CI		P value
Immunotherapy line >2	2.117	0.641	6.992	0.219
N# Metastasis sites ≥2	1.242	0.727	2.121	0.428
Performance status ≥2	2.141	1.059	4.332	0.034
Albumin >35 g/dL	0.867	0.507	1.48	0.6
LIPI Intermediate Poor	1.697 4.178	0.917 1.956	3.142 8.925	0.001
PDL1 IHC ≥1%	0.713	0.406	1.252	0.239

Conclusion: Baseline LIPI is associated with ICI outcomes in advanced NSCLC, regardless the PDL1 expression. LIPI should be evaluated in prospective clinical trials.

P1.01 ADVANCED NSCLC
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P1.01-69 VALIDATION OF THE LUNG IMMUNE PROGNOSTIC INDEX (LIPI): USEFUL TO IDENTIFY RESISTANCE TO PD-1 CHECKPOINT INHIBITORS IN PRETREATED LUNG CANCER

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Background: Derived neutrophils/(leukocytes-neutrophils) ratio (dNLR) and lactate dehydrogenase (LDH) level have been correlated with immune checkpoint inhibitors´ (ICI) outcomes. A lung immune prognostic index (LIPI) that showed association with ICI outcomes was developed by Mezquita L et al. based on these 2 systemic inflammation indicators (dNLR <3 and LDH > upper limit of normal (ULN)), characterizing 3 prognostic groups: good, 0 factors; intermediate, 1 factor; poor, 2 factors. **Method:** This is a multicenter retrospective study with the aim to validate prognostic value of LIPI score in pretreated advanced-stage non-small-cell lung cancer (NSCLC) treated with ICI. We included consecutive patients treated with nivolumab or pembrolizumab between March 2015 and April 2018 from 7 medical centers in Spain. Investigators at each institution retrospectively reviewed patients´medical records. Pretreatment LIPI score was calculated for all subjects and the primary endpoint was correlation with OS. **Result:** A total of 168 patients were included. Median age 65 years (39-85). 134(79,8%) were male and 121 (72%) were PS≦1. Predominant histologies were adenocarcinoma (50%), and squamous-cell carcinoma (42,9%). 92,3% were treated with nivolumab and 7,7% with pembrolizumab. Median number of prior lines was 1 (1-5). Median number of cycles: 11 (1-68). Most were current or former smokers (94,6%). Only 2,3% had EGFR mutations, and 0,6% ALK rearrangement. PD-L1 immunohistochemistry was only available in 25% of patients (<1%: 36,6%; 1-49%: 39%; >=50%: 24,4%). After calculating LIPI score, 56,4% were LIPI 0 (good prognosis), 38,5% LIPI 1 (intermediate prognosis), and 5,1% LIPI 2 (poor prognosis). Response rate (RR) was 30,4% and disease control rate (DCR) 52%. The median PFS and OS were 5,6 months (m) (3,9-7,3) and 11,4 m (9,4-13,5). Median OS for good, intermediate, and poor was 14m (95% CI, 11,2-16,7), 6,3m (95% CI, 0,6-12) and 1,8m (95% CI, 0-4,3), respectively (p=0,0001). LIPI showed correlation with OS in patients with known PD-L1 status and also in those with no information about it. PFS was also correlated (p=0,004) with LIPI score. A LIPI score of 2 was independently associated with poorer OS (HR 4,9; 95% CI, 2,18-11,1). **Conclusion:** Our results support the prognostic value of pretreatment LIPI score. dNLR >3 and LDH greater than ULN was correlated with worse outcomes for ICI, regardless of the knowledge of PD-L1 status. This is a useful tool, based on clinical criteria, that can help us in daily practice to identify which patients benefit from ICI.

Keywords: NSCLC, immune checkpoint inhibitors, LIPI, biomarkers

P1.01 ADVANCED NSCLC
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P1.01-70 EFFICACY AND SAFETY OF SECOND- OR THIRD-LINE NAB-PACLITAXEL + DURVALUMAB IN PATIENTS WITH ADVANCED NSCLC (ABOUND.2L+)

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Background: Cytotoxic chemotherapy may enhance the effect of immune checkpoint blockers (ICBs) through interaction with the immune system (immunostimulation) and cancer cells (increased antigenicity). The phase II ABOUND.2L+ trial investigated second-/third-line *nab*-paclitaxel monotherapy, *nab*-paclitaxel + CC-486, or *nab*-paclitaxel + durvalumab in patients with previously treated advanced-stage NSCLC. This report presents an updated analysis of the efficacy and safety from the *nab*-paclitaxel + durvalumab treatment arm. **Method:** Patients ≥ 18 years with advanced NSCLC and no more than 1 prior line of platinum-containing chemotherapy (ICBs in prior line, first/second, allowed) were included. Patients were treated with *nab*-paclitaxel on days 1 and 8 + durvalumab 1125 mg on day 15 of a 21-day cycle until unacceptable toxicity or progressive disease as per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 or immune-related RECIST v1.1. The primary endpoint was progression-free survival (PFS). Key secondary endpoints included overall response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. **Result:** A total of 79 patients were assigned to *nab*-paclitaxel + durvalumab. The median age of patients in that arm was 63.0 years; 68.4% were male, 97.5% were white, 77.2% had ECOG performance status 1, and 69.6% had nonsquamous histology; 8 patients received prior ICBs. Median and 1-year PFS were 4.5 months (95% CI: 3.45-5.88) and 25.7% (95% CI 16.3-36.2); median PFS in those with and without prior ICB treatment was NE (95% CI 1.38-NE) and 4.4 months (95% CI 2.96-5.68) and in those with squamous and nonsquamous histology was 6.0 months (95% CI 2.99-7.75) and 4.2 months (95% CI 2.86-5.75). The ORR was 27.8%, and DCR was 70.9%. Median OS was 10.1 months (95% CI: 7.75-NE). Median percentage of per protocol dose was 87.5% for *nab*-paclitaxel and 82.9% for durvalumab. All patients had at least 1 treatment-emergent adverse event (TEAE), and 67.9% had at least 1 grade 3 or 4 TEAE. Common TEAEs of special interest (all grades) included peripheral neuropathy (grouped term; 37.2%), diarrhea (34.6%), anemia (30.8%), dyspnea (25.6%), nausea (24.4%), cough (24.4%), pyrexia (19.2%), and neutropenia (17.9%). TEAEs leading to dose interruption/reduction (*nab*-paclitaxel and/or durvalumab) were reported in 73.1% of patients, and those leading to discontinuation in 11.5%. **Conclusion:** *nab*-Paclitaxel + durvalumab demonstrated promising antitumor activity and manageable toxicity in second- or third-line treatment of patients with advanced NSCLC. NCT02250326.

Keywords: nab-paclitaxel, survival, durvalumab

P1.01 ADVANCED NSCLC
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P1.01-71 CO-MUTATIONS, NATURAL HISTORY, AND OUTCOMES OF BRAF-MUTATED NON-SMALL CELL LUNG CANCER AT A SINGLE ACADEMIC CANCER CENTER

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Background: Mutations in the *BRAF* oncogene occur in 2-4% of cases of non-small cell lung cancer (NSCLC). Based on recent trials, combination therapy targeting BRAF and MEK within the MAPK pathway is now approved for *BRAF* V600E-mutated NSCLC. As *BRAF* mutations occur infrequently, however, the natural disease history of *BRAF*-mutated NSCLC remains an area of ongoing study. Our aim was to describe the natural history and outcomes of patients with *BRAF*-mutated NSCLC seen at our institution. **Method:** An IRB-approved protocol was used to query the Stanford Cancer Registry and Stanford Cancer Institute Research Database (SCIRDB) for patients with *BRAF*-mutated NSCLC presenting between January 1, 2006 and July 31, 2015. Each patient chart was then retrospectively reviewed. **Result:** The cohort included 18 patients (median age 66.5 years, 72% male). V600E mutations were most common (72%; 13/18) while non-V600E mutations included G469A (n = 2), G466V, K601E, and V600_W604delinsR. Most patients (69%; 9/13) with V600E mutations were light or never smokers whereas most patients with non-V600E mutations (80%; 4/5) were heavy smokers (>15 pack-years). Secondary mutations occurred most commonly in *TP53* (28%; 5/18). With respect to treatment, no patients received BRAF-targeted therapy upfront. Median duration of first-line platinum-based chemotherapy was 9 months (range 1.5-21.5). In the second-line setting, median duration of chemotherapy was 6 months (range 1-52) and median duration of BRAF-targeted therapy was 5.5 months (range 5.5-6.5). Median overall survival of the entire cohort was 34.8 months. Median survival from the onset of metastases (n = 16) was 26.8 months (range

2-130.5) (Table). Among patients diagnosed with stage III-IV disease, survival at 2-years was 53%, with many showing slow progression and control of oligometastatic or intrathoracic disease with systemic therapy or localized radiation.

	Stage	BRAF Mutation	Co-occurring Mutations	Overall Survival (months)	Post-Metastases Survival (months)
1	IA	V600E	None	83.5+	39.5+
2	IIIB	V600E	None	8.5	7
3	IV	G469A	None	37	37
4	IIIB	V600E	None	40+	26.5+
5	IIIA	G469A	TP53	41	27
6	IV	V600E	None	14	14
7	IV	V600E	None	130.5	130.5
8	IIA	V600E	None	65	NA
9	IV	V600E	CTNNB1	2	2
10	IV	V600E	PIK3CA	47.5	47.5
11	IIIA	G466V	Multiple (incl. TP53)	39.5	32.5
12	IA	V600E	TP53	32.5+	NA
13	IV	V600_W604	None	22.5	22.5
14	IV	V600E	None	28	28
15	IV	V600E	Multiple (incl. TP53)	13.5	13.5
16	IV	V600E	None	88.5	88.5
17	IV	K601E	TP53	6.5	6.5
18	IV	V600E	NKX2-1	19.5	19.5

Conclusion: *BRAF*-mutated NSCLC can be associated with prolonged survival in some patients. Future research should aim to identify factors predicting longer outcomes.

Keywords: non-small cell lung cancer, BRAF, outcomesP1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-72 FIND TRIAL: A PHASE II STUDY TO EVALUATE THE EFFICACY OF THE FGFR-INHIBITOR ERDAFITINIB IN FGFR-MUTATED AND -TRANSLOCATED SQUAMOUS NSCLC

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Background: Genomic FGFR alterations and their oncogenic driver potential are frequently observed in various cancers, including NSCLC, bladder cancer, glioblastoma, sarcoma and head and neck cancer. Initial clinical trials with selective FGFR inhibitors showed moderate responses in FGFR amplified squamous NSCLC (sqNSCLC) patients. However, in FGFR mutated or translocated tumor types (bladder cancer, glioblastoma, endometrial cancer) a response rate of above 30% was observed. Preclinical cell line and patient-derived sqNSCLC xenograft models with FGFR mutations or translocations indicate strong oncogenic activity and potential sensitivity to FGFR inhibitors. Thus, FGFR directed treatment in FGFR mutated and translocated sqNSCLC is of special interest. In particular as there is no approved targeted treatment in the squamous population representing about 25% of all NSCLC patients. Study challenges: Multiple FGFR translocations and mutations are known and approximately 3% of all sqNSCLC patients harbor somatic alterations within FGFR genes. However, only some of these mutations are shown to be oncogenic drivers in vitro and in vivo experiments or first in man trials. This is important given the many FGFR alterations with unknown biological significance and which confer potential resistance to FGFR inhibitors. **Method:** Screening for FGFR mutations/translocations will be performed within the national Network of Genomic Medicine (nNGM) in 15 screening centers in Germany. SqNSCLC patients with activating FGFR genetic alterations will be treated in 11 clinical centers in Germany with the selective FGFR1-4 kinase inhibitor erdafitinib. Archival samples, fresh frozen tumor samples and blood for circulating tumor DNA (ctDNA) will be collected before treatment. Patients will be treated until disease progression or unacceptable toxicity. At progression, fresh frozen tumor biopsies and ctDNA analyses will be performed to characterize resistance mechanisms. The primary objective of the trial is to analyze the efficacy of erdafitinib in sqNSCLC patients with FGFR genetic driver alterations. NSCLC patient number will be based on a statistical hypothesis aiming at increasing the response rate compared to chemotherapy / immunotherapy after standard treatment. The estimated number of patients is based on a 2-stage Simon design. Patients will be recruited into 3 cohorts: Cohort 1: high confidence activating FGFR translocations (max. 15 patients); Cohort 2: high confidence activating FGFR mutations (max. 15 patients); Cohort 3: low confidence activating FGFR alteration (ca. 20 patients) **Result:** Section not applicable **Conclusion:** The study is under development and is currently targeted to start recruitment in Q2/2018.

Keywords: FGFR mutations/translocations, advanced sqNSCLC

P1.01 ADVANCED NSCLC
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P1.01-73 PRELIMINARY RESULTS OF THE SENECA (SECOND LINE NINTEDANIB IN NON-SMALL CELL LUNG CANCER) TRIAL: AN ITALIAN EXPERIENCE.

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Background: Nintedanib is a multi-target small-molecule with anti-angiogenetic activity which confers longer progression free survival (PFS) and overall survival (OS) as second-line combination treatment with docetaxel versus standard-of-care, in non-squamous non-small cell lung cancer (nsNSCLC) patients, giving to rapidly progressing patients the greatest survival benefit. Considering the higher tolerability of weekly docetaxel than docetaxel q3wks in the real-life, the SENECA trial, a phase IIb, open label, Italian multicentre study, aims to evaluate whether treatment with nintedanib and docetaxel could be effective and safe as second-line option in nsNSCLC patients with the two different schedules. **Method:** Patients from eighteen Italian oncologic centres, with stage IIIB/IV non-oncogene addicted nsNSCLC patients, progressing after first-line chemotherapy, have been treated with docetaxel (T1: 33 mg/mq on days 1 and 8 in a 21-days cycle; T2: 75 mg/mq q3wks) plus continuous oral nintedanib, with the possibility of maintenance in case of stabilization or response. Primary endpoint was PFS (by investigator's assessment), while secondary endpoints included OS, safety and quality-of-life. Study stratifies patients into two cohorts according to relapse-timing (within or over 3 months) from end of first-line chemotherapy. **Result:** From January 2016 to data cut-off, on 30th March 2018, 197 patients have been evaluated: 30 were registered as screening failures, mainly for contraindications to nintedanib use. The 167 patients considered in this preliminary analysis had a median age of 63.4 years (range 35-86), were predominantly male (68.9%), smokers or former-smokers (84.4%) and with ECOG-performance status 0 (72.5%). According to investigator's choice, 82 patients have been treated with T1 docetaxel (49.1%), 85 (50.9%) with T2 docetaxel (median docetaxel treatment 3.5 and 3.7 21-days cycles, respectively). No significant differences in median PFS have been observed between T1 and T2 (3.83 vs 4.32 months, respectively; HR 0.889 [95% IC 0.598-1.321], p-value=0.559). After a median follow-up of 7.28 months (standard deviation=5.55), a trend of similar OS has emerged in both T1 and T2 (6.63 vs 7.91 months, respectively; HR

0.770 [95% IC 0.484-1.225], p-value=0.270). Survival data of relapse-timing cohorts are not yet mature. Commonest toxicities in T1 and T2 were: fatigue (53.6% vs 65.9%, respectively), diarrhea (50.0% vs 47.0%), afebrile neutropenia (13.4% vs 52.9%) and ALT elevation (29.3% vs 20.0%). **Conclusion:** The SENECA trial is a real-life Italian experience, whose preliminary results confirm the efficacy and safety of second-line treatment with nintedanib and docetaxel for nsNSCLC patients, regardless from docetaxel schedule, suggesting higher toxicities for docetaxel q3wks.

Keywords: nintedanib, docetaxel, non-small cell lung cancer

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-74 MET EXON 14-ALTERED LUNG CANCERS: CENTRAL NERVOUS SYSTEM (CNS) METASTASES AND PATTERNS OF CNS PROGRESSION ON MET INHIBITION.

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Background: *MET* exon 14 (*MET*ex14) alterations are targetable drivers found in 3-4% of lung cancers. The frequency of intracranial disease and patterns of central nervous system (CNS) progression on MET tyrosine kinase inhibitors (TKI) are not well characterized. **Method:** Patients with advanced *MET*ex14-altered lung cancers identified by next-generation sequencing (MSK-IMPACT) between January 2014 and March 2018 were eligible for analysis. A retrospective review of clinical features, patterns of metastases, and CNS progression on MET-TKI was performed. The frequency of intracranial disease was compared to cohorts single-center of *EGFR*-mutant (n=200), *ERBB2*-mutant (n=98) and *KRAS*-mutant (n=200) lung cancers. **Result:** 82 patients with metastatic *MET*ex14-altered lung cancers were identified. The median age was 73; 56% (n=46) were female and 54% (n=44) were former smokers. The frequency of brain metastases at baseline was 11% (n=9/82). The lifetime frequency of intracranial metastases from diagnosis of metastatic disease was 34% (n=28/82). By comparison, the frequency of brain metastases was 47% (94/200, p=0.05) with *EGFR*-, 47% (46/98), p=0.09) with *ERBB2*-, and 32% (64/200, p=0.78) with *KRAS*-driven tumors. 6% (n=5/82) of patients developed leptomeningeal disease. The overall survival (OS) of patients who developed intracranial disease on therapy compared to those who did not develop intracranial disease was not significantly different (HR 0.66, 95% CI 0.30-1.43, p=0.29). 51 patients received crizotinib, 26 of whom developed progressive disease. The frequency of intracranial (alone), intracranial and extracranial, and extracranial (alone) progression was 8% (2/26), 19% (5/26), and 73% (19/26), respectively. **Conclusion:** A third of patients with *MET*ex14-altered lung cancers develop intracranial disease. This proportion is lower than that seen in *EGFR*- and *ERBB2*-mutant lung cancers and comparable to *KRAS*-mutant lung cancers. The frequency of CNS failure on crizotinib was lower than expected compared to historical rates in *ALK*-rearranged lung cancers.

Keywords: MET exon 14 rearranged lung cancer, MET inhibitors, brain metastases

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-75 UTILITY OF CFDNA TESTING FOR ACQUIRED RESISTANCE: THE MEMORIAL SLOAN KETTERING EXPERIENCE WITH PLASMA EGFR T790M CLINICAL TESTING.

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Background: Liquid biopsy for circulating tumor DNA (ctDNA) has been increasingly adopted for the detection of oncogenic drivers and drug resistance mechanisms. Practice guidelines for liquid biopsy are lacking and biologic factors influencing ctDNA detection and shedding are poorly understood. We evaluated factors influencing ctDNA detection, using *EGFR*-T790M as a case-study, in patients with acquired resistance to first/second-generation EGFR tyrosine kinase inhibitors (EGFR-TKI). **Method:** This single-center study included metastatic sensitizing *EGFR*-mutant lung cancer patients (exon 19 deletions, L858R, G719) who underwent plasma *EGFR*-T790M testing after acquired resistance to erlotinib, gefitinib, or afatinib between January 2016 and August 2017. Plasma T790M was performed by digital PCR. Variant allele fraction (VAF) was calculated as mutant/(wildtype+mutant) allele. Concordance between plasma and tissue testing was examined if tissue analysis (MSK-IMPACT and/or targeted PCR) occurred within 90 days of blood draw. Turnaround time (TAT) was measured from date of blood draw and/or biopsy to result. ctDNA results were correlated with metastatic site and the number of organs involved. **Result:** 177 patients underwent plasma T790M testing; 65% female, 47% current/former smokers. Plasma T790M was positive in 32% (56/177) of patients, tissue testing was T790M-positive in 46% (45/97), and overall T790M-positivity by either platform was 49% (86/177). The median TAT was shorter for plasma T790M compared to tissue PCR (9 vs 15 days, p<0.0001), and led to osimertinib use in 84% (47/56) of positive patients. Concordance between plasma and tissue T790M was 80% (32/40). 15 patients with positive plasma had matched tissue, 87% (13/15) were concordant on tissue. 76% (19/25) of the patients that were T790M-negative on plasma also tested negative on tissue. Median plasma T790M-VAF was 0.98% (range 0.1–49.5%), lower than tissue T790M-VAF (12.8%, range 2.58–27.8, p<0.0001). Plasma T790M-VAF did not correlate with time on osimertinib (p=0.72). Plasma T790M status correlated with a higher number of metastatic sites (4 vs 3, p<0.0001). Plasma T790M detection by organ sites were: pleura (58% with metastases vs 34% without metastases, p=0.14), bone (80% vs 21%, p=0.0002), hepatic (61% vs 41%, p=0.28), nodal (61% vs 33%, p=0.07), adrenal (64% vs 44%, p=0.60), brain (71% vs 38%, p=0.08), and bone/hepatic concurrently (94% vs 98%, p=0.04). **Conclusion:** Using plasma T790M as an archetypal example, cfDNA testing showed concordance and a shorter turnaround compared to tissue testing. cfDNA was more likely to result positive in patients with more metastatic sites, or osseous and hepatic metastases possibly driven by increased ctDNA shedding.

Keywords: Acquired resistance, circulating free DNA (cfDNA), next generation sequencing

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-76 A PHASE II TRIAL OF ALBUMIN-BOUND PACLITAXEL AND GEMCITABINE IN PATIENTS WITH NEWLY DIAGNOSED STAGE IV SQUAMOUS CELL LUNG CANCERS

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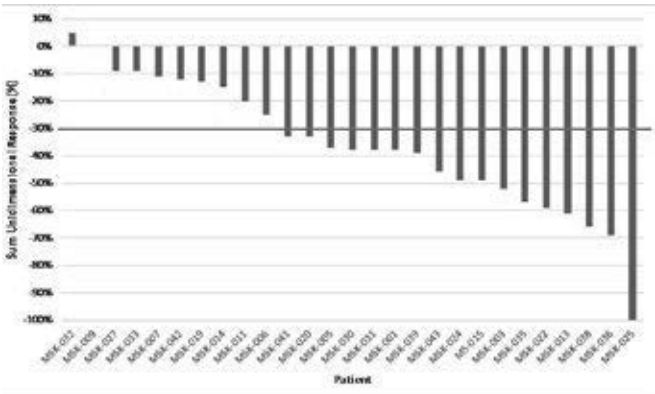
Background: Therapeutic options for SQCLC patients are limited. The efficacy of platinum-based doublets, long the standard first-line treatments, has plateaued, with ORR=30%. Anti-tumor synergy between gemcitabine and albumin-bound paclitaxel (ABP) was demonstrated by Frese et al. who showed that ABP downregulates cytidine deaminase, leading to increased intratumoral gemcitabine (Cancer Disc 2012). Based on these data, we sought to assess the efficacy of ABP + gemcitabine in patients with SQCLC. **Method:** This was a Simon two-stage phase 2 study of ABP + gemcitabine in chemotherapy-naïve, PD-L1 low/unknown advanced SQCLC patients (NCT02525653). Primary endpoint: best ORR. H0=25% (≥6/17 responses) and HA=45% (≥16/41 responses). ABP (100mg/m^2) + gemcitabine (1000mg/m^2) was initially given on D1, D8, D15 of an every 4 week cycle for up to 6 cycles (A1). After clearing H0, the study was amended to a 3 week cycle (D1, D8 treatment) and to allow maintenance ABP after C4 (A2). All patients underwent NGS by MSK-IMPACT. **Result:** N=27 patients were evaluable for the primary endpoint. Median age=70, age ≥70=60%, female=30%, median KPS=80%, smokers=93%. 46% of patients had PD-L1 IHC <50% (0-20%). 54% were PD-L1 unknown. Grade ≥3 related AEs included: fatigue-13%, neuropathy-4%; diarrhea-4%; lung infection-4%, anemia-9%; decreased platelet count-4%, and decreased neutrophils (4%). Four patients (17%) experienced related SAEs including, separately, G3 febrile neutropenia, G3 WBC decrease, G3 thrombocytopenia, and G3 anemia. ORR for the entire cohort was 63% (**Figure 1**). ORR in A2= 71% (10/14). 8 patients in A1 had dose modifications resulting in equivalency to the A2 schedule. ORR in the A2+A1 dose modified cohort=73% (16/22), meeting the primary endpoint early. Median PFS=8mo; OS not yet mature.

(See next page)



Conclusion: ABP + gemcitabine is an effective and well-tolerated regimen in patients with untreated advanced SQCLC with a response rate exceeding that associated with platinum regimens and first-line immunotherapy.

Keywords: nab-paclitaxel, Gemcitabine, squamous

P1.01 ADVANCED NSCLC
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P1.01-77 OSIMERTINIB IN THE FIRST-LINE TREATMENT OF NON-SMALL CELL LUNG CANCER HARBORING ACTIVATING EGFR MUTATION FROM CIRCULATING TUMOR DNA

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Background: Osimertinib is a potent, irreversible third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) for both EGFR activating and T790M resistant mutation. In this trial, the treatment efficacy of osimertinib was assessed in previously untreated patients with advanced or metastatic non-small cell lung carcinoma (NSCLC) harboring the EGFR activating mutation, which was detected from circulating tumor DNA (ctDNA) combined with tumor genotyping. **Method:** Venous blood sampling was performed from the patients with EGFR activating mutation confirmed by tissue genotyping. To extract ctDNA from the plasma, 15 mL of peripheral blood was withdrawn and centrifuged, immediately before storage. Cobas™ v2 and PANA Mutyper™ were used for ctDNA genotyping. Patients with the EGFR activating mutation, detected from ctDNA, were enrolled and received a once-daily administration of osimertinib, 80 mg. The primary endpoint was objective response rate (ORR), and secondary endpoints were ctDNA test sensitivity, progression-free survival (PFS), duration of response (DoR), and safety of osimertinib treatment (ClinicalTrials.gov, Identifier: NCT02769286). **Result:** Thirty-nine patients with activating EGFR mutations in tumor genotyping were screened from February 2017, and the enrollment of the last patient was completed in March 2018. The ctDNA of 29 patients was positive for activating EGFR mutation, and 19 patients were enrolled (exon 19 deletion, n=11; L858R or L861Q, n=7; G719A, n=1). Median age was 70 years (range 32-84) and the majority of patients had brain metastasis (15/19, 78.9%). In the response-evaluable population (n=17), ORR was 64.7% (11/17) and DCR was 94.1% (16/17). According to EGFR mutation type of tumor genotyping, patients with exon 19 deletion showed more favorable ORR (8/9, 88.9%) than patients with exon 21 L858R/L861Q (3/7, 42.9%). In patients evaluable for CNS response (n=14), DCR of brain metastasis was 100.0% (14/14). The sensitivity of the ctDNA tests for activating EGFR mutation was 74.4% when using both tests, and 61.5% (Mutyper) or 64.1% (Cobas V2) with either test. Only one patient experienced drug-related interstitial pneumonia of grades ≥3 and resulted in drug discontinuation. Survival data including PFS was not matured (2/19, 10.5%) and the analysis will be followed. **Conclusion:** Osimertinib had favorable efficacy in first-line treatment of NSCLC harboring the EGFR activating mutation, detected from ctDNA combined with tumor genotyping, even though in patients with old age and brain metastasis.

Keywords: osimertinib, ctDNA, non-small cell lung cancer

P1.01 ADVANCED NSCLC
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P1.01-78 THE INCIDENCE OF BRAIN METASTASES IN ROS1-REARRANGED NON-SMALL CELL LUNG CANCER AT DIAGNOSIS AND FOLLOWING PROGRESSION ON CRIZOTINIB

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Background: Central nervous system (CNS) metastases in lung cancer are a frequent cause of morbidity and mortality. There are conflicting data on the incidence of CNS metastases in ROS1+ NSCLC at diagnosis and rate of CNS progression on crizotinib. **Method:** Retrospective review of 579 patients with stage IV NSCLC between June 2008 to December 2017 was performed. We captured presence of brain metastases and oncogene status. We measured progression free survival (PFS) and time to CNS progression in ROS1+ and ALK+ patients on crizotinib. **Result:** We identified 33 ROS1+ and 115 ALK+ patients with advanced NSCLC. The incidence of brain metastases for treatment-naïve ROS1+ and ALK+ NSCLC was 36% (12/33) and 34% (39/115) respectively. There were no statistically significant differences in incidence of brain metastases across all oncogene sub-groups. Complete survival data was available for 19 ROS1+ and 83 ALK+ patients. Median PFS for the ROS1+ and ALK+ cohort was 11 and 8 months (p = 0.304). The CNS was the first site of progression for 52% (10/19) ROS1+ NSCLC and 43% (36/83) ALK+ NSCLC with no significant differences between the groups (p = 0.610). Among patients without CNS metastases prior to crizotinib therapy, 50% of ROS1+ and ALK+ patients developed CNS metastases as only site of progression at 24 and 21 months respectively. **Conclusion:** Brain metastases are common in treatment-naïve stage IV ROS1+ NSCLC, though incidence does not differ from other oncogene cohorts. The CNS is a common first site of progression in patients with ROS1+ NSCLC on crizotinib. This study reinforces the need to develop CNS-penetrant TKIs for patients with ROS1+ NSCLC, similar to ALK+ NSCLC.

Keywords: ros1, Brain metastasis, crizotinib

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-79 CHECKMATE 817: SAFETY OF FLAT-DOSE NIVOLUMAB PLUS WEIGHT-BASED IPILIMUMAB FOR THE FIRST-LINE (1L) TREATMENT OF ADVANCED NSCLC

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Background: CheckMate 227 demonstrated significant, clinically meaningful progression-free survival benefit with 1L nivolumab 3 mg/kg every 2 weeks (Q2W) plus low-dose ipilimumab 1 mg/kg Q6W vs chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) and tumor mutational burden (TMB) ≥10 mutations/megabase. The dose and schedule for this combination regimen were optimized for 1L NSCLC in CheckMate 012 and further validated in CheckMate 568 and CheckMate 227. Flat dosing of nivolumab (240 mg Q2W) may simplify treatment while providing comparable exposure, and was recently approved for previously treated NSCLC. CheckMate 817 (NCT02869789) is a multi-cohort, open-label phase 3b/4 study evaluating the safety and efficacy of flat-dose nivolumab plus weight-based low-dose ipilimumab in recurrent/metastatic NSCLC. We report safety results from Cohort A, which evaluated this regimen in the 1L setting; updated results will be presented. **Method:** Patients with ECOG PS ≤1 and previously untreated

NSCLC were eligible, regardless of tumor programmed death ligand 1 (PD-L1) expression and TMB. Nivolumab 240 mg Q2W plus ipilimumab 1 mg/kg Q6W were administered for 2 years or until disease progression/unacceptable toxicity. The primary endpoint was safety assessed by the incidence of grade ≥3 select treatment-related adverse events (TRAEs; defined as AEs of potential immunologic causes). **Result:** Enrollment occurred between October 2016 and August 2017, with 391 patients initiating treatment at 68 academic and community-based centers in Europe and North America. Median age was 65 years and 27.9% of patients had squamous histology. PD-L1 expression was evaluable in 91% of patients; of these, 50% had ≥1% tumor PD-L1 expression. At database lock (March 1, 2018), minimum follow-up was 5.4 months and 34.5% of patients remained on treatment. The median (range) number of nivolumab and ipilimumab doses received were 9 (1–28) and 3 (1–10), respectively. Any grade and grade 3–4 TRAEs occurred in 74.4% and 27.6% of patients, respectively; 14.1% of patients discontinued treatment due to TRAEs. Rates of any grade select TRAEs by category ranged from 1.3% (renal) to 28.4% (skin). The most common grade 3–4 select TRAEs by category were hepatic (4.6%), pulmonary (3.1%), and gastrointestinal (3.1%). Two treatment-related deaths were reported; one due to Guillain-Barré syndrome and one due to rhabdomyolysis leading to heart failure. **Conclusion:** The safety profile of flat-dose nivolumab plus low-dose ipilimumab was consistent with previous reports of weight-based nivolumab plus low-dose ipilimumab optimized for NSCLC. Toxicities were manageable with no new safety signals identified.

Keywords: non-small cell lung cancer, Nivolumab, Ipilimumab

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-80 ELIOS: A MULTICENTER, OPEN-LABEL, MOLECULAR PROFILING STUDY OF PATIENTS WITH EGFRM AND NSCLC TREATED WITH OSIMERTINIB

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Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are standard-of-care for locally advanced/metastatic non-small cell lung cancer (NSCLC) harbouring *EGFR* sensitizing mutations (*EGFR*m). Osimertinib, a third-generation, CNS-active EGFR-TKI potently and selectively inhibits both L858R and exon19del sensitizing *EGFR*m and T790M mutations, is now approved for first-line treatment of *EGFR*m-NSCLC. Studies of osimertinib resistance have focused on patients previously treated with first-/second-generation EGFR-TKIs; however, resistance mechanisms to first-line osimertinib are not well-described. **Method:** ELIOS (NCT03239340) is a phase 2, open-label, single-arm study designed to prospectively characterize the molecular profile of patients who progress on first-line osimertinib. The study will enroll patients (n=100) with locally advanced/metastatic non-squamous *EGFR*m-NSCLC nonamenable to curative surgery/chemoradiation, WHO performance status 0-1, and life expectancy ≥12 weeks. Patients must have *EGFR*m known to be associated with EGFR-TKI sensitivity, must be EGFR-TKI treatment-naïve, and be eligible to receive first-line osimertinib therapy. Patients with clinically significant toxicities, history of interstitial lung disease, and *EGFR* exon 20 insertion will be excluded. All patients will receive 80 mg osimertinib orally once daily and will continue treatment beyond progression if they show continued clinical benefit. Mandatory tumor biopsies will be obtained prior to treatment initiation and following investigator-assessed disease progression. An optional biopsy may be obtained following 2-3 weeks of treatment. Longitudinal plasma samples will be collected for plasma-derived circulating tumor DNA (ctDNA) analysis. Tumor- and plasma-derived specimens will be analyzed by next-generation sequencing; additional exploratory analyses are also planned. The primary endpoint is the proportion of patients with a given genetic/proteomic marker at disease progression (investigator-assessed, RECIST v1.1). Relevant genetic and proteomic markers will be selected based on the profile comparison at disease progression to baseline. Relevant markers of resistance to first-line osimertinib may include, but are not limited to, *EGFR* resistance mutations (including C797S) and c*MET/HER2* amplification; this analysis may reveal other, potentially novel, resistance mechanisms. Secondary endpoints include progression-free survival, objective response rate, duration of response, disease control rate, assessment of osimertinib efficacy post-progression using time to treatment discontinuation, and time to first subsequent therapy. Efficacy analyses based on predefined subgroups (according to the patient molecular profiles) including presence of baseline T790M mutation, *EGFR* Ex19del or L858R mutations, and *EGFR* Ex19del or L858R detectable in ctDNA, will be assessed. Safety will also be assessed. Primary analysis will be performed when ≥50 patients have paired biopsies upon progression. Recruitment is in process (May 1, 2018). **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: EGFR mutations, non-small cell lung cancer, osimertinib

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-81 PHASE 3 STUDY OF PEMETREXED-PLATINUM WITH OR WITHOUT PEMBROLIZUMAB FOR TKI-RESISTANT/EGFR-MUTATED ADVANCED NSCLC: KEYNOTE-789

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Background: In the phase 3 KEYNOTE-189 study, pembrolizumab plus pemetrexed-platinum improved OS and PFS over chemotherapy plus placebo in first-line, metastatic NSCLC without targetable *EGFR* mutations (Gandhi et al. *NEJM* 2018). The phase 3 KEYNOTE-789 (ClinicalTrials.gov, NCT03515837) study evaluates pemetrexed-platinum combined with pembrolizumab vs placebo in *EGFR*-TKI–resistant, *EGFR*-mutated, metastatic nonsquamous NSCLC. **Method:** Eligibility for this multicenter, randomized, double-blind, placebo-controlled study requires age ≥18 years; *EGFR*-TKI–resistant *EGFR*-mutated (exon 19 deletion or *L858R* mutation), histologically/cytologically confirmed stage IV, nonsquamous NSCLC; measurable disease per RECIST version 1.1; ECOG PS 0/1; and archival/newly obtained pretreatment tumor sample to evaluate PD-L1 expression. If progression on prior *EGFR*-TKI occurred with first- or second-generation TKIs (eg, erlotinib, afatinib, gefitinib) and T790M mutation is present, patients must have had subsequent progression on osimertinib; patients with progression on first-line osimertinib are eligible regardless of *EGFR* T790M mutation status. Patients are randomized 1:1 to pembrolizumab 200 mg or placebo, each in combination with pemetrexed 500 mg/m^2 plus platinum chemotherapy (carboplatin AUC 5 or cisplatin 75 mg/m^2; investigator's choice) Q3W for 4 cycles. Patients continue allocated treatment (pembrolizumab or placebo) plus pemetrexed for up to 35 cycles, followed by pemetrexed maintenance therapy until documented disease progression or intolerable toxicity. Randomization is stratified by PD-L1 tumor proportion score ≥50% vs <50%, prior osimertinib vs no prior osimertinib, and geographic region of East Asia vs non-East Asia. Tumor response is assessed radiographically at baseline, week-6, then every 9 weeks through week-54 and every 12 weeks thereafter, per RECIST version 1.1 by blinded, independent central review. Treatment decisions are based on iRECIST criteria by investigator review. PFS and OS are dual primary endpoints, which will be tested with one-sided alphas of 0.001 and 0.02, respectively. Secondary endpoints are ORR; duration of response; change from baseline global health status and quality-of-life scores on the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-Core 30; time to true deterioration in composite endpoint of cough, chest pain, or dyspnea on EORTC QLQ-Lung Cancer Module 13; and safety and tolerability. Severity of AEs will be graded per NCI CTCAE version 4.0. Approximately 480 patients will be enrolled beginning June 1, 2018. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: pembrolizumab, EGFR mutation, NSCLC

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-82 RISK OF NOT RECEIVING 2ND LINE THERAPY IS HIGH IN EGFR MT+ PTS: REAL WORLD DATA OF CERTIFIED LUNG CANCER CENTERS ON TREATMENT SEQUENCE IN EGFR MT+ PTS

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Background: Recently FLAURA study demonstrated significant PFS and numeric OS benefit for Osimertinib 1st line vs. 1st generation TKI's Erlotinib/Gefitinib. The number of patients switching from 1st generation to 3rd gen. TKI (30%) appeared to be low and it is questionable whether these data represent real world sequencing treatment patterns. Therefore, we investigated the sequence pattern, i.e. the percentage of 2nd line therapy in EGFR mt+ patients in 3 certified lung cancer centers

in Germany. **Method:** Data of 912 of 1477 patients tested for EGFR mutations (treated in Oldenburg, Bremen, Hamburg) were analyzed between 2009-2017. 140/144 patients with an activating EGFR mutation (16%) and treated with systemic therapy (4 patients received no therapy) were identified and their treatments were captured as well as their outcome. 36 patients were treated before accessibility to 3rd generation TKI and 104 patients after accessibility to 3rd generation TKI. **Result:** 130/140 patients were treated with 1st line TKI and 10 received 1st line chemotherapy. 17 patients are still on 1st line TKI, 8 patients were lost to follow-up, 3 patients died while on 1st line TKI. 112 patients were candidates for 2nd line therapy. 34/112 (30%) of these patients did not receive 2nd line therapy. Causes for not receiving 2nd line therapy were patients refusal (n=2), bad PS (n=26) frequently due to CNS metastases, fast progression and death (n=6). After accessibility of 3rd generation TKI, 20 of 66 (30%) patients did not receive 2nd line therapy. Median OS of the overall cohort was 27 months (n=140), median OS of patients receiving 2nd line (n=78) vs. no 2nd line (n=62) was 36 vs. 14 months (p<0.0001). After accessibility of 3rd generation TKI 30/104 patients (29%) receive a 3rd generation TKI after 1st line or 2nd line therapy. Median OS of patients receiving (n=30) and not receiving 3rd generation TKI (n=110) was 55 months vs. 22 months (p<0.0001). **Conclusion:** In real world, a significant number of patients treated with 1st or 2nd generation TKI do not reach 2nd line therapy even when 3rd generation TKI were accessible. Reasons for not receiving 2nd line therapy are in most cases deterioration of PS and lack of possibility to test for T790M in the minority of cases (n=28/66, 42% were not tested). These data, although favorable for the small and very selected cohort of patients treated with Osimertinib, might argue for the most effective therapy in 1st line for patients with EGFR mt+ tumors.

Keywords: advanced NSCLC, EGFR mutations, T790M

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-83 IMPOWER150: IMPACT OF CHEMOTHERAPY CYCLES IN 1L METASTATIC NSCLC IN PATIENTS TREATED WITH ATEZOLIZUMAB + BEVACIZUMAB

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Background: In the randomized Phase III IMpower150 study, atezolizumab (anti–programmed death-ligand 1 [PD-L1]) + bevacizumab + chemotherapy (Arm B) showed statistically significant and clinically meaningful improvement in both progression-free survival (PFS) and overall survival (OS) over bevacizumab + chemotherapy (Arm C) in patients with first-line (1L) nonsquamous non-small cell lung cancer (NSCLC). The study protocol allowed investigator choice of 4 or 6 chemotherapy cycles. The objective of this exploratory analysis was to assess the impact of chemotherapy cycles on safety and efficacy outcomes. **Method:** Patients were categorized based on actual chemotherapy cycles received in Arm B. Landmark analysis of PFS was performed to assess the benefit of 4 vs 6 chemotherapy cycles. Sensitivity analyses were performed to adjust the numerically imbalanced baseline factors. **Result:** A total of 356 patients were randomized in Arm B; 188 patients (53%) were planned to receive 4 cycles, and 168 patients (47%) were planned to receive 6 cycles of chemotherapy. Within these 2 groups, 143 (76%) and 98 patients (58%) completed 4 and 6 chemotherapy cycles, respectively. The demographic and baseline disease characteristics were balanced, except for race (Asian vs other), smoking status, and PD-L1 status (TC3 or IC3 vs other). The landmark PFS analysis showed no difference between patients who completed 4 vs 6 cycles (HR 0.83 [95% CI: 0.59, 1.17). The sensitivity analyses, which adjusted for race, smoking status, or PD-L1, showed comparable results (adjusted HRs of 0.80, 0.85, or 0.91, respectively). **Conclusion:** In the atezolizumab + bevacizumab + chemotherapy arm, patients who received 4 cycles of chemotherapy appeared to have similar PFS benefit as those who received 6 cycles of chemotherapy. Detailed analyses of varying chemotherapy cycles, safety analyses, and impact on OS will be presented.

Keywords: chemotherapy, bevacizumab, Atezolizumab

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-84 HIGH BASAL SERUM EGF LEVELS PREDICTS RESPONSE TO CIMAVAX-EGF, A THERAPEUTIC VACCINE FOR ADVANCED NSCLC

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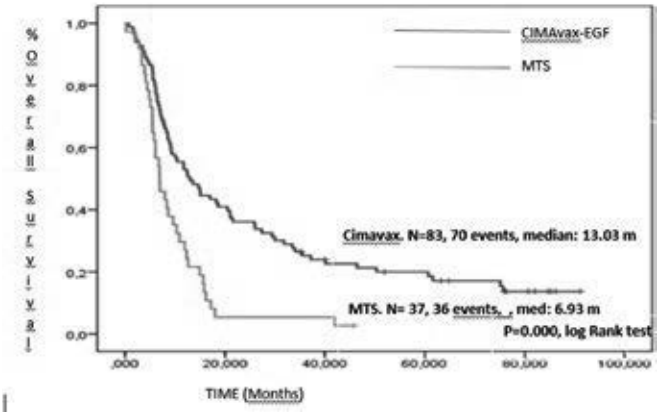
Background: CIMAvax-EGF is a therapeutic vaccine for the treament of advanced NSCLC. The rationale of its use is to create an immune response against circulating plasmatic EGF and by doing this prevent its binding to EGFR. Previous early stage trials have shown its safety and efficacy. Recently a randomized controlled phase III pivotal trial have confirmed its efficacy and safety in open population when used according to stablished protocols. Exploratory results from this study suggested EGF could function as prognostic and predictive biomarker. In this study we aim to evaluate whether basal EGF plasmatic levels can predict patients response to this immunotherapeutic product. **Method:** To know the effect of biomarker status on CIMAvax-effect we pooled data from two previously published controlled trials that used the product in a population of advanced non small cell lung cancer after First Line platinum based chemotherapy. Low doses of cyclophosphamide (200mg/m2) were administered IV three days before the first administration of the vaccine. 2.4 mg/dose of the product were administered during induction phase and then monthly for maintenance treatment. Both studies used Best Support Care as Control Arm. The main outcome was Overall Survival. **Result:** Out of 485 patients included in both studies, 229 were screening for EGF levels (56.5%), (120 and 109 in the high and low level subgroup, respectively). All patients were considered in the analyses. A significant biomarker/treatment effect was found (p=0.000). Hazard ratio (CIMAvax-EGF vs BSC) in the high egf subgroup favoured CIMAvax-EGF (0.44, p=0.000).

Overall Survival according to basal EGF level and treatment arm.



Conclusion: Basal level of plasmatic EGF predicts clinical benefit from CIMAvax-EGF therapeutic cancer vaccine in advanced NSCLC after First Line of Treatment based on Platinum. Vaccinated patients in the subgroup of high EGF levels significantly benefit from CIMAvax-EGF.

Keywords: Therapeutic Vaccine, Non Small Cell Lung Cancer, Immunotherapy

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-85 THE PREVALENCE OF DIFFERENT EGFR EXON20 MUTATIONS IN 12,833 CHINESE LUNG CANCER PATIENTS

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Background: Mutations in *EGFR* exon20 are relatively rare in lung cancers compared to L858R/exon19 mutations, some of which have shown sensitivity to EGFR tyrosine kinase inhibitors (TKIs), and have been actively tested in clinical trials. However, due to the high-variety of *EGFR* exon20 alterations, it becomes increasingly difficult for their functional studies in related to clinical practice. **Method:** We retrospectively screened 12,833 Chinese lung cancer patients that have underwent genotyping on their tumor and/or liquid biopsy samples using targeted

next-generation sequencing between 2014 and 2017 for *EGFR* exon20 mutations as well as other concurrent *EGFR* mutations in the same patient. **Result:** A total of 442 patients (3.4%) were found harboring 493 different *EGFR* exon20 variations, among which 49 patients (11%) carried more than one exon20 mutations. The frequencies of the most prevalent alterations were summarized in Table 1. 18% of these mutations have concurrent TKI-sensitive mutations L858R or exon19 deletion. In-frame deletion/insertions (delins or ins) and missense mutations were identified at a frequency of 53% and 47%, respectively. The short delins/ins occurred between 763~773 residues, while missense mutations dwelled at 768~820 residues, suggesting that these two types of alterations have their own manners for regulating EGFR kinase domain function. The most prevalent insertion is p.M766delinsMASV, occurred in 15.2% of all patients. Meanwhile, the diversity of inserted peptides at p.D770 and p. D771 positions is much higher than other positions with a total of 17 and 19 different insertion peptides composed of 1-5 amino acids, respectively. Missense mutations at S768 were detected in 20.4% of patients, but 60% of them were accompanied by mutations at G719.

Conclusion: This is the largest cohort of Chinese lung cancers for studying *EGFR* exon 20 mutations, which should be informative for functional studies, the design of targeted drugs, and the testing for existing therapies.

Keywords: lung cancer, EGFR exon 20, next-generation sequencing

Table 1. The most common mutations in EGFR exon20.

Insertions			
Exon 20 variations	Concurrent TKI-sensitive mutations (N)	% in Exon20(+) patients (N)	Most prevalent variations (N)
p.M766delins	-- (63)	15.2% (67)	p.M766delinsMASV (67)
	p.L858R (3)		
	p.19del (1)		
p.D770delins*	-- (51)	11.5% (51)	p.D770delinsDNPH (16)
			p.D770delinsDNPH (11)
p.A767delins	-- (47)	10.9% (48)	p.A767delinsASVD (48)
	p.L858R (1)		
p.N771delins	-- (38)	10.2% (45)	p.N771delinsNPH (6) p.N771delinsNH (6) p.N771delinsGY (5)
	p.L858R (4)		
	p.19del (3)		
p.P772delins	-- (26)	6.1% (27)	p.P772delinsPH (10) p.P772delinsPHV (8) p.P772delinsPHA (7)
	p.L858R (1)		
p.A763_Y764ins*	-- (9)	2.0% (9)	p.A763_Y764insFQEA (9)

"--", indicates no concurrent EGFR TKI-sensitive mutations. "*" indicates exon20 insertions that were observed responsive to TKI in previous studies.

Missense mutations			
Exon 20 variations	Concurrent TKI-sensitive mutations (N)	% in Exon20(+) patients (N)	Most prevalent variations (N)
p.S768I/N/T	-- (24)	20.4% (90)	p.S768I (86)
	p.G719A/C/R/S (54)		
	p.L858R(10)		
	p.19del (1)		
	p.L861Q (1)		
p.R776H/C/G	p.L858R (18)	6.8% (30)	p.R776H (20) p.R776C (9)
	p.G719 (7)		
	p.L861 (3)		
	p.19del (2)		
p.V774M	-- (15)	4.1% (18)	--
	p.G719A/C (2)		
	p.19del (1)		
p.G796R/S/C/M	-- (1)	3.2% (14)	p.G796S (9) p.G796R (2) p.G796C (2)
	p.L858R (8)		
	p.19del (5)		
p.H773L/Y	-- (10)	2.5% (11)	p.H773L (6) p.H773Y (5)
	p.G719 (1)		

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

POSTER SESSION 1
MONDAY, SEPTEMBER 24, 2018

P1.01-86 BTCRC-LUN15-017: PHASE-IB STUDY OF IMPRIME PGG AND PEMBROLIZUMAB IN STAGE IV NSCLC AFTER PROGRESSION ON PLATINUM BASED THERAPY

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Background: Imprime PGG (Imprime) is a β-glucan isolated from a proprietary strain of *Saccharomyces cerevisiae*. It acts as pathogen associated molecular pattern, creating 'non-self' signals, enhancing innate immune cell killing, and possibly T-cell cross-talk, thereby enhancing efficacy of checkpoint inhibitor therapy like pembrolizumab. Clinical use of Imprime in combination with chemotherapy and monoclonal-antibodies has been reported, however no studies to date have evaluated its use with anti-PD-1 therapy. We aimed to evaluate safety and tolerability of Imprime with pembrolizumab. **Method:** This is a single-arm, phase-1b, open-label, dose-escalation trial for patients with stage IV NSCLC after progression on platinum-based chemotherapy. Key eligibility included measurable disease, adequate organ function and ECOG performance status of 0-2. Patients received 2 mg/kg or 4 mg/kg IV Imprime on day 1, 8, 15, and 200mg IV pembrolizumab on day 1, every 21 days. "3+3" design was used to establish highest tolerated dose. The dose with toxicity rate of <33% in first cycle would be considered the recommended phase-II dose i.e.≤1 out of 6 patients experience dose limiting toxicity (DLT). Primary endpoint was to establish highest tolerated dose of Imprime for recommendation for phase-II study. Secondary objectives were to define safety and tolerability, and to correlate clinical benefit with biomarkers on immune cells, soluble PD-L1 levels, anti-β-glucan antibody and FcγRIIa polymorphism. This trial is registered with ClinicalTrials.gov, NCT03003468. **Result:** Between 07/2017-02/2018, nine patients were enrolled: three patients received 2 mg/kg and six received 4 mg/kg dose of Imprime. Eight out of nine patients had one line of treatment prior to participation, and one had two lines. Two patients received eleven cycles with 4 mg/kg Imprime. To date, no DLTs have been recorded and the highest dose of Imprime was well tolerated. Five patients stopped treatment due to progression. Four patients are continuing treatment. No patients stopped treatment due to toxicity. Most common adverse event (AE) at 2 mg/kg was grade 1 sore throat in two patients. One Grade 3 diarrhea and one grade 3 neutropenia were reported. Most common AE in the 4 mg/kg group was grade 1 headache in three patients. One episode of grade 3 diarrhea was reported. There were no grade 4 or 5 toxicities. The results of the immunopharmacodynamic analysis will be reported when available. **Conclusion:** Imprime in combination with pembrolizumab is well tolerated in outpatient settings and the role of this combination in treatment of NSCLC warrants further investigation. Phase-II enrollment of this trial is ongoing.

Keywords: Imprime PGG, pembrolizumab, non small cell lung cancer

P1.01-87 A PHASE 1B STUDY OF TRC105 IN COMBINATION WITH PACLITAXEL/CARBOPLATIN AND BEVACIZUMAB IN PATIENTS WITH STAGE 4 NON-SQUAMOUS CELL LUNG CANCER

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Background: Endoglin plays a critical role in angiogenesis and is implicated in resistance to VEGF inhibition. TRC105, an endoglin antibody, has been shown to potentiate the anti-angiogenic effect of bevacizumab (B) in pre-clinical models of human angiogenesis. Given the critical role of anti-angiogenic therapy in the treatment of advanced NSCLC and the tendency of the tumor to develop escape pathways of angiogenesis following treatment with anti-VEGF agent, investigation of dual anti-angiogenic therapy in advanced NSCLC is indicated. **Method:** A standard (3+3) dose-escalation design of TRC105 with15 mg/kg bevacizumab (B), 200 mg/m^2 paclitaxel (P) and 6 AUC carboplatin (C) given IV on day 1 of each 21-day cycle was employed, followed by an expanded cohort to further assess the safety and tolerability of the recommended phase 2 dose (RPTD) of TRC105. Patients completed induction therapy with TRC105 + B, P and C for a maximum of 6 cycles with those demonstrating no evidence of disease progression transitioned to a maintenance phase of TRC105 + B. Secondary endpoints: ORR, PFS, OS, PK, immunogenicity and angiogenic biomarkers. Key inclusion criteria: chemotherapy-naïve stage 4 NSQ-NSCLC, ECOG < 1, measurable disease and no significant cardiovascular comorbidities. **Result:** Fifteen pts have been enrolled; three were unevaluable for efficacy due to DLT of Grade 3 rash and unrelated SAE's of Grade 3 weakness and Grade 3 hypoxia. Four of 12 evaluable pts achieved PR, one with 81% tumor reduction. Median PFS was 6.54 months. Common adverse events regardless of relationship included epistaxis, fatigue, telangiectasia, diarrhea, headache and nausea. Common TRC105 related AEs included epistaxis, telangiectasia, fatigue and headache. One patient experienced Grade 5 neutropenic sepsis considered unrelated to TRC105 or B. Analysis of the angiogenic biomarkers will be presented. **Conclusion:** Induction treatment for six 3-week cycles withTRC105 + B, P, and C, followed by maintenance therapy with TRC105 + B until disease progression was tolerable and did not potentiate the toxicity of B, P or C. The combination of TRC105 + B, P and C demonstrated signs of activity including PR in 4 of 12 evaluable pts.

Keywords: NSCLC, TRC105, angiogenesis

P1.01-88 OSIMERTINIB MAINTENANCE AFTER DEFINITIVE CHEMORADIATION IN PATIENTS WITH UNRESECTABLE EGFRM-POSITIVE STAGE III NSCLC (LAURA)

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Background: The standard of care for patients with stage III unresectable NSCLC is definitive platinum-based chemoradiation, regardless of epidermal growth factor receptor mutation (*EGFR*m) status. There is evidence that following chemoradiation, patients with *EGFR*m-positive NSCLC have superior local control but inferior distant control, including an increased incidence of CNS metastases, compared with patients with *EGFR* wild type (*EGFR*wt)-NSCLC. This supports the rationale for evaluation of EGFR tyrosine kinase inhibitor (TKI) maintenance in *EGFR*m-positive patients without disease progression following chemoradiation. Osimertinib is a third-generation, CNS-active EGFR-TKI that potently and selectively inhibits both sensitizing *EGFR* and T790M mutations. It has shown superior progression-free survival (PFS) vs. standard EGFR-TKIs in first-line treatment of patients with *EGFR*m-positive advanced NSCLC, including patients with or without CNS metastases at trial entry.[1] These data further support the rationale for evaluation of osimertinib in the even earlier disease setting of EGFR-TKI-naïve stage III NSCLC following definitive chemoradiation where it has the potential to prevent/delay progression, including in the CNS, and improve survival compared with chemoradiation alone. **Method:** LAURA is a double-blind, randomized, placebo-controlled, multicenter, phase 3 study designed to assess efficacy and safety of osimertinib as maintenance therapy in patients with locally advanced, unresectable, *EGFR*m-positive, stage III NSCLC without disease progression following definitive platinum-based chemoradiation therapy. All patients will have tumors bearing exon 19 deletion or L858R mutation (centrally or locally confirmed by cobas®EGFR Mutation Test v2), age >18 years, and a WHO performance status of 0-1. Patients will have received prior concurrent (CCRT) or sequential (SCRT) chemoradiation treatment (including ≥2 cycles of platinum-based chemotherapy and radiation of 60 Gy ±10% [54-66 Gy]). Key exclusion criteria include a history of interstitial lung disease, symptomatic pneumonitis following chemoradiation, other unresolved toxicity >Grade 2, cardiac abnormalities, and inadequate organ function. Approximately 200 patients will be randomized 2:1 to osimertinib 80 mg oral once daily or placebo, within 6 weeks of completion of chemoradiation, until disease progression. Stratification factors are prior chemoradiation strategy (CCRT vs SCRT), tumor stage (IIIA vs IIIB/IIIC), and China vs non-China. The primary endpoint is RECIST 1.1 assessed PFS based on blinded independent central review (BICR). Key secondary endpoints include time to CNS PFS, overall survival, objective response rate, disease-related symptoms and health-related QoL, safety and tolerability, and pharmacokinetics. Study enrollment will commence from July 2018. [1]Soria et al N Engl J Med 2018; 378:113-125 **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: osimertinib, EGFR mutations, non-small cell lung cancer

P1.01-89 ANALYSIS AND MONITORING CTCS AND CTDNA IN CSF DEMONSTRATES CLINICAL CONCORDANCE IN TESEVATINIB TREATED NSCLC PATIENTS WITH LM

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Background: Liquid biopsy using blood has emerged as a non-invasive and economical method to assess cancer biomarkers. Applying liquid biopsy methods to evaluate cerebrospinal fluid (CSF) is less well documented and provides key information to supplement routine cytology in patients with brain metastases or leptomeningeal disease (LM). Current first line tyrosine kinase inhibitor (TKI) therapy of (non-small cell lung cancer) NSCLC patients with activating *EGFR* mutations, exhibits poor penetration to the central nervous system (CNS). About 28% of patients treated with erlotinib or gefitinib progress with CNS involvement. Here we present Biocept's Target Selector™ technology to evaluate circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) in the CSF of NSCLC patients with LM, who were treated with tesevatinib in Kadmon's KD019-206 study. **Method:** CSF samples were collected in Biocept CEE-Sure™ blood collection tubes that are validated to preserve CTCs and ctDNA at room temperature for up to 96 hours from collection. The Target Selector™ CTC platform uses an antibody capture cocktail and microfluidic channel for CTC capture and biomarker analysis; the quantitative ctDNA platform incorporates switch-blockers, real time PCR, and sequencing to detect a mutant allele frequency down to 0.05% against wildtype. **Result:** CSF collections from 6 NSCLC patients with LM were obtained at baseline, C1D14, and C3D1 of tesevatinib therapy. In all 6 patients, *EGFR* mutations detected in CSF were concordant to the original tissue mutations. Baseline or emergent T790M ctDNA that was detected in CSF, paralleled progression in 3 patients. CTC enumeration mirrored response to therapy, decrease of symptoms, or progression in 5 of 6 patients; T790M emerged at C1D14 in the patient whose CTCs decreased at progression. Serial CSF CTC and ctDNA analyses were consistent with the overall clinical course of disease. **Conclusion:** Biocept's Target Selector™ technology in CSF analysis demonstrated both highly sensitive detection of CTCs and mutant ctDNA in NSCLC patients with LM as well as concordance with tissue and clinical course. Hence, serial monitoring of CSF with CTCs and ctDNA can be utilized to evaluate drug response and disease progression, providing pertinent vital information for disease management and care of LM patients.

Keywords: CSF, liquid biopsy, NSCLC

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-90 A PILOT TRIAL ASSESSING APATINIB COMBINED WITH DOCETAXEL (DTX) AS SECOND-LINE CHEMOTHERAPY FOR EGFR NEGATIVE ADVANCED NSCLC)

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Background: Apatinib is a new tyrosine kinase inhibitor against vascular endothelial growth factor receptor 2 and improves outcomes in patients (pts) with metastatic gastric cancer as a third line of treatment. Recently, it has been reported effective as third- or later-line treatment in advanced NSCLC. This prospective study tried to assess the efficacy and safety of apatinib combined with DTX as second-line treatment of EGFR negative NSCLC. **Method:** In this open-label single-arm study, pts recived oral apatinib (500mg, p.o. qd) with DTX(60mg/m^2, i.v. d1 q3w) as second-line therapy. The primary endpoint was progression-free-survival (PFS) and the tumor response was determined according to the RECIST 1.1. Treatment was continued until disease progression, death, or intolerable toxicity. **Result:** Between September 2016 and April 2018, 27 pts were enrolled. In 27 pts, there were 23 pts available for efficiency evaluation and 27 pts available for safety evaluation. In the first evaluation of efficacy at one month, computed tomography scan evaluation revealed that partial response (PR) occurred in 7 of 23 pts and other 15 showed stable disease (SD). The median PFS was 4.0667 months (95% CI: 2.5333–6.3333 months). The median OS was 10.5667 months (95% CI: 10.5667– ~ months). The objective response rate(ORR) was 30.43% and disease control rate(DCR) was as high as 95.65 %. Most of the adverse reactions (AEs) were at grade 1 or 2. The grade 3 AEs were hypertension (n=12, 44.44%), hand-foot syndrome (n=3, 11.11%), diarrhea (n=2, 7.41%), mouth ulceration (n=3, 11.11%), thrombocytopenia (n=1, 3.70%). No grade 4 AE or drug-related mortality occurred. **Conclusion:** Apatinib has a potential application prospect in second-line therapy combined with DTX for EGFR negative NSCLC pts. The research team will continue the study.

Keywords: NSCLC, Apatinib, second-line chemotherapy

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-91 A PHASE I STUDY OF FIXED DOSE VINORELBINE AND ESCALATING DOSES OF IFOSFAMIDE IN FIRST-LINE ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Platinum doublet chemotherapy is generally the backbone treatment of advanced NSCLC (aNSCLC), although toxicity and limited benefit necessitated the need for investigation of alternatives. We examined vinorelbine and ifosfamide combination chemotherapy as a possible alternative in first-line aNSCLC. **Method:** 31 patients were enrolled and treated between January 2004 and July 2006. Vinorelbine (25 mg/m^2) and escalating doses of ifosfamide were given on days 1 and 8 q21 days. The starting dose of ifosfamide was 2.0 g/m^2. If ≤1/6 patients experienced dose-limiting toxicities (DLT) in cycle 1, the next cohort was recruited and given an additional 0.25 g/m^2 of ifosfamide. If ^{3} 2/6 patients within a cohort experienced DLT, recruitment was halted, and previous cohort's dose was determined to be ideal for phase II study. DLT were defined as grade 4 hematologic or grades 3 or 4 non-hematologic toxicities. **Result:** The ideal phase II ifosfamide dose was determined to be 2.0 g/m^2. Median PFS and OS were 5.5 and 9.2 months, respectively. The ORR was 12.9% and the 1-year OS was 21%, both lower than historical reports of platinum doublet efficacy and even vinorelbine monotherapy at 30 mg/m^2. Six "excellent responders" were identified who survived between 20 and 45 months. DLT were experienced by 58% of patients. DLT were largely hematologic, but higher doses of ifosfamide produced non-hematologic toxicities. **Conclusion:** There was no significant evidence that vinorelbine and ifosfamide combination could provide an alternative to platinum doublet chemotherapy based on inferior efficacy and the high rate of DLT. The 6 "excellent responders" may be explained by chance or secondary to subsequent treatment with erlotinib while harbouring occult EGFR mutations. Further study may be relevant to examine synergy between vinorelbine or ifosfamide with modern targeted therapies.

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-92 A PHASE II STUDY OF AFATINIB TREATMENT FOR ELDERLY PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED NSCLC HARBORING EGFR MUTATIONS

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Background: The efficacy and safety of afatinib (an epidermal growth factor receptor [EGFR] tyrosine kinase inhibitor) in elderly patients with *EGFR* mutated non-small cell lung cancer (NSCLC) has not been evaluated. Therefore, the aim of this study was to assess the efficacy and safety of afatinib in elderly chemotherapy-naive patients with NSCLC harboring sensitive *EGFR* mutations. **Method:** We prospectively assessed the clinical effects of afatinib as a first-line treatment for elderly (≥70 years) NSCLC patients with *EGFR* mutations (exon 19 deletion or exon 21 L858R mutation). All patients were initially administered afatinib (30 mg/day) at ten Japanese institutions. **Result:** Between May 2014 and August 2017, 40 patients (13 men, 27 women) with a median age of 77 years (range, 70–85 years) were included in our analysis. All patients had adenocarcinoma. Dose reduction was recognized in 19 patients. The objective overall response and disease control rates were 72.5% and 100%, respectively, and the median progression-free survival and overall survival were 15.2 months and 30.0 months, respectively. Common adverse events included diarrhea, rash/acne, and anemia. Major grade 3 or more toxicities included diarrhea (12.5%), mucositis (7.5%), and pneumonitis (7.5%), respectively. Afatinib treatment was discontinued owing to adverse events of elevation of amylase in 1, liver dysfunction in 1, rash/acne in 1, nail change in 1, anorexia in 2 patients, pneumonitis in 2, and diarrhea in 2. Two treatment-related death because of pneumonitis occurred. **Conclusion:** This is the first study that verified efficacy and feasibility of first-line chemotherapy with afatinib of 30mg/day in elderly patients with advanced NSCLC harboring sensitive *EGFR* mutations. First-line afatinib of 30mg/day could be a preferable treatment in this population.

Keywords: EGFR mutations, afatinib, Elderly patients

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-93 QUALITY OF LIFE IN PATIENTS WITH ADVANCED NSCLC TREATED IN SECOND- OR THIRD-LINE WITH NAB-PACLITAXEL + DURVALUMAB: ABOUND.2L+

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Background: Quality of life (QoL) can be adversely affected in patients with advanced NSCLC, particularly those receiving second- or third-line treatment. In these patients, checkpoint inhibitors are a recommended treatment option. Through multiple mechanisms, including the release of tumor antigens via tumor cell lysis, chemotherapy can augment immunotherapeutic effects, which is the rationale for combining chemotherapy with immunotherapy agents. The phase II ABOUND.2L+ trial investigated second- or third-line *nab*-paclitaxel either alone or in combination with CC-486 or durvalumab in patients with advanced NSCLC. The objective of this analysis is to report QoL outcomes in patients treated with *nab*-paclitaxel + durvalumab from the ABOUND.2L+ trial. **Method:** Enrolled patients were ≥ 18 years with advanced NSCLC and no more than 1 prior line of platinum-containing chemotherapy. Immunotherapy in a prior line, first or second, was allowed. Patients were treated with *nab*-paclitaxel on days 1 and 8 + durvalumab 1125 mg on day 15 of a 21-day cycle. Treatment continued until unacceptable toxicity or disease progression per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 or immune-related RECIST v1.1. The primary endpoint was progression-free survival. QoL was a prespecified exploratory endpoint assessed using the Lung Cancer Symptom Scale (LCSS), EuroQol 5D-5L, and EORTC QLQ-C30 on day 1 of each cycle, and was examined through 6 cycles of treatment for this analysis. **Result:** A total of 79 patients were assigned to the *nab*-paclitaxel + durvalumab arm. The median age was 63.0 years. Most patients were white (97.5%), male (68.4%), and had ECOG PS of 1 (77.2%). For the entire study, baseline and ≥ 1 postbaseline QoL assessments were completed by 58 (73.4%) patients. 41 patients completed 6 cycles of treatment with *nab*-paclitaxel + durvalumab. After cycle 6, the mean change from baseline in LCSS total score and pulmonary symptom score was 0.1 and −0.2, respectively. LCSS hemoptysis score improved relative to baseline at every treatment cycle; mean change from baseline after 6 cycles was 0.8. Mean change from baseline in the EuroQol 5D-5L visual analog scale score and EORTC QLQ-C30 global health status/QoL scale score after 6 cycles of treatment was 2.5 and −1.19, respectively. **Conclusion:** In general, patients with advanced NSCLC treated with second- or third-line *nab*-paclitaxel + durvalumab maintained their QoL through 6 cycles of treatment. NCT02250326.

Keywords: quality of life, durvalumab, nab-paclitaxel

P1.01 ADVANCED NSCLC
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P1.01-94 PHASE I TRIAL TO ESTABLISH MAXIMUM TOLERATED DOSE SAFETY AND PHARMACOKINETIC PROFILE OF ORAL PACLITAXEL

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Background: Paclitaxel has been the mainstay of chemotherapy for the treatment of solid tumors like lung ,ovarian, breast, , esophageal, bladder, and head and neck cancers. It is a novel anti microtubule agent which arrests a cell mitotic phase of the cell cycle. Intravenous Paclitaxel is given as every 3 weeks (high dose) or every one week (low dose; metronomic) for many solid tumors. Therapeutic concentration above 85ng/ml for four hours is adequate for efficacy if given every week and is associated with lower toxicity but more frequent clinic visits. To reduce visits, attempts are made to prepare oral formulation without Cremophor. This phase I study was conducted to evaluate pharmacokinetic parameter of novel oral Paclitaxel. (CTRI/2016/02/006607). **Method:** In this phase I study three dose levels of Paclitaxel oral liquid (100 mg, 200 mg and 300 mg) were evaluated in patients with advanced solid tumors except gastrointestinal cancer under fasting condition. **Result:** Total 9 patients were enrolled in the study, 3 patients in each dose level, with Male: Female ratio of 1:2. The plasma samples from all the patients were analyzed for Paclitaxel concentration. The mean Cmax with 100 mg was 514.9 ng/ml, increased to 767.9 ng/ml with 200 mg and decreased to 380.9 ng/ml with 300 mg. Similar trend was observed with AUC, 1383.7 ng*h/ml, 2732.5 ng*h/ml and 1023.9 ng*h/ml at 100 mg, 200 mg and 300 mg, respectively. These data revealed that Cmax and AUC having linear PK characteristics from 100 to 200 mg and nonlinear PK characteristics from 200 to 300 mg. With 200mg dose therapeutic concentration above 85ng/ml was maintained for about 4 hours indicating its utility as weekly therapy. There were nineteen adverse events (AE) s reported by 8 patients in the form of Malaise,Anemia, Hyponatremia, Rash, Mouth Ulcer, Pain at wound site, Breathlessness, Swelling lips, Vomiting and Weakness. Out of 19 AEs; 09 were mild (Grade I), 09 were moderate (Grade II) and one was severe (Grade III): none of these were related to the study drug. **Conclusion:** Oral Paclitaxel was found to be safe and tolerable up to 300 mg dose without any significant safety issues. Its potential in management of advanced solid tumors needs further evaluation as metronomic therapy.

Keywords: solid tumors, metronomic therapy, Cmax

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-95 CRIZOTINIB TREATMENT IN 29 ADVANCED NSCLC CHINESE PATIENTS WITH ROS1 REARRANGEMENT——A SINGLE CHINESE CANCER INSTITUTE EXPERIENCE

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Background: Approximately 1%~2% of NSCLC patients harbor ROS1 rearrangement. Crizotinib, a tyrosine kinase inhibitor that targets ALK, MET and ROS1, has shown marked antitumor activity in patients with ROS1-positive advanced NSCLC. **Method:** A total of 29 patients with ROS1 rearrangement advanced or metastatic NSCLC were treated with crizotinib between Apr 1st, 2016 and Feb 6th, 2018 at Shanghai Cancer Center, Fudan University. Patients were administered with oral crizotinib at dose of 250 mg twice daily. **Result:** The median age was 51 years old. Twenty patients (69.0%) were female. Twenty-three(79.3%) were never-smokers. Six patients (20.7%) had brain metastases. Sixteen patients (55.2%) had received chemotherapy prior to crizotinib therapy. Patients' characteristics were showed in table 1. The ORR and DCR were 65.5% and 93.1%, respectively. The estimated median PFS has not been reached yet. Transaminases increase (15/29,51.7%), vision disorder (6/29,20.7%), blood creatinine increase (6/29,20.7%), vomiting (6/29,20.7%), fatigue (5/29,17.2%) and diarrhea (5/29,17.2%) were the most commonly reported adverse effects. Two patients (6.9%) discontinued crizotinib because of crizotinib-related vomiting, one of whom had reduced to 200mg twice daily.

(See next page)

Table 1. Baseline Patient Characteristics

Characteristic	No.of Patients	%
No.of patients	29	
Age,years		
Mean	50	
Median	51	
Range	26-82	
Age group		
<65 years	25	86.2%
≥65 years	4	13.8%
Sex		
Male	9	31.0%
Female	20	69.0%
Smoking history		
Never-smoker	23	79.3%
Former or current smoker	5	17.2%
Unknown	1	3.4%
Histology		
Adenocarcinoma	29	100.0%
ECOG PS at baseline		
0	0	0.0%
1	27	93.1%
2	2	6.9%
Stage at baseline		
IIIA	1	3.4%
IIIB	3	10.3%
IV	25	86.2%
Brain metastases at baseline		
Yes	6	20.7%
Metastasis sites at baseline		
Lung	6	20.7%
Brain	6	20.7%
Bone	11	37.9%
Liver	1	3.4%
Adrenal gland	0	0.0%
Supraclavicular lymph node	10	34.5%
Pleural	8	27.6%
Others	9	31.0%
No.of metastatic sites		
0	6	20.7%
1	12	41.4%
2	7	24.1%
3	3	10.3%
≥4	1	3.4%
ROS1 detection methods		
FISH	24	82.8%
RT−PCR	4	13.8%
NGS	1	3.4%
Lines of crizotinib therapy		
1	13	44.8%
2	9	31.0%
≥3	7	24.1%

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Conclusion: Crizotinib was effective and well tolerated in Chinese patients with ROS1-positive, advanced NSCLC in real-world clinical practice.

Keywords: crizotinib, ros1, NSCLC

P1.01-96 CONCURRENT ALK/EGFR ALTERATIONS IN CHINESE LUNG CANCERS: FREQUENCY, CLINICAL FEATURES, AND DIFFERENTIAL RESPONSE TO THERAPY

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Background: *ALK* rearrangement and *EGFR* alterations are oncogenic driver mutations in lung cancers. Generally considered mutually exclusive, some studies suggested that these two mutations might occur concomitantly. Limited studies have reported the underlying association of molecular features and drug response to EGFR-TKIs in lung cancers with such co-alterations. Here, we performed next-generation sequencing (NGS) analysis in Chinese lung cancer patients, and evaluated distinct features of *EML4*- vs. non-*EML4-ALK* fusions in *EGFR*-mutated cases. **Method:** A retrospective review was performed on genomic profiling data from either tissue or plasma of 419 *ALK*-rearranged lung cancer patients, sequenced in a CLIA-certified laboratory from 2015 to 2017. Patient characteristics (n=21) and clinical outcomes of patients harboring concurrent *EGFR* and *ALK* alterations were collected. **Result:** Among the 419 *ALK*-rearranged lung cancers, a total of 21 patients (5.01%) were detected harboring concurrent *ALK* and *EGFR* (exon 18-20) genomic alterations. The concomitant rate of *EGFR* in patients harboring *EML4-ALK* (3.06%, 11/359) was dramatically lower than in non-*EML4-ALK* patients (16.67%, 10/60, p<0.001). Four *EML4-ALK* and 1 non-*EML4-ALK* patients were found to have de novo *ALK/EGFR* co-mutations whereas 1 *EML4-ALK* and 3 non-*EML4-ALK* patients acquired their *ALK* alterations after EGFR TKI treatment. For dual-positive patients who received past EGFR-TKI with unknown *ALK* status before the treatment, *EML4-ALK/EGFR* patients (n=6) commonly had shorter PFS to EGFR-TKI as well as higher relative *ALK/EGFR* allele frequency compared to non-*EML4-ALK/EGFR* (n=6; mPFS, 5.45 vs 15 months, p=0.11; mRAF, 1.52 vs 0.41, p=0.01), suggesting that *EML4-ALK* was more likely to be *de novo* whereas non-*EML4-ALK* acquired after EGFR-TKI. In addition, we found that for 9 dual-positive patients who had prior first-generation EGFR-TKI treatment, the clinical efficacy of single TKI use varied greatly, and patients might benefit from combination therapy of ALK+EGFR TKIs. **Conclusion:** This study revealed that *EML4-ALK/EGFR* and non-*EML4-ALK/EGFR* co-alterations displayed distinct prevalence in Chinese lung cancer patients. Our analyses suggested that non-*EML4-ALK* might be an acquired gene alteration and function as a resistance mechanism to EGFR-TKI, which might explain the observed discrepancy in prevalence as our sequencing cohort consisted of both previously treated or untreated patients. In addition, we observed that patients with dual *ALK/EGFR* alterations may benefit from combinatorial TKIs therapy.

Keywords: Chinese Lung Cancer, EGFR-TKI, Concurrent ALK/EGFR alterations

P1.01-97 CLUSTER TRIAL: PH2 BIOMARKER-INTEGRATED STUDY OF SINGLE AGENT ALPELISIB, CAPMATINIB, CERITINIB AND BINIMETINIB IN ADVNSCLC

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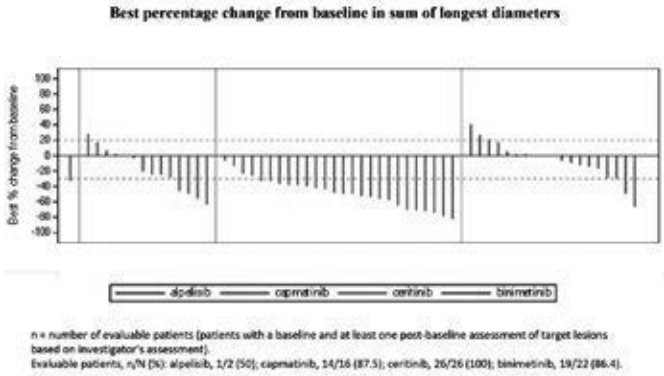
Background: Several genetically altered signaling pathways have been profiled in NSCLC, enabling advanced management of NSCLC using targeted therapies. This study investigated the therapeutic spectrum of NSCLC with uncommon molecular alterations by allocating patients to treatment arms based on molecular aberrations; targeted therapies alpelisib (PI3Kαi), capmatinib (METi), ceritinib (ALKi), and binimetinib (MEKi) were evaluated. **Method:** The study was based on the umbrella design. Key objectives: investigate feasibility of using one trial for different agents based on biomarker-integrated analysis, assess anti-tumor activity, characterize safety, tolerability and PK profiles of individual agents. Key eligibility criteria: age ≥18 years; ECOG PS ≤2; failed prior treatment/unsuitable for chemotherapy. Documentation of

locally determined molecular alterations before treatment allocation was required (alpelisib, 350 mg QD: *PIK3CA* mutation/amplification; capmatinib, 400 mg BID (tablet): *MET* IHC overexpression/amplification; ceritinib, 750 mg QD: *ALK* or *ROS1* rearrangement; binimetinib, 45 mg BID: *KRAS*, *NRAS* or *BRAF* mutation). **Result:** Sixty-six patients with advNSCLC were enrolled (median age 58 years; 65.2% male: alpelisib, n=2; capmatinib, n=16; ceritinib, n=26; binimetinib, n=22). As of Feb 28, 2018, 10 patients in ceritinib and 2 in binimetinib arms were ongoing. Twenty-four patients had confirmed partial responses (36.4%): alpelisib, 0%; capmatinib, 18.8%; ceritinib, 73.1%; binimetinib, 9.1% (Figure). Longest mPFS (14.4 months) was in ceritinib arm. Among the most common treatment-related AEs: alpelisib: malaise, hyperglycemia, dysgeusia; capmatinib: nausea, anemia, peripheral edema, decreased appetite; ceritinib: diarrhea, vomiting, ALT/AST elevation; binimetinib: mouth ulceration, AST, blood CPK increased, rash. Most AEs were grade 1/2.



Conclusion: Objective responses/tumor shrinkage were observed in the study; highest ORR and mPFS were observed with ceritinib, although patient numbers differed between arms. All treatments were well tolerated; no new safety signals were observed. This study demonstrated the feasibility of an umbrella trial and importance of precision medicine in the management of advNSCLC with uncommon molecular alterations.

Keywords: NSCLC, biomarker-integrated study, umbrella trial design

P1.01 ADVANCED NSCLC
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P1.01-98 A PHASE IIIB TRIAL OF AFATINIB IN EGFRM+ NSCLC: ANALYSES OF OUTCOMES IN PATIENTS WITH BRAIN METASTASES OR DOSE REDUCTIONS

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Background: We previously reported interim results of a large (n=479) open-label, single-arm Phase IIIb study of afatinib in EGFR TKI-naïve patients with *EGFR*m+ NSCLC, in a setting similar to 'real-world' practice (Wu et al, WCLC, 2017). In this broad population of Asian patients, the tolerability profile of afatinib was predictable and manageable. Adverse events (AEs) were consistent with the LUX-Lung 3, 6 and 7 trials; 3.8% of patients discontinued due to drug-related AEs. Progression-free survival (PFS) and time to symptomatic progression (TTSP) was encouraging, in patients with both common and uncommon *EGFR* mutations. TTSP data suggested effective treatment beyond progression. Here, we assess the impact of baseline brain metastases and use of dose reductions on efficacy outcomes. **Method:** Patients with locally advanced/metastatic *EGFR*m+ NSCLC were recruited in China, Hong Kong, India, Singapore and Taiwan. Afatinib 40mg/day was given until disease progression (investigator-assessed) or lack of tolerability. Treatment-related AEs could be managed by protocol-specified tolerability-guided dose adjustment. **Result:** At data cut-off (13 Feb 2017), patient characteristics were as follows: median age, 59.0 years; female, 52.4%; *EGFR* mutations: Del19+/-L858R+/-uncommon, 86.0%; uncommon only, 14.0%; ECOG PS0, 19.8%; PS1, 78.1%. Prior chemotherapy lines: 0, 59.7%; 1, 30.1%; ≥2, 10.2%. Overall, dose reductions from 40mg/day to 30mg/day occurred in 119 patients (25%). Incidences of the most frequently reported AEs before and after dose reduction were (any grade): diarrhea, 96/51%; rash/acne, 69/58%; stomatitis, 65/42%; (≥grade 3) diarrhea, 27/4%; rash/acne, 24/11%; stomatitis, 11/5%. A total of 96 patients had a dose reduction during the first six months; median PFS in this subgroup was 14.1 months (95% CI: 10.0–19.3) versus 11.33 (10.7–13.6) months in those who remained on the starting dose (n=383); HR=1.37 (1.01–1.85), p=0.041. Median TTSP was 17.7 (13.5–23.7) and 14.7 (12.7–17.0) months, respectively; HR=1.26 (0.92–1.72), p=0.15. Among 92 patients (19.2%) with brain metastases at baseline, median PFS was 10.9 (8.3–14.3) months, versus 12.4 (10.8–13.9) months in those without metastases (n=387); HR=1.23 (0.91–1.65), p=0.18. Median TTSP was 14.8 (12.7–20.7) and 15.4 (12.9–18.0) months, respectively; HR=1.0 (0.71–1.40), p=1.0. **Conclusion:** These findings demonstrate that tolerability-guided dose adjustment of afatinib is an effective measure to reduce treatment-related AEs, while maintaining therapeutic efficacy. TTSP was similar between patients with and without brain metastasis. This is additional evidence for the efficacy of afatinib in patients with brain metastases.

Keywords: afatinib, dose reductions, NSCLC

P1.01 ADVANCED NSCLC
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P1.01-99 DETECTING HER2 ALTERATIONS BY NEXT GENERATION SEQUENCING (NGS) IN PATIENTS WITH ADVANCED NSCLC FROM THE UNITED STATES AND CHINA

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Background: Advances in NGS have led to an increase in identifying specific actionable gene alterations across tumor types. We collected data on *HER2* gene alterations detected by NGS from patients with advanced NSCLC and analyzed clinical characteristics and HER2 targeted treatments. **Method:** Patients diagnosed with advanced NSCLC and underwent NGS testing from Jun 2014 to Dec 2017 at Memorial Sloan-Kettering Cancer Center (MSK) and Guangdong General Hospital (GGH) were included. NGS platforms were MSK-IMPACT™ in MSK and GeneSeek or BurnStone in GGH. Descriptive statistics are used in data analysis. **Result:** 2200 patients from MSK and 490 patients from GGH underwent NGS testing. *HER2* mutation and/or amplification were detected in 91/2200(4.1%) patients and 28/490(5.7%) patients from MSK and GGH respectively. Clinical characteristics were listed in Table1. 37.4%(34/91) and 21.4%(6/28) patients from MSK and GGH received HER2 targeted therapies. More patients were enrolled to HER2 inhibitors clinical trials in MSK(24.2%) than GGH(7.1%). The characteristics of HER2 alterations are summarized in Table2.

Table 1. Comparison of HER2 alterations in advanced NSCLC patients from U.S. and China

	MSK N (%)	GGH N (%)
Total Patients	91	28
Age at Diagnosis (years)		
<=60	34 (37.4%)	13 (46.4%)
>60	57 (62.6%)	15 (53.6%)
Sex		
Male	37 (40.7%)	14 (50%)
Female	54 (59.3%)	14 (50%)
Smoking History		
Former/Current Smoker	53 (58.2%)	7 (25%)

Table 1. Comparison of HER2 alterations in advanced NSCLC patients from U.S. and China

	MSK N (%)	GGH N (%)
Non-Smoker	38 (41.8%)	21 (75%)
Histology		
Adenocarcinoma	84 (92.3%)	25 (89.3%)
Squamous Cell Carcinoma	5 (5.5%)	0
Misc	2 (2.2%)	3 (10.7%)
HER2 status		
Mutation	48 (52.7%)	16 (57.1%)
Amplification	32 (35.2%)	11 (39.3%)
Mutation + Amplification	11 (12.1%)	1 (3.6%)
HER2 targeted treatment	34 (37.4%)	6 (21.4%)
Enrolled to HER2 inhibitors clinical trials	22 (24.2%)	2 (7.1%)

Table 2. HER2 alteration in advanced NSCLC patients from U.S. and China combined

NGS Result	Mutation Only N (%)	Amplification Only N (%)	Mutation + Amplification N (%)
Total Patients	64	43	12
Age at Diagnosis (years)			
<=60	31 (48.4%)	20 (46.5%)	8 (66.7%)
>60	33 (51.6%)	23 (35.9%)	4 (33.3%)
Sex			
Male	39 (60.9%)	19 (44.2%)	7 (58.3%)
Female	25 (39.1%)	24 (55.8%)	5 (41.7%)
Smoking History			
Former/Current Smoker	31 (48.4%)	24 (55.8%)	5 (41.7%)
Non-Smoker	33 (51.6%)	19 (44.2%)	7 (58.3%)
Histology			
Adenocarcinoma	58 (90.6%)	39 (90.7%)	12 (100%)
Squamous Cell Carcinoma	1 (1.6%)	4 (9.3%)	0
Misc	5 (7.5%)	0	0
HER2 targeted treatment			
Yes	19 (29.7%)	14 (32.6%)	7 (58.3%)
No	45 (70.3%)	29 (67.4%)	5 (41.7%)

Conclusion: The incidence and clinical characteristics of *HER2* alterations in advanced NSCLC were similar between two large cancer centers in the U.S. and China. These data support U.S.-China collaboration in clinical trials for patients with rare molecular subsets of NSCLC to accelerate new cancer drug development.

Keywords: non-small cell lung cancer, Target therapy, clinical trials

P1.01 ADVANCED NSCLC
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P1.01-100 CONCURRENT BRAIN RADIOTHERAPY AND EGFR-TKI HAVE BETTER SURVIVAL BENEFITS IN PATIENTS WITH BRAIN METASTASES FROM EGFR-MUTANT NSCLC

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Background: Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) has intracranial activity in EGFR-mutant Non-Small Cell Lung Cancer (NSCLC). The optimal timing of brain radiotherapy and appropriate patients who need early brain radiotherapy remains controversial. We performed a retrospective analysis of patients with brain metastases (BM) from EGFR-mutant NSCLC to evaluate the preferred treatment of EGFR-TKIs in this population. **Method:** Of 128 initial or recurrent patients diagnosed BM from EGFR-mutant NSCLC between Jan 1, 2012, and Dec 31, 2016, 68 EGFR-TKI combined with concurrent brain RT, and 60 upfront EGFR-TKI then brain RT. Disease-specific-graded prognostic assessment was similar between two groups. The Kaplan-Meier method and log-rank tests were used to compare overall survival rates and intracranial progression-free survival rates, and a bootstrapped Cox proportional hazards model was used to determine significant contributors to overall survival. **Result:** Compared with upfront EGFR-TKI group, the median OS was significantly longer in EGFR-TKI combined with concurrent brain radiotherapy group (24.1 vs 17.8 months; P=0.046). According to multivariate COX analysis, KPS (≥ 70) and intracranial metastasis alone was associated with a longer OS. The median intracranial progression-free survival was significantly improved in patients receiving EGFR-TKI combined with concurrent brain radiotherapy compared with upfront EGFR-TKI (32.3 vs 10.2 months; P=0.022). **Conclusion:** The present study suggests that the use of EGFR-TKI combined with concurrent brain radiotherapy may result in superior OS in patients with brain metastases from EGFR-mutant NSCLC. Also, early brain radiotherapy could significantly reduce the risk of intracranial progression compared with EGFR-TKI alone. Participation in clinical trials is essential to define the indications and relative efficacy of concurrent management and EGFR-TKI alone in a selected population. We expect that further molecular biomarkers will improve estimation of prognosis and patient selection in the future.

Keywords: EGFR-mutant brain metastases, EGFR-TKI, brain radiotherapy

P1.01 ADVANCED NSCLC
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P1.01-101 SURVIVAL BENEFIT OF SEQUENTIAL THERAPY IN ALK POSITIVE OLIOPROGRESSIVE NSCLC PATIENTS AFTER CRIZOTINIB RESISTANCE

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Background: Crizotinib is recommended as first-line standard therapy for advanced anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC).Despite initial efficacy of crizotinib, patients ultimately acquired resistance, which leading to tumor progression within one year of crizotinib initiation. However,optimal sequential therapy option among patients with olioprogressive disease remains unknown.Therefore, this study aimed to explore which therapy pattern was advantageous for those patients with extracranial and intracranial metastasis. **Method:** This retrospective single-center study enrolled 116 Chinese advanced ALK positive NSCLC patients resistant to prior crizotinib treatment,between Jan 2013 and Dec 2016.Based on the site of olioprogressive metastasis, patients were divided into two groups: extracranial (n=57,49.1%) and intracranial (n=59, 50.9%).Sequential therapies mainly included continuation of crizotinib with local therapeutics and next-generation ALK inhibitors. The primary end-point was median overall survival (OS) from the time of crizotinib resistance to death or last follow-up. **Result:** Among 116 patients,45 patients (38.8%) had died. For extracranial group,26 patients continued crizotinib with local treatment (local radiotherapy or ablation therapy),31 received next-generation ALK inhibitor. Patients followed by next-generation ALK inhibitor beyond crizotinib resistance exhibited a longer OS of 27.6 months than crizotinib continuation with

local therapy of 10.8months(p=0.009).Among intracranial group,36 patients continued crizotinib with local treatment including whole brain radiotherapy or stereotactic radiotherapy,23 were next-generation ALK inhibitors users. Continution of crizotinib with local therapy had a non-inferior OS than next-generation ALK inhibitors (28.9 month vs 32.8months, p=0.538) . **Conclusion:** Next-generation ALK inhibitors had more survival benefit than continuation of crizotinib with local therapy for extracranial olioprogressive patients.While crizotinib continuation with local therapy might be a feasible strategy among patients with intracranial olioprogressive metastasis after crizotinib resistance.

Keywords: non-small cell lung cancer, ALK, Sequential therapy

P1.01 ADVANCED NSCLC
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P1.01-102 RETROSPECTIVE ANALYSIS OF IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH EGFR MUTATED NON-SMALL CELL LUNG CANCER IN A JAPANESE COHORT

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Background: EGFR-TKIs led to initial clinical response in most patients with EGFR mutated non-small cell lung cancer (NSCLC). In contrast, little is known the subpopulation of NSCLC patients with EGFR mutations who had clinical outcomes to treat for immune checkpoint inhibitors (ICIs). Therefore, to seek for the eligible cases to treat with ICIs, we retrospectively analyzed the correlations between clinical feature and the efficacy of ICIs in patients with EGFR mutations. **Method:** We analyzed a retrospective study of patients with advanced NSCLC harboring with EGFR mutations who were treated with ICIs after the resistance to EGFR-TKIs between February 2016 and April 2018 at five institutions in Japan. The association between clinical outcome and the efficacy or ICIs was investigated. **Result:** We enrolled 27 patients who had EGFR activating mutation. The objective response and disease control rates were higher in patients with uncommon EGFR mutations than in those with common EGFR mutations (57.1% versus 6.3% and 71.4% versus 31.3%, p= 0.003 and p = 0.06, respectively). Patients with uncommon EGFR mutations were associated with a significantly longer median progression-free survival than those with common EGFR mutations (7.0 months versus 1.9 months, p = 0.009). **Conclusion:** Uncommon EGFR mutations are associated with better outcomes for the treatment with immunotherapy among EGFR mutated NSCLC in the retrospective analysis. Further research is needed to validate for the clinical biomarkers involved in ICI responders.

Keywords: EGFR mutation, immune checkpoint inhibitor

P1.01 ADVANCED NSCLC
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P1.01-103 LEUKOCYTE TELOMERE LENGTH AS A NOVEL BIOMARKER IN ADVANCED LUNG ADENOCARCINOMA PATIENTS TREATED WITH GEFITINIB

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Background: Gefitinib is currently one of the mostly used epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) recommended for treating non-small cell lung cancer. However, drug resistance was observed among the majority of patients after initial treatment. The factors that predict treatment prognosis and drug resistance to EGFR-TKIs remain elusive. Leukocyte telomere length has been previously proved to be associated with lung cancer risk. However, it is still unclear whether telomere length can be used as biomarker of EGFR-TKIs therapy. The objective of this study is to exam the association between leukocyte relative telomere length (RTL) and prognosis or drug resistance of advanced lung adenocarcinoma to gefitinib treatment. **Method:** In this study, three hundred and sixty-nine patients with stage IIIB or IV lung adenocarcinoma were recruited between January 2009 and June 2013. All patients were treated with gefitinib orally at a daily dose of 250 mg as first-line monotherapy. Leukocyte RTL of each patient was measured using quantitative polymerase chain reaction (qPCR) protocol on an ABI PRISM 7900HT Sequence Detection System (Applied Biosystems) and calculated according to Cawthon's formula. Differences in patients' characteristics were calculated by Pearson's χ^2 tests or Student's *t* test. Cox proportional hazard regression analyses were used to calculate univariate and multivariate hazard ratios (HRs) and their 95% confidence interval (95% CIs). Multivariate analyses were adjusted for sex, age, smoking status and *EGFR* mutation status, as appropriate. Survival differences were examined using the log-rank test. A *P* value of less than 0.05 was used as the criterion of statistical significance, and all statistical tests were two-sided. **Result:** Among 369 patients, *EGFR* mutations were positive in 181 patients (49.1%). Compared to long RTL, short leukocyte RTL was significantly associated with poor prognosis in all patients after gefitinib treatment (overall survival: 12.9 months vs. 17.8 months, $P=1.2\times10^{-4}$; progression free survival: 7.8 months vs. 13.0 months, $P=0.043$ for log-rank test). Additionally, statistically significant association between short leukocyte RTL and shorten OS still existed among the *EGFR* mutant patients with gefitinib treatment (HR = 1.65, 95% CI=1.28-2.12; $P = 0.006$). Besides *EGFR* mutation status, short RTL also contributed to significantly elevated risk of gefitinib primary resistance (HR = 1.50, 95% CI = 1.05-2.15, $P = 0.027$). **Conclusion:** Our results highlight the potential of leukocyte RTL as a novel biomarker in advanced lung adenocarcinoma patients treated with EGFR-TKIs and the possibility of patient-tailored decisions based on leukocyte RTL.

Keywords: biomarker, leukocyte relative telomere length, EGFR-TKIs treatment

P1.01 ADVANCED NSCLC
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P1.01-104 UPDATED PHASE I RESULTS OF CARBOPLATIN, PEMETREXED AND EXEMESTANE IN POSTMENOPAUSAL WOMEN WITH METASTATIC NON-SQUAMOUS NSCLC

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Background: Estrogen receptors (ERa, ERb) and aromatase (key enzyme for estrogen synthesis) are expressed in most human NSCLCs. High intratumoral estrogens and elevated aromatase expression in NSCLC predicts poor outcome. *In vitro* preclinical models show that estrogen stimulates NSCLC gene expression, induces proliferation, and diminishes apoptosis. Furthermore, preclinical NSCLC models demonstrate that antiestrogens or aromatase inhibitors prevent these processes and that the combination of cisplatin and aromatase inhibitors elicits dramatic growth inhibition (Marquez *et al., Annals NY Acad Sci.* 2009;1155:194). Additionally, depletion of autocrine/paracrine estrogen production hypersensitizes cells to DNA-damaging effects of platinum therapy, thereby providing support for this early phase trial. **Method:** The primary objective of this phase 1b, open-label, single-center study (NCT01664754) was to evaluate safety and tolerability of escalating doses of exemestane in combination with carboplatin and pemetrexed in postmenopausal women with stage IV non-squamous NSCLC. Key exclusion criteria included untreated CNS involvement, major surgery in prior 4-weeks to therapy, prior/concurrent investigational or standard therapy (with exception of TKI and/or immunotherapy in prior 4-weeks). Patients received escalating doses of exemestane (starting 1-week before chemotherapy) at 25 mg PO daily (Cohort 1) or 50 mg PO daily (Cohort 2) combined with carboplatin (AUC 6 mg x min/mL) and pemetrexed (500 mg/m2) IV q3 weeks for 4 cycles. After 4 cycles, patients were eligible for continued therapy with exemestane and/or pemetrexed. Area under the curve (AUC) was extrapolated using linear trapezoidal methods. **Result:** Ten patients consented for therapy; 2 patients screen-failed. Three patients completed therapy in Cohort 1, and five patients were treated in Cohort 2. One patient in Cohort 2 exited the trial for alternative therapy after one treatment cycle. The median number of cycles given was 15 (range 1-54). The mean of the maximum serum concentration (Cmax) of exemestane for Cohort 1 was 12.98 ng/mL and for Cohort 2 was 41.38 ng/mL. The AUC_{inf} for the two cohorts was 51.73 and 184.17 ng x h/mL, respectively. The established maximum tolerated dose (MTD) was exemestane 50 mg PO daily with pemetrexed (500 mg/m2 IV q3 weeks) and carboplatin (AUC 6 mg x min/mL IV q3 weeks). No patients were removed from the study for adverse events. Clinical outcome, biomarker

and QOL correlates are being collected. **Conclusion:** The combination of carboplatin, pemetrexed and exemestane in post-menopausal women with metastatic non-squamous, NSCLC is safe and well-tolerated. This data supports future clinical trials to establish efficacy with this combination therapy.

Keywords: estrogen receptor, Exemestane, NSCLC

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-105 LUNG CANCER PATIENTS WITH CONCURRENT EGFR AND MET MUTATIONS: A RETROSPECTIVE ANALYSIS OF 29 CASES

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Background: It has been reported that about 5%-20% of EGFR-TKIs resistant NSCLC patients harbors *MET* amplification or activating mutations. However, the extent that *MET* abnormal activation contributes to EGFR-TKIs resistance remains widely unknown. Here, we describe the clinical and genetic characteristics of 29 lung cancer patients harboring concurrent *EGFR* and *MET* mutations. **Method:** Genetic mutations were reviewed in 6000 lung cancer patients who underwent genetic testing at our institute from 2016 to 2018. Mutation profiles were analyzed using hybridization capture based next-generation sequencing (NGS), which enables the simultaneous detection of single-nucleotide variants, insertions/deletions, rearrangements, and copy-number alterations of at least 59 genes (range 59 – 1021 genes). **Result:** The selected patients included 24 lung adenocarcinoma patients, 1 squamous cell lung cancer patient and 3 lung cancer patients with unspecified pathology. Both *MET* amplification and activating mutations were included for analysis. *MET* amplification was detected in 90% (27/30) of samples, while activating mutations was present in 13.3% (4/30) of samples, including H1112Y, D1228N, D1246Y and D1246H. 14% (4/29) of patients had not received EGFR-TKIs treatment before genetic testing, which were considered as primary resistance. 79% (23/29) of patients were treated with EGFR-TKIs. Surprisingly, 60% (18/30) of cases had other functional mutations which may also affect the effectiveness of EGFR-TKIs, such as *EGFR* T790M mutation (3 cases), rare *EGFR* mutations (I744M, R108K and C769S, 3 cases), *EGFR* amplification (7 cases), *CDK4* amplification (2 cases), loss-of-function mutations of *CDKN2A* (2 cases) and so on. One patient had two samples tested. He was resistant to gefitinib and osimertinib, and *EGFR* L858R mutation and *MET* amplification were detected in the first sample. Later, he was treated with combined gefitinib and crizotinib and reached PR at the 2nd month. However, his disease finally progressed probably due to an additional *MET* mutation (D1246Y) that caused resistance to crizotinib. **Conclusion:** *MET* amplification and activating mutations may lead to primary and acquired resistance of EGFR-TKIs. Moreover, additional potentially resistant mechanisms were detected in most cases. Therefore, it is apparently requisite to provide a comprehensive genetic testing to lung cancer patients.

Keywords: lung cancer, Concurrent EGFR and MET Mutations, EGFR-TKIs Resistance

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-106 PEMBROLIZUMAB RANDOMIZED, PHASE 1 STUDY IN CHINESE PATIENTS WITH ADVANCED NSCLC: KEYNOTE-032.

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Background: Multicenter studies have shown improved clinical outcomes and favorable safety with pembrolizumab (pembro) in 1L and 2L settings in advanced NSCLC. We present pembro data in Chinese patients (pts) with advanced NSCLC. **Method:** This open label phase 1 study (NCT02835690) enrolled Chinese pts aged ≥18 years with histologically/cytologically confirmed advanced, unresectable NSCLC; measurable disease per RECIST v1.1; ECOG PS 0/1; and prior failure/intolerance/ineligibility for standard therapy. Pts were randomized (stratified by gender) 1:1:1 to IV pembro 2 mg/kg, 10 mg/kg, or 200 mg (each Q3W after initial 28-day cycle). Safety and PK were primary objectives. Responses were assessed centrally per RECIST v1.1. PK was based on noncompartmental analysis. **Result:** 42 pts received ≥1 pembro dose (2 pts randomized were not treated thus excluded from analyses; 2 mg/kg, n = 14; 10 mg/kg, n = 13; 200 mg, n = 15): median age 59 (range, 28–71) y, 64% male, 62% adenocarcinoma, and 76% 1–2 prior therapies. Median follow up was 7.9 mo (range, 0.7–13.1). 29 pts (69%) had treatment-related AEs, most commonly fatigue and rash (24% each). 4 pts (10%) had grade 3-4 treatment-related AEs (no grade 5): eyelid ptosis, fatigue, anaphylactic reaction, dermatitis acneiform, and rash (1 each). AEOSIs (predefined list with possible immune etiology) were hypothyroidism (n = 2) and hyperthyroidism, anaphylactic reaction, and rash (n = 1 each). Geometric mean PK values for 2 mg/kg, 10 mg/kg, and 200 mg, respectively, were: t1/2 (days; CV%), 15 (33), 16 (25), and 12 (41); AUC0-21d (μg·d/mL; 95% CI), 730.9 (627.4–851.6), 2819.2 (2009.4–3955.4), and 931.0 (724.4–1196.6); and Cmax (μg/mL; 95% CI), 66.7 (56.9–78.1), 268.6 (217.8–331.2), and 92.2 (81.7–104.2). Anti-drug antibodies did not impact pembro exposure. Overall, ORR was 14.3% (6/42; 95% CI, 5.4–28.5); median DOR was 5.2 mo (range, 2.00 [ongoing]–6.28), PFS was 2.1 mo (range, 2.1–4.2), and OS was not reached. **Conclusion:** In Chinese pts with advanced NSCLC, pembro had approximately linear serum exposure at the dose range studied (2 to 10 mg/kg), was well tolerated, and showed antitumor activity consistent with the multicohort study KEYNOTE-001. The phase 3 KEYNOTE-033 study (NCT02864394), enrolling mostly Chinese pts, evaluates pembrolizumab versus docetaxel in pts with previously treated NSCLC with PD-L1 TPS ≥1% and is ongoing.

Keywords: pembrolizumab, NSCLC, biomarker

P1.01 ADVANCED NSCLC
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P1.01-107 THE IMPACT OF ANLOTINIB ON QUALITY OF LIFE IN PATIENTS WITH ADVANCE NSCLC: POST-HOC ANALYSIS OF A PHASE III RANDOMIZED CONTROL TRIAL (ALTER0303)

X. Si[1], L. Zhang[2], H. Wang[1], X. Zhang[2], M. Wang[1], B. Han[3], K. Li[4], Q. Wang[5], J. Shi[6], Z. Wang[7], Y. Cheng[8], J. He[9], Y. Shi[10], W. Chen[11], X. Wang[12], Y. Luo[13], K. Nan[14], F. Jin[15], B. Li[16], Y. Chen[17], J. Zhou[18], D. Wang[19]

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Background: Anlotinib is a novel multi-target tyrosine Kinase inhibitor that inhibits VEGFR2/3, FGFR1-4, PDGFD α/β, c-Kit and Ret. In the phase III ALTER-0303 trial (Clinical Trial Registry ID: NCT 02388919), anlotinib significantly improved overall survival versus placebo in advanced non-small-cell lung cancer (NSCLC) patients who had received at least two previous chemotherapy and epidermal growth factor receptor /anaplastic lymphoma kinase targeted therapy regimens. This study assessed quality of life (QoL) in these patients. **Method:** Patients were randomized (2:1) to anlotinib or placebo up to progression or intolerable toxicity. The QoL were assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the associated EORTC Quality of Life Lung Cancer Specific Module (QLQ-LC13) at baseline, end of cycle 1, end of every two cycles, and at the final visit. The analyses were conducted in the first 6 cycles. Differences in scores of 10 points or more between two arms or from baseline were considered clinically meaningful. **Result:** A total of 437 patients were assigned to anlotinib (n=294) and placebo (n=143). The completion rates of the QoL questionnaires were from 69.9 % to 97.0%. Mean scores of QLQ-C30 and QLQ-LC13 subscales were similar in the anlotinib and placebo arms at baseline. Compared to placebo, anlotinib improved role functioning (at cycle 2), social functioning (at cycle 4), dyspnea (at cycle 2, 4), insomnia (at cycle 6), constipation (at cycle 2) and financial problems (at cycle 2). Only sore mouth or tongue symptom was worse in the anlotinib arm (at cycle 2, 4, 6) than in the placebo arm. **Conclusion:** Anlotinib improved quality of life versus placebo in advanced NSCLC patients who had received at least two previous chemotherapies. The QoL analyses provided evidence that anlotinib should be a choice for the third-line treatment or beyond in advanced NSCLC.

Keywords: Anlotinib, non-small cell lung cancer, quality of life

P1.01-108 MANAGEMENT OF ANLOTINIB-RELATED ADVERSE EVENTS: DATA FROM ALTER 0303

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Background: Anlotinib is an oral tyrosine kinase inhibitor targeting VEGFR, FGFR, PDGFR and c-kit. In the phase III ALTER-0303 trial (Clinical Trial Registry ID: NCT 02388919), anlotinib significantly improved overall survival versus placebo in advanced non-small-cell lung cancer (NSCLC) patients who had received at least two previous chemotherapy and epidermal growth factor receptor /anaplastic lymphoma kinase targeted therapy regimens. This study summarized adverse event management in this trial. **Method:** Patients were randomized (2:1) to anlotinib or placebo up to progression or intolerable toxicity. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 4.0) and managed by investigators. Adverse events and key strategies for preventing and managing the most common adverse events were described. Proportions were compared using the χ^2 test or Fisher's exact test, as appropriate. Two-sided values of P <0.05 were considered statistically significant. Analyses were calculated by SAS 9.4. **Result:** Between February 2015, and August 2016, a total of 437 patients were randomized to anlotinib group (n=294) and placebo group (n=143). The most common anlotinb related adverse events were hypertension (64.6%), fatigue (46.3%), TSH elevation (44.6%), hand-foot syndrome (HFS) (43.2%), hypertriglyceridemia (38.8%), anorexia (38.4%). The most common anlotinib related grade ≥3 adverse events were hypertension (13.3%), HFS (3.7%), and hypertriglyceridemia (2.4%). The median onset time of hypertension, HFS, and hypertriglyceridemia were 6 days, 30 days, and 22 days respectively. To monitor blood pressure, every patient had an electronic manometer. One hundred and eight (36.7%) patients received dihydropyridine calcium channel blockers, 79 (26.9%) patients received converting enzyme inhibitors of angiotensin / angiotensin receptor blockers, 57 (19.4%) patients received diuretics, 35 (11.9%) patients received beta-blockers. Only 3 (1.0%) patients need dose modification due to hypertension. Prophylactic measures of HFS were recommended. Frequent emollients should be used on hands and feet to maintain skin hydration, manicure or pedicure to control calluses, protect pressure points and tender areas of feet with insole cushions, shock-absorbing soles, comfortable shoes. Seven (2.3%) patients required dose reduction due to hand-foot skin syndrome. Eleven (3.7%) patients received cortisone cream for topical therapy. Twenty-four patients received fibrates to reduce plasma triglyceride level. Two (0.7%) patients required dose reduction due to hypertriglyceridemia. **Conclusion:** Anlotinb-related adverse events could be controlled by prophylactic measures, and early intervention.

Keywords: non-small cell lung cancer, adverse event, Anlotinib

P1.01 ADVANCED NSCLC
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P1.01-109 PHASE I STUDY OF APATINIB PLUS GEFITINIB AS FIRST-LINE THERAPY IN PATIENTS WITH EGFR MUTANT ADVANCED NON-SMALL CELL LUNG CANCER

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Background: EGFR-TKI plus bevacizumab (anti-VEGF) has brought significant progression-free survival (PFS) improvement for advanced NSCLC patients (pts) as first-line therapy compared to EGFR-TKI alone (16.0 *vs.* 9.7 months, HR 0.41, Lancet Oncol, 15(11):1236-1244). Apatinib, a TKI that selectively inhibits VEGFR-2, has shown strong antitumor activity in both preclinical and clinical studies in NSCLC. This phase I study aims to evaluate the safety and efficacy of Gefitinib plus Apatinib in the first line setting. **Method:** Treatment-naïve advanced NSCLC pts with *EGFR* 19 Del or 21 L858R mutation were eligible. Two prespecified groups were designed: Cohort 1: Apatinib 500mg QD PO + Gefitinib 250mg QD PO; Cohort 2: Apatinib 250mg QD PO + Gefitinib 250mg QD PO. Pharmacokinetics (PK) profile of Apatinib plus Gefitinib was also evaluated. 6 pts in each cohort should be enrolled for PK analysis. **Result:** From July 2016 to April 2017, 12 pts were enrolled. Most common AEs were rash (91.7%, 11/12), diarrhea (66.7%, 8/12), proteinuria (58.3%, 7/12), hypertension (25.0%, 3/12), and hand-foot-skin reaction (8.3%, 1/12). And most of AEs were grade 1-2. SAE was observed in 1 case with grade 3 hypertension (8.3%). The PK parameters in this combination setting were similar to those of single agent from the previous literature reports (Table 1). Among all evaluable patients, ORR was 83.3% (10/12), and DCR was 91.7% (11/12). Median PFS was 19.0 months (95% CI 0.0–43.9) in the Apatinib (500mg) + Gefitinib group and 13.4 months (13.0–13.8) in the Apatinib (250mg) + Gefitinib group (*P*=0.657). **Table 1. Pharmacokinetic parameters (geometric mean, SD) of apatinib and gefitinib**

	Apatinib 250mg	Apatinib 500mg	Gefitinib 250mg
Cmax (ng/ml)	446(283)	499(257)	468(28)
$Cmax_{multi}$ (ng/ml)	415(184)	603(438)	469(134)
Tmax (h)	2.6(1.0)	2.8(1.9)	3.9(1.2)
AUC_{0-24} (ng·h/ml)	3315(2367)	4155(2564)	3330(852)
$AUC_{0-24multi}$(ng·h/ml)	4875(4439)	4914(3898)	8132(2311)

Conclusion: Apatinib (500mg) in combination with Gefitinib (250mg) shows a manageable tolerability profile and prolonged PFS tendency for *EGFR*-mutant NSCLC patients in first-line treatment setting. **Clinical trial information: NCT02824458**

Keywords: non-small cell lung cancer, gefitinib, Apatinib

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-110 THREE SPECIFIC HER2 MUTATIONS PREDICT FAVORABLE OUTCOMES IN ADVANCED LUNG CANCER PATIENTS TREATED WITH AFATINIB

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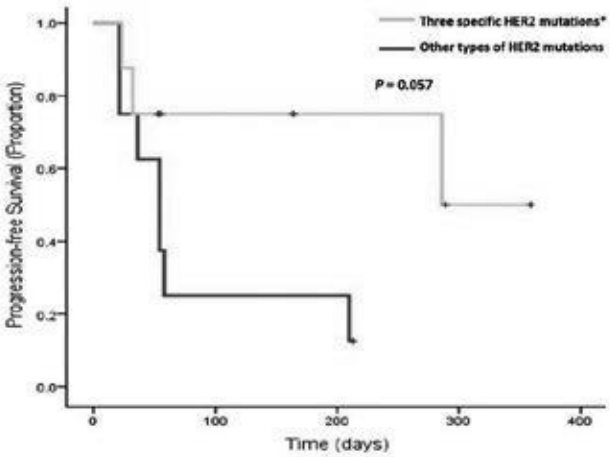
Background: HER2 mutation is a potential therapeutic target for non-small cell lung cancer (NSCLC). However, HER2-targeting therapies including trastuzumab, afatinib and T-DM1 show limited and inconsistent efficacies in HER2-mutant NSCLC, suggesting its heterogeneity and the need to refine patient selection strategy for this population. **Method:** To investigate the efficacy of afatinib in HER2-mutant NSCLC and develop NGS (next generation sequencing)-based patient selection strategy, we reviewed afatinib-treated, HER2-mutant advanced NSCLC in 8 different institutions across China. HER2 status of all included cases were tested using NGS. Patients with EGFR/ALK co-mutations were excluded. The primary endpoint was investigator-assessed objective response rate (ORR) using RECIST v1.1. The secondary endpoint was progression-free survival (PFS). Adopting the binomial exact method (one-sided type I error=10%, power=80%, P_0=20%, P_1=30%), at least 21 patients were needed. **Result:** As of 30 January 2018, a total of 23 afatinib-treated, HER2-mutant NSCLC patients were identified. Among 16 evaluable patients, 4 patients achieved partial responses (PR; ORR=25%), 7 achieved stable diseases (SD) and 5 had disease progression (PD) within 6 weeks. Median PFS (mPFS) for patients achieving disease control (n=11; 69%) was 9.53 months (range: 1.77-11.97). Two of the four partial responders had p.G778_P780dup, one had p.Y772_A775dup and one had p.G776delinVC. Same mutations were detected in five other patients. Patients harboring the three specific HER2 mutations (**p.G776delinsVC** (n=3); **p.Y772_A775dup** (n=3); **p.G778_P780dup** (n=2)) had marginally higher ORR (ORR=50%, *P*=0.077) and longer PFS (mPFS=9.53m,

P=0.057) than those carrying other types of HER2 mutations (n=8: ORR=0%, mPFS=1.80m) (Figure 1). TP53 co-mutation was observed in 6 patients, who showed similar responses to afatinib (PR=2, SD=2, PD=2) comparing to patients without co-occurring TP53 (n=10: PR=2, SD=5, PD=3).



Conclusion: HER2-mutant NSCLC represents a heterogenous group of diseases. Although afatinib failed to show the expected ORR in the overall population, patients harboring three specific HER2 mutations may still benefit from afatinib treatment.

Keywords: afatinib, HER2 mutation, NGS-based patient selection

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-111 EGFR EXON20 INSERTION PATIENTS TREATED WITH FIRST-LINE CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER

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Background: Epidermal growth factor receptor exon20 insertion(EGFR 20-ins) is a low frequency mutation among EGFR mutations, and chemotherapy is a major choice for these patients. The outcomes between different types of EGFR 20-ins and with EGFR sensitive mutation and wild type are not well studied. **Method:** From Oct 2011 to Feb 2018, EGFR 20-ins was detected using ARMS method. The mutation positive samples were subsequently confirmed by DNA sequencing. Clinicopathological features and outcomes between different kind of EGFR 20-ins patients as well as EGFR 20-ins patients with EGFR sensitive mutation and wild type patients were analyzed. **Result:** Eighty-four 20-ins patients were detected in this study. Eight were not enough for DNA sequencing, 11 were wild type and 65 were mutation positive. The three major subtypes were: 28 c.2308_2309insCCAGCGTGG, 9 c.2311_2312insGCGTGGACA and 10 c.2319_2320insAACCCCCAC. Of the 45 patients who could access treatment effect in first-line chemotherapy, objective response rate(ORR) was 28.9%(13/45), disease control rate(DCR) was 86.7%(39/45) and median progression-free survival (mPFS) was 5.7 month. There were no significant differences in sex, age, smoking status, pathological types, ORR, DCR and PFS between c.2308_2309insCCAGCGTGG mutation and other 20-ins mutations. We compared the PFS of EGFR sensitive mutation, wild type and 20-ins patients, and found no significant difference(p=0.324). **Conclusion:** EGFR 20-ins is a distinct EGFR mutation. The clinicopathological features and clinical outcome were not significantly different between different EGFR 20-ins subtypes, as well as between EGFR 20-ins, EGFR sensitive mutation and wild type patients. Target drugs for this kind of patients are needed.

Keywords: EGFR exon20 insertion, chemotherapy

P1.01 ADVANCED NSCLC
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P1.01-112 OSIMERTINIB VS STANDARD OF CARE (SOC) EGFR-TKI AS FIRST-LINE TREATMENT IN CHINESE PATIENTS WITH EGFRM ADVANCED NSCLC

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Background: Osimertinib is an irreversible, central nervous system (CNS) active EGFR-TKI, selective for both EGFRm and T790M resistance mutations. FLAURA (NCT02296125) is a PhIII, double-blind, randomized study assessing efficacy and safety of osimertinib vs SoC EGFR-TKI (erlotinib/gefitinib) in first-line patients with EGFRm advanced NSCLC. FLAURA results (556 patients, globally) are published. We present the China cohort results. **Method:** The cohort included self-identified Chinese patients, enrolled in China. Eligible patients: ≥18 years, Ex19del/L858R EGFRm advanced NSCLC, no prior EGFR-TKI/systemic anti-cancer therapy for advanced disease. Neurologically stable patients with CNS metastases were allowed, if definitive treatment/corticosteroids were completed ≥2 weeks before enrolment. Patients were randomized 1:1 to osimertinib 80 mg once daily (qd) orally or SoC EGFR-TKI (gefitinib 250 mg qd orally selected by all Chinese sites), stratified by mutation status (Ex19del/L858R). Primary endpoint: progression-free survival (PFS) by RECIST v1.1, per investigator. Data cutoff: 10/01/2018. **Result:** Overall, 136 patients were randomized (osimertinib n=71; SoC n=65); 19 were also included in the global analysis. Baseline characteristics were balanced across arms (osimertinib/SoC): female 61/71%; smoking history 25/23%; WHO performance status 1 90/80%; Ex19del 51/51%, L858R 49/49%; CNS metastases 24/32%.

Efficacy endpoint	Osimertinib n=71	SoC n=65
PFS events, total patients (% maturity)	40 (56%)	51 (78%)
PFS hazard ratio (HR)* (95% CI)	0.56 (0.37, 0.85); p=0.007	
Median PFS, months (95% CI)	17.8 (13.6, 20.7)	9.8 (8.3, 13.8)
Objective response rate (ORR), % (95% CI)	83% (72, 91)	75% (63, 85)
Median duration of response (DoR), months (95% CI)	16.4 (12.3, NC)	10.9 (8.3, 13.8)

*A hazard ratio <1 favours osimertinib.

PFS benefit was observed across all subgroups, irrespective of EGFR mutation status and including patients with/without CNS metastases at study entry. Median total treatment duration: osimertinib, 18.9 months; SoC, 13.6 months. No new safety signals were reported. Numerical increase in grade ≥3 AEs was reported in the osimertinib arm (49%) versus SoC arm (23%). Most grade ≥3 AEs in the osimertinib arm were investigator-reported laboratory and disease-related AEs; incidence of non-laboratory-related events was low. AEs leading to discontinuation: osimertinib, 13%; SoC, 6%. In the osimertinib arm, most AEs leading to discontinuation were fatal disease-related events. **Conclusion:** Osimertinib improved PFS vs SoC EGFR-TKI (HR: 0.56) as first-line treatment in Chinese patients with EGFRm advanced NSCLC, consistent with the global analysis.

Keywords: osimertinib, China, NSCLC

P1.01 ADVANCED NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.01-113 ANALYSIS OF CLINICOPATHOLOGICAL FEATURES AND CLINICAL EFFICACY OF CRIZOTINIB IN ROS1 POSITIVE NON-SMALL CELL LUNG CANCER

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Background: ROS1 gene-rearrangement in non-small-cell lung cancer (NSCLC) patients has recently been identified as a driver gene and benefited from crizotinib treatment. The aim of this study is to explore clinicopathological features and clinical efficacy of crizotinib in c-ros oncogene 1 receptor tyrosine kinase (ROS1) positive non-small cell lung cancer (NSCLC). **Method:** A retrospective analysis of 2617 cases of NSCLC from January 2013 to December 2016, *ROS1* fusion gene were detected by real-time reverse transcriptase-polymerase chain reaction (RT-PCR), fluorescent in situ hybridization (FISH) or next-generation sequencing (NGS) technique and part ROS1 fusion gene positive patients were received oral treatment with crizotinib. **Result:** ROS1 fusion was found in 67 of 2167 cases (2.56%). 21 cases were male and 46 cases were female. The median age was 68 years old. Among these cases, 59 (88.05%) were adenocarcinoma and 8 were non-adenocarcinoma. According the TNM staging,4 cases were I-IIIa and 63(94.02%) cases were IIIb-IV. EGFR gene status included 60 cases wild type, 1 case co-mutation and 6 cases unknown. There were statistical difference in sex, TNM staging and EGFR gene status between ROS1 fusion gene positive and negetive patients (P<0.001). 23 patients were received oral treatment with crizotinib and PR, SD, PD patients were 13 (56.52%), 5 (21.74%) and 5 (21.74%) respectively. The ORR was 56.52% and DCR was 78.26%. Of all the cases, median PFS was14.5 months and OS was 27.3 months. The one-year PFS was 50.4%.There were no difference of median PFS in age, sex, smoking history, PS score, pathology type, TNM staging ,TP53 gene status, EGFR gene status and the first line crizotinib treatment whether or not by single and multiple factor analysis. The 3/4 grade treatment-related adverse events were gastrointestinal disturbance, followed by increased transaminase. **Conclusion:** The rate of ROS1 fusion of NSCLC is lower. Crizotinib is an effective and safe drug for the treatment of ROS1 positive advanced NSCLC.

Keywords: clinicopathology, Gene, Lung neoplasms

P1.02 ADVOCACY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.02-01 IMAGING OF LUNG CANCER AT THE UNIVERSITY COLLEGE HOSPITAL, IBADAN, NIGERIA: DOES NUCLEAR MEDICINE HAVE ANYTHING TO OFFER?

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Background: Lung cancer is the most common cause of cancer mortality worldwide. Majority of lung cancer cases occur in less-developed regions. In cancer medicine; bone scintigraphy, a highly sensitive nuclear medicine technique, is often used as a simple whole-body imaging method for metastatic survey. However most recent clinical guidelines on lung cancer management do not recommend the routine use of bone scans to exclude bone metastases, PET/CT (Positron Emission Tomography/Computed Tomography) imaging being the method of choice. In a country where routine PET/CT imaging is not yet available, we investigated bone scan requests in lung cancer patients at our institution since inception of Nuclear Medicine services. **Method:** Bone scan requests over an eleven-year period (2006-2017) at the Nuclear Medicine Centre of the University College Hospital, Ibadan, Nigeria were reviewed. Indications involving lung cancer patients were noted and images as well as reports were reviewed. Standard procedure of planar bone scintigraphy with a gamma camera was employed in all patients following intravenous injection of 15-25mCi ^{99m}Tc- Methylene Diphosphonate (MDP). **Result:** Of over 6,000 patients who had bone scintigraphy during the period under review, only 12 scans (in eleven patients) were done for detection of bone metastases in known lung cancer patients. The mean age was 50.3 years (range 33 – 68) with male to female ratio of 1.2: 1. Histologic sub-type of all but one was non-small cell lung cancer (NSCLC). All of these patients had skeletal related events, primarily severe bone pains requiring radiation therapy/analgesia, while two had known metastases prior to imaging. Bone scan revealed multiple foci of bone metastases in the vast majority (75%) of the cases. Two cases were negative and one equivocal. Only one required additional tomographic (SPECT) imaging to arrive at a conclusive report. **Conclusion:** With an average of one bone scan per year and <0.2% of total bone scans in an eleven-year period, bone scintigraphy appears to be underutilized in the setting of lung cancer in our environment. In the absence of PET/CT imaging, bone scintigraphy still has an important role to play in patients' management and referring physicians are encouraged to embrace this imaging modality.

Keywords: Bone scintigraphy, Lung cancer, UCH Ibadan

P1.02 ADVOCACY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.02-02 'LISTEN TO YOUR LUNGS' – AN AWARENESS CAMPAIGN FROM THE MARIE KEATING FOUNDATION

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Background: In Ireland, lung cancer is the biggest cancer related killer in both men and women, accounting for over 2,300 cancer cases and over 1,800 deaths. Incidence and mortality rates are projected to increase further in the coming years, particularly in women. In the absence of a national screening programme, there is a need to improve lung cancer awareness, particularly as 1 in 4 Irish people cannot identify one lung cancer symptom. Recent research undertaken by our Foundation has also established that only 7% of adults believe that lung cancer is the leading cause of cancer related deaths in Irish women, and 98% believe that only smokers get lung cancer. These figures underscore the necessity for a national awareness campaign. **Method:** During Lung Cancer Awareness Month, our Foundation launched an accessible multifaceted national campaign to reach out to, and educate men and women on symptoms and risk, to aid in the early detection of lung cancer. Our campaign aligned with the National Cancer Strategy and focused on symptom awareness, specifically those of a persistent cough, linked with a change in a long-term cough and breathlessness. Our campaign slogan was 'Listen To Your Lungs' and our call to action 'If you have a cough lasting longer than 3 weeks, go see your GP'. The campaign consisted of videos, activities on social media and our website, a radio advertisement and outdoor advertising which included Ireland's first 'coughing billboard'. A central part of our campaign was a video produced in conjunction with a lung cancer survivor who talked about his journey and his main symptom – a persistent cough. **Result:** The campaign was covered nationally in terms of radio and print. Our radio advertisement reach was 1.4 million adults. Images on 12 standard bus shelters and the 'coughing billboard' were shared widely and generated significant social media activity. Through the Foundation's own channels, engagement rate was high on Twitter, Facebook and Instagram. Indeed some posts were the best performing posts in the history of the Foundation's social media channels. The campaign video was the best performing post of the campaign; it attained a reach of nearly 200,000 people with approximately 150,000 views. **Conclusion:** Our first multifaceted national awareness campaign was well received and generated much needed conversation around lung cancer symptoms and risk. We believe that a campaign of this nature can contribute in a meaningful way to the early detection of lung cancer.

Keywords: awareness, Education, symptoms

P1.02 ADVOCACY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.02-03 THE ROLE OF LUNG CANCER ADVOCACY ORGANIZATIONS IN BIOMARKER TESTING

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Background: In the past 10 years, major advances have been made in our understanding and treatment of lung cancer. Lung cancer is now recognized as not just a single disease, but rather comprises many subtypes, each with unique molecular characteristics or biomarkers. Most new treatment options developed and under development for non-small cell lung cancer (NSCLC) target specific biomarkers, and these targeted therapies are improving outcomes in patients with the applicable biomarker. Despite this progress, biomarker testing is often viewed as an optional service by both patients and their healthcare team. **Method:** In

March 2018, a roundtable was convened consisting of executives from lung cancer advocacy organizations and key opinion leaders in the lung cancer field to discuss trends in biomarker testing for patients with lung cancer. The main objective of the roundtable was to develop an action plan to increase awareness of biomarker testing to ensure all lung cancer patients receive the most effective treatment. **Result:** Several barriers were identified that may contribute to suboptimal biomarker testing including lack of patient and physician awareness, inadequate tissue sampling, slow turn-around time, limited availability in some community settings, and health policy issues surrounding access, cost, and reimbursement. Patient advocacy groups are well positioned to address the lack of patient awareness with education campaigns. However, the lack of consistent language to describe biomarker testing among organizations is a barrier. To address this issue, advocacy groups need to align on common terminology and messaging with regard to biomarkers. Two potential approaches to achieve this goal include: 1) collaboration to develop joint educational material or 2) collaboration to develop a shared consensus statement including best practices and common core items or 'building blocks' for use by each organization to develop their own materials. As a first step, consistent messaging with regard to the Who, What, When, Where, Why, and How of biomarker testing are needed. Understanding gaps in physician knowledge regarding biomarker testing and development of initiatives to address these gaps are also warranted. **Conclusion:** Additional patient and physician education are needed to establish biomarker testing as part of standard of care in patients with advanced-stage NSCLC, with the ultimate goal being that the patient has a full biomarker panel available (or at least tests in progress) at their first appointment with an oncologist. A unified effort from lung cancer advocacy organizations, healthcare providers, and industry partners is needed to achieve this goal.

Keywords: Barriers, consensus statement, awareness

P1.02 ADVOCACY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.02-04 THE EGFR RESISTERS LUNG CANCER GROUP: A PATIENT-DRIVEN INITIATIVE TO UNDERSTAND & IMPROVE TREATMENTS FOR EGFR+ LUNG CANCER

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Background: Lung cancer patients harboring mutations in the EGFR gene represent a significant amount of patients diagnosed with non-small cell lung cancer (NSCLC). Approximately 10-15% of patients with NSCLC in the United States (U.S.) and 35% in Asia have an EGFR mutation. In the U.S., more than 20,000 people with EGFR-positive lung cancer are diagnosed each year. Although there has been an increase in progression-free survival in patients due to EGFR tyrosine kinase inhibitors (TKIs), patients eventually develop acquired resistance. With each generation of TKIs developed, more mechanisms of resistance are discovered; therefore the development of drugs to target resistance mutations and other mechanisms of resistance are desperately needed. **Method:** The EGFR Resisters is a group of people living with and/or personally affected by EGFR-positive lung cancer. The purpose of founding the group is to build a community of survivors and caregivers to share knowledge, provide support, and confidentially collect patient data (such as patient demographics, details of lung cancer diagnosis, specific type of EGFR mutation, acquired resistance and mechanism of resistance). Patient data will be aggregated and analyzed to identify trends such as commonalities and differences in mechanisms of resistance. The goal of the EGFR Resisters is to improve outcomes for people with EGFR-positive lung cancer by accelerating research. Our ultimate objective is changing EGFR-positive lung cancer into a manageable chronic disease. **Result:** EGFR Resisters is comprised of nearly 400 members from 20 countries. Out of the 60% of members who have provided data, 65% have already developed acquired resistance to their current EGFR TKI. The types of resistance mechanisms seen in this community are consistent with results that have been published from other studies. Since the launch of our website (www.egfrcancer.org) in February, we have been contacted by numerous stakeholders from academia, research and industry who are interested in collaborating with the EGFR Resisters to help further our goal. **Conclusion:** We are working to increase the size of our EGFR Resisters community with the assistance of advocacy groups and medical professionals. We are also building relationships with EGFR thought leaders in the scientific and medical community to identify practice gaps and develop an action plan for educational and research efforts. Our aim is to use the strength of our collaborations to drive important research questions and fund novel research and clinical trials.

Keywords: EGFR, Resistance, Patient-Driven

P1.02 ADVOCACY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.02-05 ALK POSITIVE LUNG CANCER: PATIENT ENGAGEMENT AND PARTNERSHIP

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Background: Approximately four (4) to seven (7) percent of non-small cell lung cancer (NSCLC) is driven by the ALK transfusion. In the United States, approximately 11,000 people are diagnosed with ALK-positive NSCLC every year. There is an array of treatment options for the ALK-positive patient, and these options have improved overall survival rates in this subset of NSCLC patients. Currently, there are four FDA approved tyrosine kinease inhibitors (TKIs) that treat ALK-positive NSCLC: crizotinib, ceritinib, alectinib, and brigatinib. A fifth, lorlatinib, is expected to be approved shortly, and there are other drugs that are in clinical trials. Invariably, patients develop acquired resistance to each of these drugs, but the mechanisms of resistance can vary. The proper sequencing of these drugs also remains an open question. **Method:** ALK Positive is a community of over 1,000 people from 38 countries, who are either living with or personally affected by ALK-positive NSCLC. It was founded with the goal of bringing information, empathy, and support to survivors and caregivers alike. The ALK Positive community also encourages the sharing of patient information so that patients can make informed treatment decisions. **Result:** A primary goal of the ALK Positives is to improve survival for people with ALK-positive NSCLC by accelerating research. To that end, in less than a year, the ALK Positives have raised about $400,000 to fund two (2) research grants relating to ALK-positive NSCLC. In consultation with the scientific advisory panel provided by the Lungevity Foundation, ALK-positive patients themselves will decide which research to fund. Announcements of the grant awards are anticipated in May 2018. The group is also engaged with researchers, treating physicians, other lung cancer organizations, and the pharmaceutical industry, so as to advance cutting edge research and treatment of those living with ALK-positive NSCLC, with the long term goal of finding a cure. **Conclusion:** The ALK Positive community is a crucial component of the "patient-first" movement that has been gaining momentum in the lung cancer field recently. Just in the first four months of 2018 alone, the ALK Positive group grew close to twenty percent (20%), and the trend is likely to continue, as patients become more educated about their disease and increasingly desire to truly be partners with the medical community in their care.

Keywords: patient, ALK

P1.02 ADVOCACY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.02-06 USEFULNESS OF WORKSHOP TO PROMOTE COMMUNICATION BETWEEN PATIENT AND FAMILY

K. Hasegawa
Patient Network Onestep, Kanagawa/JP

Background: In the study of YoongJ who conducted early palliative care and explored the reason for achieving survival extension, the "talk with family members" factor emerged as a feature of the intervention group about disease. Human relations that can talk about anything suggests an improvement in quality of life and appropriate ties to medical care. What can the patient association do after receiving this research? We held a workshop to encourage communication between family members and patients and examined its usefulness. **Method:** September 10, 2017. Participants 53 (3 babies) STEP 1 Outline of "What is Family" by nurses. Families are "subjects of great support", while "subjects of great stress". Then discuss the deviation of the consciousness of the patient and the family. STEP 2 After a lecture, "Discussion on communication methods without causing stress" by psychologists Discuss contrivances each can do. STEP 3 "Let's change our eyes" lecture by nurses. "Enter third parties" "Change the place to talk". After that, did your feelings change before and after joining? How has it changed? questionnaire. Respondents were obtained from 21 (11 patients, 9 families, 1 other). **Result:** There are a lot of answers that express the change of mind. My family "do not have to endure" "They all have the same trouble." The patient often said that "I knew that my family was suffering". **Conclusion:** From the questionnaire, it was thought that the family lost heart and the patient got "awareness" to remember the family, and the usefulness of the workshop was suggested. Continuously, it is important to continually implement programs that better communicate between patients and families and contribute to QOL improvement.

Keywords: Early palliative care, Family, communication

P1.02-07 THE ROLE OF VOLUNTEERS IN QUALITY PALLIATIVE CARE DELIVERY FOR ADVANCE LUNG CANCER

A. Manna

Palliative Care, Narikeldaha Prayas, East Medinipur/IN

Background: Here in India most of the cancer patient including lung cancer patient die a sad death of neglect due to lack of awareness about palliative care and low economic level. Surveys in India show that two third of cancer patient do not get proper care during the terminal phase of their life. Palliative care through volunteers can make a significant difference in this respect. To identify and try to solve, to the extent possible, the main difficulties in giving palliative care to the terminal cancer patients of the area. And evaluate the impact of volunteer's direct care of palliative patients and their families. **Method:** Feedback from patients and their relatives regarding the palliative care they receive from nursing home and from volunteers and compare the two. Also feedback from volunteers regarding their positive and negative experience while delivering palliative care service. Then evaluate the data to compare and improve the quality of service. **Result:** We carried out two studies. One study was undertaken in nursing home palliative care and another was in home setting by volunteers. Both studies were in adult palliative care services. Since January 2015, 496 cases were studied to enquire about their experience in both home based care and nursing home care. Both the studies fulfilled our quality appraisal criteria. One found that those families and patients who received home visits from volunteers were significantly more satisfied. The study highlighted the value of the role of volunteers in better satisfaction of patients and their families. **Conclusion:** Further research is needed to evaluate the role of volunteers in palliative care and how it can be delivered appropriately and effectively. We also wish to compare our findings with similar studies elsewhere.

Keywords: rural india, palliative care, lung cancer

P1.02-08 HOPE FOR PEOPLE LIVING WITH METASTATIC LUNG CANCER

A. Manna

Palliative Care, Narikeldaha Prayas, East Medinipur/IN

Background: As in any developing countries state of West Bengal in India has a huge burden of metastatic lung cancer patients in advanced stage coming from rural area where awareness regarding the usefulness of palliative care in rather poor. Our goal is to give a pain free good quality of life in these advanced stage lung cancer patients. Objective of this study is to identify the main difficulties in achieving the above goal in a rural village setting in India. **Method:** Advanced lung cancer patients in need of palliative care in various villages in of rural India were selected for this study. Their symptoms and managements in that rural surroundings were evaluated by an NGO (under the guidance of a senior palliative care specialist) working in that area. An attempt was made to identify the main obstacles in getting proper palliative care in a rural setting. **Result:** Pain, fatigue, respiratory distress are the main symptoms effecting these patients. In most patients pain and other symptoms control were grossly inadequate due to lack of properly trained manpower in the rural India. However regular homecare visits by a group of social workers were of immense help in the last few months of life. NGO team was well guided by a palliative care specialist. **Conclusion:** There is a wide gap of trained manpower in this filled in rural areas of India. Dedicated groups from rural area itself need encouragement, repeated home visit, awareness built up, proper training to home care giver, so that difficult symptoms can be managed locally along with necessary social and psychological support to these patients.

Keywords: ruaral ngo, lung cancer, metastatic cancer

P1.02-09 IDENTIFYING GAPS IN MESSAGING FOR BIOMARKER TESTING IN THE LUNG CANCER COMMUNITY: NEED FOR CONSISTENT AND ACTIONABLE MESSAGING

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Background: Since 2015, the US Food and Drug Administration has approved more than fifteen lung cancer treatment approaches, the majority of which are biomarker-driven. However, not all eligible patients benefit from these treatments, partly due to lack of tumor testing. To help assess whether inconsistent messaging could be a contributor to the suboptimal biomarker testing rates, we conducted a messaging audit to determine the messages being conveyed to lung cancer patients and healthcare providers (HCP). **Method:** We analyzed marketing and education materials from 7 lung cancer patient advocacy groups (PAGs), 2 professional associations, 10 pharmaceutical companies, and 5 diagnostic companies that provide genomic testing to lung cancer patients. The materials included were those used by PAGs geared toward patients and those used by industry and testing companies for both patients and HCPs (oncologists). Privately used marketing materials were solicited from pharmaceutical companies. All materials were de-identified, and the rubric of analysis involved assessing whether materials answered six key questions: What *is biomarker testing?* Why is it important? Who (which patients) should get tested? When (at what point in the treatment journey)? How and where is testing done? Materials were audited by two independent reviewers and checked for inter-reviewer reliability. The audit was presented to a stakeholder group (organizations included in the audit) to elicit feedback, discuss gaps, and identify solutions. **Result:** When analyzing patient-facing materials, PAGs were successful in answering Why, Who, and What, whereas pharmaceutical industry-developed campaigns were adept at answering the Why, How, and What. Deeper analysis revealed that patients were receiving mixed messages from PAGs and industry developed-campaigns. PAGs analyzed did not produce HCP-facing materials. However, industry-generated HCP-facing materials' strength was their responses to Why *patients should be tested* and their gap was their responses to When *patients should be tested.* A qualitative trend noted was that most HCP-facing materials did not focus on the benefit to a patient that testing provides. All materials audited lacked a consistent "call-to-action" to patients. **Conclusion:** Our audit identified gaps in education materials, and highlights the importance of consistent and actionable messages for lung cancer patients and HCPs so that the importance of biomarker testing is appropriately conveyed. When presented to the stakeholder group, meeting participants agreed that all materials should at least answer the Why, Who, and When. Furthermore, they suggested that educational materials should include the importance to patients of tissue–based biopsies and tissue acquisition for biomarker testing.

Keywords: biomarker, biomarker testing

P1.02-10 "WE ARE AMBASSADORS FOR SURVIVORS:" EXPERIENCES OF LUNG CANCER SUPPORT GROUP ATTENDEES AND FACILITATORS

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Background: Each year, 1.8 million people are diagnosed with lung cancer globally. Compared with other cancers, lung cancer patients experience higher levels of distress and have greater unmet physical and emotional needs. A significant unmet need is social support. Face-to-face support groups can meet this need and may increase feelings of control and decrease distress. While lung cancer patients tend to prefer lung cancer-specific over general cancer groups, for many reasons these groups can be challenging to start and maintain. The number of lung cancer support groups in the world is not known. In the US, where over 230,000 people are diagnosed annually, there are typically fewer than 100 groups running at any given time, and many of those are not thriving. The goal of this project was to solicit and compile the real-world experiences of lung cancer support group attendees and facilitators to increase the chance of success for new groups and provide struggling groups with tips and ideas that can be used anywhere in the world. **Method:** The perspectives of support group attendees (patients, survivors and loved ones) and facilitators were gathered and analyzed. Attendee perspectives were

gained through: -- 10 focus groups, with questions related to motivation for group attendance, group benefits and suggestions to improve the group -- Analysis of 17 pre- and post- attendance questionnaires to measure group impact -- A review of relevant literature Facilitator perspectives were gained through: -- A 21 question online survey to 131 lung cancer support group facilitators, 7 in Australia, 42 in the United Kingsom nd 82 in the United States, with questions related to greatest challenges in group startup and maintenance and soliciting creative solutions used to overcome difficulties -- In-depth interviews with two successful facilitators -- A review of relevant literature **Result:** s have been analyzed and categorized according to benefits of group attendance, facilitator perspectives and identifcation of challenge and solution themes. The most difficult issue for facilitators is getting the word out and maintaining attendance. A clear benefit to attendees is the opportunity to join with others who truly understand their experiences. **Conclusion:** Only through listening to both lung cancer support group facilitators and attendees can we identify indicators of group success. The results of this project are diseminated to help facilitators of new groups consider a number of factors known to foster successful groups and provide direction to facilitators of groups that are struggling, anywhere in the world.

Keywords: distress, groups, support

P1.02 ADVOCACY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.02-11 LUNG CANCER SYMPTOM AWARENESS: FINDINGS FROM A GLOBAL CONSUMER SURVEY

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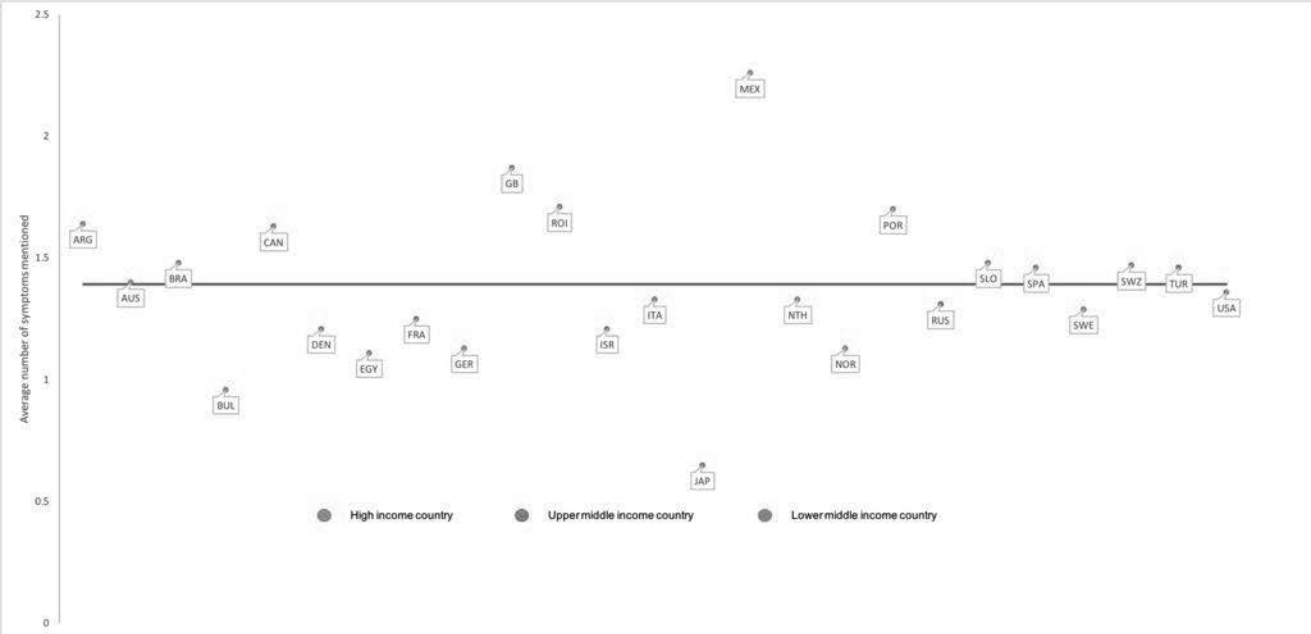
Background: Diagnosed early, lung cancer outcomes are more positive. Absent national screening programs, symptom recognition is critical. In 2017, the Global Lung Cancer Coalition (GLCC) commissioned Populus to undertake an international consumer survey of symptom awareness in each of the 25 member countries. **Method:** In July 2017, 1,000 adults, in each of 25 countries, were asked (unprompted) to name as many symptoms of lung cancer as they could. Findings were analysed to determine any correlation between symptom awareness and country income, using World Bank data. **Result:** There was no correlation between the country's income and symptom awareness (Figure 1). Four out of ten people (42%) were unable to name any symptoms of lung cancer. On average, people could only name one or two symptoms of lung cancer. The three most commonly named symptoms were coughing (38%), shortness of breath (35%) and coughing up more blood, spit or phlegm (15%).

Conclusion: No country has room for complacency on lung cancer symptom awareness, irrespective of country income. Approaches in countries with higher symptom recognition, like Mexico, should be examined for lessons. More must to be done to reach and educate those who cannot name any symptoms of lung cancer to encourage symptom recognition and earlier presentation.

Keywords: symptoms, awareness



POSTER SESSION 1
MONDAY, SEPTEMBER 24, 2018

P1.03 BIOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.03-01 ASSOCIATION OF APC MUTATIONS WITH CHINESE PATIENTS MOLECULAR SPECTRUM IN NON-SMALL-CELL LUNG CANCER

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Background: The role of adenomatous polyposis coli (*APC*) gene in mitosis might be critical for regulation of genomic stability and chromosome segregation. *APC* gene mutations have been associated to have a role in colon cancer and since gastric and colon tumors share some common genetic lesions, it is relevant to investigate the role of *APC* tumor suppressor gene in gastric cancer. While the genetic sites of *APC* mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *APC* mutations. **Method:** A total of 294 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *APC* mutation and other genes were detected by next generation sequencing. **Result:** *APC* gene mutation rate was 4.08% (12/294) in non-small cell lung cancer, including R232* (1 patient), Y159* (1 patient), R564* (1 patient), E984Dfs*21 (1 patient), K534Nfs*15 (1 patient), Q161* (1 patient), K1437* (1 patient), K792* (1 patient), T1556Nfs*3 (1 patient), N32S (1 patient), R259W (1 patient) and N372D (1 patient) , and median overall survival (OS) for these patients was 9.0 months. Among them, all patients were *APC* gene with co-occurring mutation. Briefly, patients with (n=8) or without (n=4) co-occurring *EGFR* mutations had a median OS of 9.0 months and 6.0 months respectively (P=0.01); patients with (n=6) or without (n=6) co-occurring *TP53* mutations had a median OS of 6.5 months and 11.0 months respectively (P=0.04); patients with (n=4) or without (n=8) co-occurring *KRAS* mutations had a median OS of 16.5 months and 9.0 months respectively (P=0.27); patients with (n=2) or without (n=10) co-occurring *CDKN2A* mutations had a median OS of 6.5 months and 11.5 months respectively (P=0.68). **Conclusion:** The present study expanded the database on *APC* gene mutations in NSCLC and enriched the spectrum of known somatic mutations of the *APC* gene. Chemotherapy may be considered as a possible treatment for carriers of the mutation. *EGFR* mutated accompanied mutations might play a good prognosis in *APC* gene mutation NSCLC.

Keywords: Non-small-cell lung cancer, Prognosis, APC mutation

P1.03 BIOLOGY
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P1.03-02 ANALYSIS OF SMAD4 ABERRATIONS IN CHINESE PATIENTS WITH NON-SMALL-CELL LUNG CANCER

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Background: Mothers against decapentaplegic homolog 4 (*SMAD4*) is an important protein in cancers. It plays pivotal roles in cellular pathways, including apoptosis. While the genetic locus of *SMAD4* mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *SMAD4* mutations. **Method:** A total of 451 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *SMAD4* mutation and other genes were detected by next generation sequencing. **Result:** *SMAD4* gene mutation rate was 1.77% (8/451) in non-small cell lung cancer, including R361H (3 patients), C324Y (1 patient), E526Q (1 patient), Q289* (1 patient), D493G (1 patient) and P522R (1 patient), and median overall survival (OS) for these patients was 13.0 months. Among them, all patients were *SMAD4* gene with co-occurring mutation. Briefly, patients with (n=2) or without (n=6) co-occurring *EGFR* mutations had a median OS of 10.0 months and 15.0 months respectively (P=0.18); patients with (n=5) or without (n=3) co-occurring *TP53* mutations had a median OS of 10.0 months and 19.5 months respectively (P=0.18); patients with (n=3) or without (n=5) co-occurring *KRAS* mutations had a median OS of 10.0 months and 15.0 months respectively (P=0.30); patients with (n=3) or without (n=5) co-occurring *CDKN2A* mutations had a median OS of 10.0 months and 15.0 months respectively (P=0.22). **Conclusion:** There are some significant difference of clinical features in *SMAD4* gene mutations with smoking advance NSCLC. *SMAD4* gene inactivation is associated with poorer prognosis in patients with NSCLC.

Keywords: Non-small-cell lung cancer, SMAD4 mutation, Prognosis

P1.03 BIOLOGY
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P1.03-03 MOLECULAR CHARACTERISTICS OF CHINESE PATIENTS WITH TSC2-MUTATED NON-SMALL-CELL LUNG CANCER: A RETROSPECTIVE STUDY

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Background: Tuberous sclerosis complex 2 (*TSC2*) is a rare autosomal dominant disorder causing benign tumors in the brain and other vital organs. There is some clinical evidence for the use of TSC2 mutations as prognostic and predictive biomarker. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *TSC2* mutations. **Method:** A total of 554 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *TSC2* mutation and other genes were detected by next generation sequencing. **Result:** *TSC2* gene mutation rate was 4.51% (25/554) in non-small cell lung cancer, including M286V (2 patients), R1743W (1 patient), V550G (1 patient), D1004Y (1 patient), E546K (1 patient), K1065E (1 patient), R1329P (1 patient), K1585R (1 patient), S1221L (1 patient), A678T (1 patient), F15V (1 patient), D1406N (1 patient), P237L (1 patient), V1144M (1 patient), V1034I (1 patient), D1406N (1 patient), N1224I (1 patient), Q371H (1 patient), P1770S (1 patient), R1268G), A1141T (1 patient), R537C (1 patient), M649I (1 patient) and A1294V (1 patient), and median overall survival (OS) for these patients was 20.0 months. Among them, 23 patients with co-occurring mutations had a median OS of 20.0 months, and median OS of the 2 patients without complex mutations was 7.0 months. No statistically significant difference was found between the two groups (P=0.15). Briefly, patients with (n=8) or without (n=17) co-occurring *EGFR* mutations had a median OS of 19.0 months and 20.0 months respectively (P=0.93); patients with (n=18) or without (n=7) co-occurring *TP53* mutations had a median OS of 20.0 months and 27.5 months respectively (P=0.67). **Conclusion:** There is no significant difference of molecular features in *TSC2* gene mutations in NSCLC. Patients with complex mutations benefited more from therapy than those with single mutations. Next generation sequencing provides a simplified strategy and reasonably high detection rate for *TSC2* mutation, which suggested application of the strategies into clinical molecular diagnostics.

Keywords: TSC2 mutation, Non-small-cell lung cancer, Prognosis

P1.03 BIOLOGY
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P1.03-04 MOLECULAR CHARACTERISTICS OF ALK PRIMARY POINT MUTATIONS NON-SMALL-CELL LUNG CANCER IN CHINESE PATIENTS

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Background: Anaplastic lymphoma kinase (*ALK*) gene rearrangements have been identified in lung cancer at 3-7% frequency, thus representing an important subset of genetic lesions that drive oncogenesis in this disease. While the genetic locus of *ALK* primary point mutations NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *ALK* primary point mutations. **Method:** A total of 339 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *ALK* primary point mutation and other genes were detected by next generation sequencing. **Result:** *ALK* gene primary point mutation rate was 8.55% (29/339) in non-small cell lung cancer, including V163L (3 patients), F921Gfs*16 (2 patients), K1416N (2 patients), A585T (2 patients), P1442Q (1 patient), A348T (1 patient), K1525E (1 patient), S737L (1 patient), P115L (1 patient), Q515E (1 patient), E314D (1 patient), R395H (1 patient), S1219F (1 patient), S341G (1 patient), P1543S (1 patient), G129V (1 patient), Q167H (1 patient), L550F (1 patient), T1012M (1 patient), D302Y (1

patient), H755Q (1 patient), H331Q (1 patient), G1474E (1 patient) and E119D (1 patient), and median overall survival (OS) for these patients was 20.0 months. Among them, 27 patients with co-occurring mutations had a median OS of 20.0 months, and median OS of the 2 patients without complex mutations was 8.5 months. Statistically significant difference was found between the two groups (P=0.02). Briefly, patients with (n=8) or without (n=21) co-occurring *EGFR* mutations had a median OS of 24.0 months and 20.0 months respectively (P=0.73); patients with (n=21) or without (n=8) co-occurring *TP53* mutations had a median OS of 20.0 months and 17.0 months respectively (P=0.83). **Conclusion:** *EGFR* and *TP53* gene accompanied may have less correlation with *ALK* primary point mutation in NSCLC patients. Results of ongoing studies will provide a platform for further research to offer individualized therapy with the purpose of improving outcomes.

Keywords: Non-small-cell lung cancer, Prognosis, ALK primary mutation

P1.03 BIOLOGY
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P1.03-05 TRANSCRIPTOME LANDSCAPE OF LUNG ADENOCARCINOMA PATIENTS REVEALED DISTINCT TRAJECTORY PATTERNS

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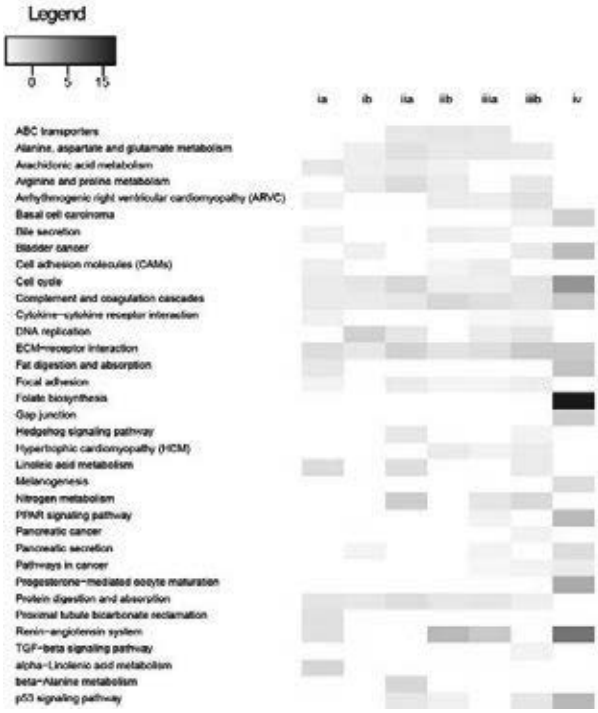
Background: The hallmarks of cancer was proposed to elucidate the common trajectory of tumors of different tissues of origin and genetic makeups, which were expected to attributed to disruption of regulatory pathways conferring survival and growth advantages to tumor tissues. However, the specific biological processes involved in each milestones in the trajectory of development of lung adenocarcinoma, particularly regarding tumor stages, remain elusive. The datasets of The Cancer Genome Atlas (TCGA) project lend potential for discovering the distinctive expressional patterns of differentiated subpopulations, and exploring the dynamic evolution of biological activities within tumor cells. **Method:** RNA sequencing level 3 data of 56 pairs of tissue and adjacent normal samples were obtained from TCGA. Differential expression analysis was conducted using 'edgeR' package across the each tumor stage. Differentially expressed genes were derived with fold change>=4 and FDR <= 0.01, followed by KEGG pathway analysis. Odd ratios (ORs) were extracted to indicate the degrees of dysregulation of each pathway. **Result:** After removing non-cancer associated pathways from the 77 pathways identified as dysregulated in those samples, we arrived at 35 pathways. In "Cell cycle" and "Pathways in cancer", ORs display positive correlation with tumor stages, and the Stage IV showed appreciably higher OR than other stages. Noteworthily, Stage IV has very high Ors in "PPAR signaling pathway", "Renin-angiotensin system" and "p53 signaling pathway", which represents canonical pathways implicated in cancer pathologies.



Conclusion: We identified pathways that display correlation with tumor stages, although some deviations are expected to stem from differences in treatment, complicated disease, and health conditions, etc. These results display considerable linear correlation between the degree of dysregulation of cancer pathways, which promise applying RNA sequencing in characterizing the bona fide cell fate of tumor tissues.

Keywords: Cancer trajectory pattern, transcriptome, TCGA

P1.03 BIOLOGY
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P1.03-06 MOLECULAR LANDSCAPE OF FGFR1 POINT MUTATIONS IN CHINESE NON-SMALL-CELL LUNG CANCER PATIENTS: A RETROSPECTIVE STUDY

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Background: Mutations of the fibroblast growth factor receptor 1 (*FGFR1*) is believed to predict response to FGFR inhibitors, but the genetic spectrum of *FGFR1* mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *FGFR1* mutations. **Method:** A total of 469 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *FGFR1* mutation and other genes were detected by next generation sequencing. **Result:** *FGFR1* gene mutation rate was 2.99% (14/469) in non-small cell lung cancer, including S99L (3 patients), S107L (2 patients), N546K (1 patient), R756H (1 patient), G70R (1 patient), R661Q (1 patient), V94I (1 patient), R50Q (1 patient), D312V (1 patient), R6Q (1 patient) and M427V (1 patient), and median overall survival (OS) for these patients was 11.4 months. Among them, all patients were *FGFR1* gene with co-occurring mutation. Briefly, patients with (n=3) or without (n=11) co-occurring *EGFR* mutations had a median OS of 16.7 months and 11.0 months respectively (P=0.56); patients with (n=11) or without (n=3) co-occurring *TP53* mutations had a median OS of 11.4 months and 20.7 months respectively (P=0.48); patients with (n=2) or without (n=12) co-occurring *STK11* mutations had a median OS of 5.0 months and 11.4 months respectively (P=0.57); patients with (n=3) or without (n=11) co-occurring *PTCH1* mutations had a median OS of 5.7 months and 11.4 months respectively (P=0.11). **Conclusion:** It demonstrated that *FGFR1* mutation was an infrequent genetic alteration, and for firstly, and we found *FGFR1* mutation also was an independent delayed adverse prognostic factor only in early stage NSCLC patients, suggesting that *FGFR1* mutation may be a viable prognostic factor in these patients.

Keywords: Non-small-cell lung cancer, Prognosis, FGFR1 mutation

P1.03 BIOLOGY
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P1.03-07 A COMPARISON OF CONSISTENCY OF DETECTING HER2 GENE MUTATIONS IN PERIPHERAL BLOOD AND TUMOR TISSUE OF NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: HER2 is expressed in solid carcinomas including cancers of the breast, stomach, lung and pancreas. Preclinical and clinical studies have confirmed that HER2 is a driver gene in non-small-cell lung cancer (NSCLC). Three principal mechanisms of HER2 alteration include: protein overexpression, gene amplification and gene mutations. In NSCLC, HER2 mutations were identified to represent a distinct subset of driver genes that usually excluded with other common driver genes like EGFR, KRAS and ALK, based on published studies. The aim is to detect the consistency of the HER2 gene mutation in peripheral blood and tumor tissue of patients with NSCLC and discuss the clinical application value of HER2 gene mutation in peripheral blood. **Method:** Real-time fluorescent quantitative PCR was used to determine the HER2 gene mutation of peripheral blood and tumor tissue specimens collected from 185 cases of NSCLC. A comparison of HER2 gene mutation consistency of peripheral blood and tumor tissue specimens was conducted. The correlation

between HER2 gene mutations and clinical characteristics of the patients was analyzed. **Result:** The HER2 gene mutation rate was 3.78% in peripheral blood of 7 patients with NSCLC, and was 2.16% in 4 cancer tissues, the mutation consistency was 75.00% in peripheral blood tumor tissue matched samples. The consistency was statistically significant (κ=0.553, P<0.001). The incidence of HER2 gene mutation in peripheral blood correlate with smoking history (P<0.05), but did not correlate with age, gender and pathological type (P>0.05). The incidence of HER2 gene mutation in tumor tissue correlated with gender and smoking history (P<0.05), but did not correlate with age and pathological type. **Conclusion:** The consistency of the HER2 gene mutation in peripheral blood and tissue is high. HER2 gene mutations of peripheral blood could be used for clinical diagnosis and treatment in cases when tissue specimen is hard to get.

Keywords: HER2 mutations, Consistency, Non-small-cell lung cancer

P1.03 BIOLOGY
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P1.03-08 DETECTION OF PTCH1 GENE VARIANTS IN NON-SMALL CELL LUNG CANCER PATIENTS FROM CHINA

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Background: Recently, the Patched homolog 1 gene (*PTCH1*) gene mutations are identified in non-small-cell lung cancer (NSCLC). While the genetic spectrum of *PTCH1* mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *PTCH1* mutations. **Method:** A total of 269 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *PTCH1* mutation and other genes were detected by next generation sequencing. **Result:** *PTCH1* gene mutation rate was 6.32% (17/269) in non-small cell lung cancer, including S827G (2 patients), G445S (1 patient), A1130T (1 patient), L1036F (1 patient), E173D (1 patient), P1210L (1 patient), Y820* (1 patient), D710E (1 patient), C37W (1 patient), N258I (1 patient), F614Y (1 patient), P681S (1 patient), V1381G (1 patient), G37R (1 patient), A741V (1 patient) and P1282L plus R893H (1 patient), and median overall survival (OS) for these patients was 18.0 months. Among them, all patients were *PTCH1* gene with co-occurring mutation. Briefly, patients with (n=5) or without (n=12) co-occurring *EGFR* mutations had a median OS of 22.0 months and 18.0 months respectively (P=0.25); patients with (n=11) or without (n=6) co-occurring *TP53* mutations had a median OS of 18.0 months and 14.0 months respectively (P=0.28); patients with (n=2) or without (n=15) co-occurring *BRAF* mutations had a median OS of 4.0 months and 18.0 months respectively (P=0.14); patients with (n=2) or without (n=8) co-occurring *PIK3CA* mutations had a median OS of 17.0 months and 18.0 months respectively (P=0.96). **Conclusion:** *PTCH1* gene mutation coexists with other gene mutation in NSCLC. *EGFR*, *TP53*, *BRAF* and *PIK3CA* gene accompanied may have less correlation with *PTCH1* mutation in NSCLC patients. Analysis of *PTCH1* mutations shows promise as a way to refine individual patients with NSCLC, and provides more insight into effective treatment strategies for patients with *PTCH1* mutations.

Keywords: Non-small-cell lung cancer, PTCH1 mutation, Prognosis

P1.03 BIOLOGY
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P1.03-09 ROS1 REARRANGEMENT IN PULMONARY SARCOMATOID CARCINOMA: A RETROSPECTIVE STUDY OF THE REAL WORLD

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Background: Pulmonary sarcomatoid carcinoma (PSC) is a recognized category of highly aggressive and poorly differentiated non-small-cell lung carcinoma (NSCLC), with five different subtypes: pleomorphic, spindle, giant cell, carcinosarcoma, and pulmonary blastoma. Although uncommon (0.1% to 0.4% of all pulmonary malignancies), their clinical importance is underscored by poorer prognosis and higher rate of resistance to conventional chemotherapy than other NSCLCs. And the incidence of c-ros oncogene 1, receptor tyrosine kinase (*ROS1*) rearrangement in PSC is controversial. The aim of this study was to reveal the reliable frequency and the clinical-pathologic characteristics of PSC with *ROS1* rearrangement in Chinese population. **Method:** A total of 35 patients with PSC were recruited between September 2007 and December 2017. The status of *ROS1* rearrangement was detected by reverse transcription polymerase chain reaction (RT-PCR). **Result:** Of this study, three patients were identified with ROS1 rearrangement in Chinese PSC population (2.86%, 1/35). The patient was a pulmonary pleomorphic carcinoma (PPC). **Conclusion:** The incidence rates of ROS1 rearrangement in PSC in the Chinese population are more than those of other subtypes of NSCLC. Crizotinib may serve as an effective treatment for *ROS1*-rearranged PSC.

Keywords: Pulmonary sarcomatoid carcinoma, ROS1 fusion, RT-PCR

P1.03 BIOLOGY
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P1.03-10 THE MOLECULAR SPECTRUM OF NF1 VARIANTS IN CHINESE NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: Activation of the RAS/MAPK pathway is critical in non-small-cell lung cancer. Non-small-cell lung cancer can be grouped into four molecular subtypes based on their main genetic driver: *EGFR*-mutant, *ALK*-fusion, *ROS1*-fusion, and triple wild-type tumors. The NF1 protein, neurofibromin 1, negatively regulates RAS proteins through GTPase activity. Somatic mutations in NF1 cause neurofibromatosis type I, a common genetic tumor syndrome caused by dysregulation of the RAS/MAPK pathway, ie, RAS pathy. While the genetic sites of *NF1* mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *NF1* mutations. **Method:** A total of 337 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *NF1* mutation and other genes were detected by next generation sequencing. **Result:** *NF1* gene mutation rate was 6.23% (21/337) in non-small cell lung cancer, including M645V (3 patients), A1998V (1 patient), Q83E (1 patient), P654T (1 patient), Q912* (1 patient), C324* (1 patient), C1032S (1 patient), I1628M (1 patient), L43V (1 patient), A861Qfs*17 (1 patient), Q239E (1 patient), D1623N (1 patient), T586Vfs*18 (1 patient), R2328C (1 patient), E41* (1 patient), V437Nfs*35 (1 patient), P2046L plus G1219* (1 patient), D2055Mfs*6 plus T2133Sfs*45 (1 patient) and C1288F plus K2252* (1 patient), and median overall survival (OS) for these patients was 10.0 months. Among them, all patients were *NF1* gene with co-occurring mutation. Briefly, patients with (n=3) or without (n=18) co-occurring *EGFR* mutations had a median OS of 15.5 months and 10.0 months respectively (P=0.69); patients with (n=18) or without (n=3) co-occurring *TP53* mutations had a median OS of 10.0 months and 6.0 months respectively (P=0.21); patients with (n=3) or without (n=18) co-occurring *RB1* mutations had a median OS of 19.5 months and 9.0 months respectively (P=0.27); patients with (n=3) or without (n=18) co-occurring *SMARCA4* mutations had a median OS of 20.5 months and 9.0 months respectively (P=0.19). **Conclusion:** Patients with complex mutations benefited more from therapy than those with single mutations. *NF1* genetic alter occurs in a subset of NSCLC, and improved understanding of the implications of *NF1* aberrations is critical for the identification of therapeutic target candidates.

Keywords: Prognosis, NF1 mutation, Non-small-cell lung cancer

P1.03 BIOLOGY
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P1.03-11 ANALYSIS OF T-CELL REPERTOIRES IN BENIGN AND MALIGNANT SOLITARY PULMONARY NODULES TO EVALUATE TUMOR IMMUNE MICROENVIROMENT

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Background: The identification of malignancy of solitary pulmonary nodule (SPN) is important for lung cancer eraly detection. Carcinogenesis may result from accumulation of molecular evolution and escaping from

host immunoediting. However, the immune landscape such as T cell repertoire of benign and malignant SPNs have not been systemically studied. **Method:** We have collected resected solitary pulmonary nodules (SPNs) and peripheral blood including benign SPNs (N=10), LUSC (N=11) and LUAD (N=38) from 59 patients. T cell repertoire of infiltrating T cells in SPNs were sequenced their T cell receptor b genes (TCRb) , as well as their abundance in peripheral blood. Enrichment clonotypes were defined as 500 fold enrichment as compared to blood. **Result:** Comparison to the peripheral blood, T cell repertoire diversity of infiltrating T cells in SPNs showed significant differences among benign and malignant. T cell clonality was higher in the benign SPNs than Malignant, however no significant differences among LUSC and LUAD. Additionally, we observed that Tumors from smokers had higher T cell clonality than no-smokers as reported earlier. Interestingly, many T cell clones, including major clones, were shared between lung tissues and matched peripheral blood; furthermore, the higher shared clonotypes of T cell clones between lung tissues and blood in benign SPNs than Malignant. Enrichment analysis demonstrated more enriched clonotypes observed in LUSC and LUAD. **Conclusion:** Our preliminary data demonstrate the distinct immune microenvironment in SPNs may be associated with the benign and malignant features. And implies a significant proportion of infiltrating T cells in SPNs may be a function of constant lung infiltrating rather than an anti-tumor response.

Keywords: Early Detection, T-cell repertoires, solitary pulmonary nodule

P1.03 BIOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.03-12 PD-L1 EXPRESSION IS PREDOMINANT IN CD68+ TUMOR-ASSOCIATED MACROPHAGES IN STAGE I-III NON-SMALL CELL LUNG CANCERS

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Background: PD-L1 tumor expression is a leading biomarker in metastatic non-small lung cancer (NSCLC). Its role and expression in surgically resectable lung cancers is not yet defined. The association between PD-L1 expression on tumor and CD68+ tumor-associated macrophages (TAMs) and the inflammatory cells within the tumor microenvironment continues to be studied. We analyzed 97 surgically resected lung cancers utilizing immunofluorescence profiling and flow cytometry (n=47) with the aim of defining PD-L1 expression and its association with tumor inflammatory cells. **Method:** Multiplex immunofluorescence profiling of lung cancers was performed with the focus on malignant cells (MC), MC PD-L1%, CD3+, CD8+, PD-1+ cells, CD68+, CD68+ PD-L1%, and CD20+ cells. Data on cell populations were expressed as the number of cells per mm^2, PD-L1 expression as percentage. Flow cytometry was performed on freshly disaggregated tumor samples. The associations of cell populations with clinical and pathologic characteristics were assessed using Spearman's rank correlation coefficient and Wilcoxon rank-sum test. **Result:** 97 patients, 55 (57%) female and 42 (43%) male, with median tumor size 4.0 cm underwent surgical resection for pathologic stage I (N=39), stage II (N=34), and stage III (N=24) NSCLC. 85 (88%) were former smokers, 12 (12%) never smokers. 62 (65%) had adenocarcinoma, 25 (25%) squamous cell carcinoma, 10 (10%) other histology. Neoadjuvant chemotherapy was administered in 16 (16%) patients. R0 resection was achieved in 89 (92%) patients. At the median follow-up duration of 16 months, 18 patients experienced recurrence. CD68+ cells were less abundant than MC within tumor environment (median 120 cell/mm^2 vs 4699, p<0.0001). However, PD-L1% expression was significantly higher on CD68+ vs MC within the tumor (median 33% vs 0.02%, p<0.0001); this was true for all stages. CD68+ PD-L1% in SCC was higher compared to adenocarcinoma (median 55% vs 30%, p=0.26). Induction chemotherapy increased CD68+ PD-L1% (median 31% no chemo vs 58%, p=0.05) without affecting the proportion of effector CD8+ TIL expressing its receptor, PD-1 (p=0.757). Tumors with > median CD68+ PD-L1% expression were associated with higher CD3+ (p=0.006), CD8+ (p=0.06), and CD68+ (p=0.004) cell numbers within the tumor. **Conclusion:** In early NSCLC PD-L1% expression appears to be predominant in CD68+ TAMs rather than in malignant cells. Higher than median PD-L1% expression on CD68+ is associated with increased in CD3+ and CD8+ T cells. Further studies are required to understand the role of CD68+PD-L1 cells within tumor microenvironment, the influence of neoadjuvant chemotherapy or immunotherapy regimens on these cells, and their effect on outcomes.

Keywords: Immunoprofiling, non-small cell lung cancer, tumor-associated macrophage

P1.03 BIOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.03-13 EIF2β, A SUBUNIT OF TRANSLATION-INITIATION FACTOR EIF2, AS A POTENTIAL THERAPEUTIC TARGET FOR NON-SMALL CELL LUNG CANCER

D. Goto[1], I. Tanaka[1], M. Sato[1], T. Kato[1], A. Miyazawa[1], T. Hase[1], M. Morise[1], Y. Sekido[2], L. Girard[3], J. Minna[3], L. Byers[4], J. Heymach[5], K. Coombes[6], M. Kondo[7], Y. Hasegawa[1]

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Background: To identify potential therapeutic targets for non-small cell lung cancer (NSCLC), we recently performed a semi-genome wide shRNA screen in a NSCLC cell line H460 . Through this approach, we identified multiple potential targets for NSCLC (Kakumu et al. *Cancer Sci*, 2017). In the present study, to search for genes with more generalized potential as therapeutic targets, we did shRNA screen using the alternative NSCLC cell line H358 and combined its results with those of our previous screen. **Method:** 19 NSCLC cell lines, two *cdk4/hTERT*-immortalized normal human bronchial epithelial (HBEC) cell lines and primary NHBE culture were used. A semi-genome wide shRNA screen was performed with the DECIPHER library in H358, and its results were integrated with those of our previous screen in H460. Gene silencing was done with RNA interference followed by growth and cell cycle analyses. **Result:** 24 genes overlapped between results of two shRNA screens in H460 and H358 and we identified these as more generalized targets. Gene-annotation enrichment analysis showed that the RNA transport pathway including three genes is one of the overrepresented pathways in the 24 genes. Among the three genes, we determined to focus on *eIF2*β, a subunit of translation-initiation factor EIF2 because other two genes included in the RNA transport pathway, *XPO1* and *RAN* are well characterized therapeutic targets for human cancers including lung cancer. eIF2β protein was more abundantly expressed in all the 19 lung cancer cell lines analyzed than in NHBE used as a control. To determine the clinical relevance of *eIF2*β in lung cancer, we examined *eIF2*β mRNA expression in lung adenocarcinoma tissues using TCGA dataset. These analyses showed significantly higher expression of *eIF2*β mRNA in lung adenocarcinoma tissues than in normal adjacent tissues. Importantly, we found that expression of *eIF2*β mRNA correlated with worse prognosis in patients with lung adenocarcinoma in multiple independent datasets, suggesting its potential as a prognostic marker. Next, we examined the effects of *eIF2*β knockdown on the growth of the H460 and H1975. Colorimetric growth and colony formation assays showed that *eIF2*β knockdown in H460 and H1975 suppresses cell growth and colony formation. **Conclusion:** *eIF2*β is highly expressed in NSCLC cells, and its expression correlates with poor prognosis in patients with lung adenocarcinoma. Knockdown of *eIF2*β caused G1 arrest in lung cancer cell lines. These results suggest that *eIF2*β is a potential therapeutic target for NSCLC and that it is a prognostic marker for lung adenocarcinoma.

Keywords: Adenocarcinoma, Eukarryotic Initiation Factor-2

P1.03 BIOLOGY
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P1.03-14 INTERACTION BETWEEN CELECOXIB AND CISPLATIN IS DEPENDENT ON THE P53 STATUS IN HUMAN NSCLC CELL LINES

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Background: As a cyclooxygenase-2 inhibitor, the potential of celecoxib, to enhance the efficacy of chemotherapy is being investigated in clinical

trials related to cancer treatment. **Method:** In this study, we investigated whether celecoxib would increase the anti-proliferative effects of cisplatin in human lung cancer cell lines. **Result:** The results demonstrated the synergistic effects of celecoxib with cisplatin in wild-type p53 cells and their antagonistic effects in mutated or deleted p53 cells. Combination indices of 0.82–0.93 reflected a synergistic effect between celecoxib and cisplatin in lung cancer cells with wild-type p53. Combination indices of 1.63–3.00 reflected antagonism between celecoxib and cisplatin in lung cancer cells with mutated or deleted p53. Apoptosis was shown to increase with the addition of celecoxib and cisplatin. Apoptosis was accomplished by the downregulation of slug expression. Celecoxib increased the nuclear localization of active p53 in lung cancer cells of wild-type p53. **Conclusion:** Taken together, our data demonstrated clear synergistic effects in wild-type p53 cells and antagonistic effects in mutated or deleted p53 cells when celecoxib and cisplatin are combined.

Keywords: lung cancer, p53, celecoxib

P1.03 BIOLOGY
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P1.03-15 TMS REDUCED GEFITINIB RESISTANCE IN NSCLCS VIA SUPPRESSING MAPK/AKT/BCL-2 PATHWAY BY UPREGULATION OF MIR-345 AND MIR-498

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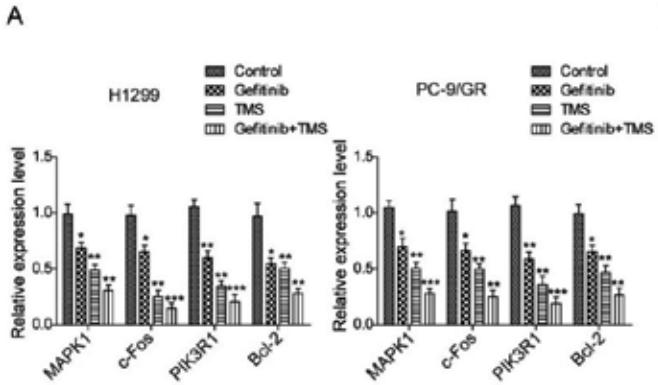
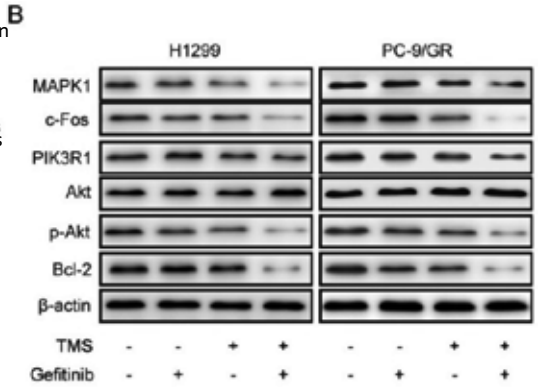
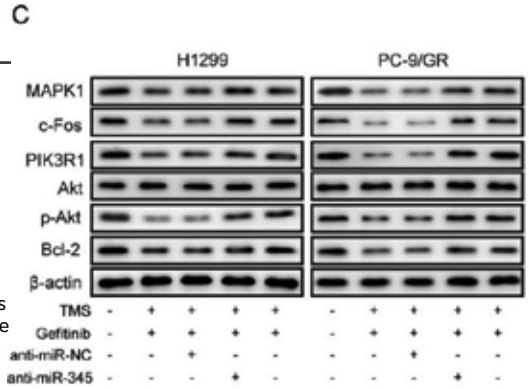
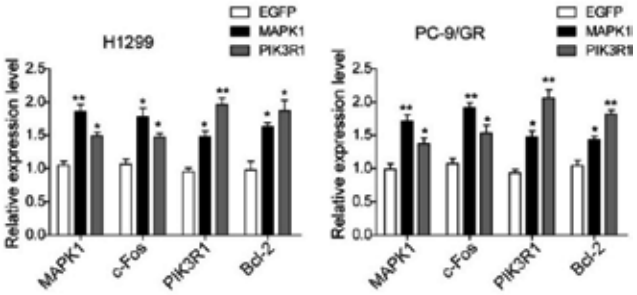
Background: Despite initial dramatic efficacy of EGFR tyrosine kinase inhibitors (EGFR-TKIs) in EGFR-mutant lung cancer patients, subseqent emergence of acquired resistance is almost inevitable. Resveratrol and its derivatives have been found to exert some effects on EGFR-TKI resistance in non-small cell lung cancer (NSCLC), but the underlying mechanisms remain unclear. **Method:** We screened several NSCLC cell lines with gefitinib-resistance by MTT assay, and analyzed the miR-345/miR-498 expression levels. NSCLC cells were pre-treated with a resveratrol derivative, trans-3, 5, 4-trimethoxystilbene (TMS), and subsequently challenged with gefitinib treatment. The changes of apoptosis and miR-345/miR-498 expression were analyzed by flow cytometry and q-PCR, respectively. The functions of miR-345/miR-498 were verified by CCK-8 assay, cell cycle analysis, dual-luciferase reporter gene assay and immunoblotting analysis.

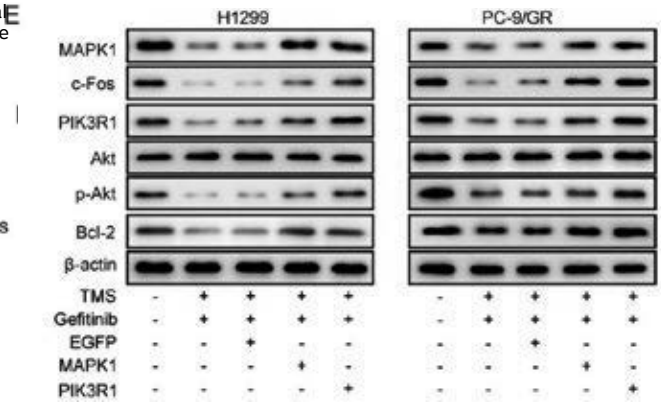
Result: Our results showed that the expression of miR-345 and miR-498 significantly decreased in gefitinib-resistant NSCLC cells. TMS pre-treatment significantly upregulated the expression of miR-345 and miR-498, increasing the sensitivity of NSCLC cells to gefitinib and inducing apoptosis. MiR-345 and miR-498 were verified to inhibit proliferation by cell cycle arrest, and regulate the MAPK/c-Fos and AKT/Bcl-2 signaling pathways by directly targeting MAPK1 and PIK3R1, respectively. The combination of TMS and gefitinib promoted apoptosis also by miR-345 and miR-498 targeting the MAPK/c-Fos and AKT/Bcl-2 signaling pathways. **Conclusion:** Our study demonstrated that TMS reduced gefitinib resistance in NSCLCs via suppressing MAPK/Akt/Bcl-2 pathway by upregulation of miR-345/498. These findings would lay the theoretical basis for the future study of TMS for the treatment of EGFR-TKI resistance in NSCLCs.











Keywords: TMS, NSCLC, gefitinib resistance

POSTER SESSION 1
MONDAY, SEPTEMBER 24, 2018

P1.03 BIOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.03-16 ANLOTINIB INHIBITS ANGIOGENESIS OF REFRACTORY ADVANCED NON-SMALL CELL LUNG CANCER VIA BLOCKING CCL2 EXPRESSION

J. Lu[1], H. Zhong[1], T. Chu[1], X. Zhang[1], R. Li[1], J. Sun[1], R. Zhong[1], Y. Yang[2], M.S. Alam[3], Y. Lou[1], J. Xu[1], Y. Zhang[1], J. Wu[3], X. Li[3], X. Zhao[3], K. Li[4], L. Lu[2], B. Han[5]

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Background: Anlotinib has been demonstrated to be effective in prolonging progression free survival (PFS; Anlotinib: 5.37 months vs Placebo: 1.40 months) and overall survival (OS; Anlotinib: 9.63 months vs Placebo: 6.30 months) of refractory advanced Non-Small Cell Lung Cancer (NSCLC) patients in clinical trials. Clinical evidences suggested that Anlotinib-induced anti-tumor efficacy could be attributed to anti-angiogenesis. However, the underlying molecular mechanisms and predictive biomarker of Anlotinib are still unclear. **Method:** 437 patients with advanced NSCLC enrolled in clinical study, and 294 patients received Anlotinib therapy. Retrospectively analysis of the Anlotinib-administrated 294 NSCLC patients was performed to screen out underlying biomarker for Anlotinib-responsive patients. Transcriptome and functional assays were performed to understand the anti-tumor molecular mechanism of Anlotinib *in vitro*. CCL2 levels and their roles in angiogenesis were evaluated by ELISA detection, RT-qPCR quantification, and immunofluorescence assay, *in vivo*. Changes in serum CCL2 levels were analyzed to reveal the correlation of Anlotinib response between responders and non-responders. **Result:** Anlotinib therapy is more beneficial to prolong OS for NSCLC patients harboring positive driver gene mutations, especially for patients harboring $EGFR^{T790M}$ mutation. Moreover, our data indicated that Anlotinib-induced cell viability downregulation, cell apoptosis induction, cell invasion inhibition, cell cycle arrest, and cell migration inhibition are associated with CCL2 levels *in vitro*. We demonstrated that Anlotinib inhibits angiogenesis of NCI-H1975 derived xenografts model via inhibiting CCL2 *in vivo*. Lastly, we found that Anlotinib-induced serum CCL2 level decreases are associated with the benefits of PFS and OS, in refractory advanced NSCLC patients (n = 28). **Conclusion:** Our study reports a novel anti-angiogenesis mechanism of Anlotinib via inhibiting CCL2 in NCI-H1975 derived xenografts model, and suggests the changes in serum CCL2 levels may be used to monitor and predict clinical outcome in Anlotinib-administered refractory advanced NSCLC patients. The biomarker of serum CCL2 alteration may guide precision therapy of Anlotinib for NSCLC patients at third-line or over third-line.

Keywords: Anlotinib, NSCLC, Anti-angiogenesis

P1.03 BIOLOGY
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P1.03-17 FUNCTIONAL MECHANISM OF GLDC GENE ALTERNATIVE SPLICING IN NON-SMALL CELL LUNG CANCER

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Background: Lung cancer is the leading cause of death in the world and non-small cell lung cancer (NSCLC) accounts for approximately 85%.While, the mechanism is not fully understood.Therefore,exploring new molecules is of great significance to clarify the mechanism.Glycine decarboxylase (GLDC) is an oncogene associated with lactic acid metabolism,highly expressed in cancer stem cell-riched NSCLC.Both growth and tumorigenicity are dependent on the expression of high levels of GLDC, so which can be used as a stem cell surface marker to identify cancer stem cells.Alternative splicing (AS) is one of the important mechanisms of human gene regulation,which is closely related to the occurrence of tumor.However,the mechanism of AS regulation for GLDC in NSCLC has not been reported.Therefore,understanding the biological role of GLDC and its regulatory mechansim can lay a theoretical foundation for the early diagnosis and treatment of tumors.This experiment aims to clone human GLDC gene AS,analyze biological activity,and provide guidance for NSCLC development mechanism **Method:** 1.Construction of cloning vectors:Primers were designed based on the full length of GLDC (GLDCfl) and GLDC varient 1 (GLDCV1) cDNA,and mRNA expression in A549 and MRC5 cells was determined by RT-PCR combined with DNA sequencing;

2.Functional experiments:MRC5 cells were transfected with overexpression plasmids,MTT assay,plate clone,western blot,lactic acid formation assay,and tumor-bearing test in vivo were used to detect MRC5 cells viability and proliferation. **Result:** 1.Both GLDCfl and GLDCV1 of A549 and MRC5 existed at the RNA level,the expression of which only in A549.Transfection of the target gene in MRC5 cells showed increased expression of both GLDCfl and GLDCV1. 2.GLDCfl and GLDCV1 were over-expressed in MRC5 cells,and the cell viability was increased by MTT assay.Plate clone experiments proved the proliferation of MRC5 cells,and the expression of P-ERK and P-P38 proteins on the ERK/MAPK signaling pathway were increased.The supernatants of the cells for 24 hours were collected and assayed for lactic acid,then both GLDCV1 and GLDCfl promoted lactic acid production. Meanwhile,in vivo nude mice tumor test,each 100 µl dose was inoculated subcutaneously at the back shoulder of 4-6 week old nude mouse,and the GLDCV1 group shown the tumorigenicity **Conclusion:** 1This study first analyzed the expression pattern of GLDC gene AS in tumor cells and revealed the biological effects in tumor cells; 2.Both GLDCV1 and GLDCfl can enhance the cell viability,promote luciferase activity,enhance cell clonal formation,and also find that GLDCV1 can enhance the tumorigenic ability. 3.Both GLDCV1 and GLDCfl have effect on the expression of ERK/MAPK pathway protein.

Keywords: non small cell lung cancer, GLDC, Alternative splicing

P1.03 BIOLOGY
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P1.03-18 MECHANOBIOLOGY OF LUNG CANCER CELLS: REGULATION OF PD-L1 EXPRESSION BY MATRIX STIFFNESS

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Background: Expression of programmed death-ligand 1 (PD-L1) in tumor cells plays an important role in mechanisms underlying evasion of an immune check point system. PD-L1 expression is regulated by multiple mechanisms such as the tumor microenvironment. Lung cancer tissue with increased deposition of extracellular matrix is much stiffer than normal lung tissue. There is emerging evidence that the matrix stiffness of cancer tissue affects the phenotypes and properties of cancer cells. Nevertheless, the effects of substrate rigidity on expression of PD-L1 in lung cancer cells remain elusive. This study was designed to determine whether substrate stiffness affects the regulation of PD-L1 in lung cancer cells. **Method:** We evaluated PD-L1 expression levels in HCC827 human lung cancer cell line. Commercially available polyacrylamide hydrogels of different stiffnesses bound to 6-well polystyrene plates or polystyrene dishes coated with type I collagen were utilized. We used 2 and 25 kPa gels as substrates of normal (soft) human lung and cancer-associated (stiff) tissue. Western blotting and Immunofluorescence staining were performed for evaluating PD-L1 expression levels. A colorimetric viability assay was performed for evaluating of PD-L1 expression and cell proliferation by using transfection with short interfering RNA (siRNA) for PD-L1. **Result:** Expression of PD-L1 protein was higher on the stiffer substrates (25 kPa gel and plastic dish) than on the soft 2 kPa gel. PD-L1 expression was reduced by detachment of cells adhering to the substrate. Interferon-γ enhanced expression of PD-L1 protein cultured on stiff (25 kPa gel and plastic dishes) and soft (2 kPa gel) substrates and in the cell adhesion-free condition. As the stiffness of substrates increased, formation of actin stress fiber and cell growth were enhanced. Transfection of the cells with siRNA for PD-L1 inhibited cell growth without affecting stress fiber formation. Treatment of the cells with cytochalasin D, an inhibitor of actin polymerization, significantly reduced PD-L1 protein levels. **Conclusion:** Stiff substrates enhanced PD-L1 expression via actin cytoskeleton-dependent mechanisms in HCC827 lung cancer cell line. It is suggested that stiffness as a tumor environment regulates PD-L1 expression, which leads to evasion of the immune system and tumor growth.

Keywords: microenvironment, PD-L1, mechanotransduction

P1.03 BIOLOGY
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P1.03-19 ANTIBODY BLOCKADE OF INTEGRIN ALPHA-V-BETA-6 (AVB6) AS A NOVEL TREATMENT FOR NSCLC

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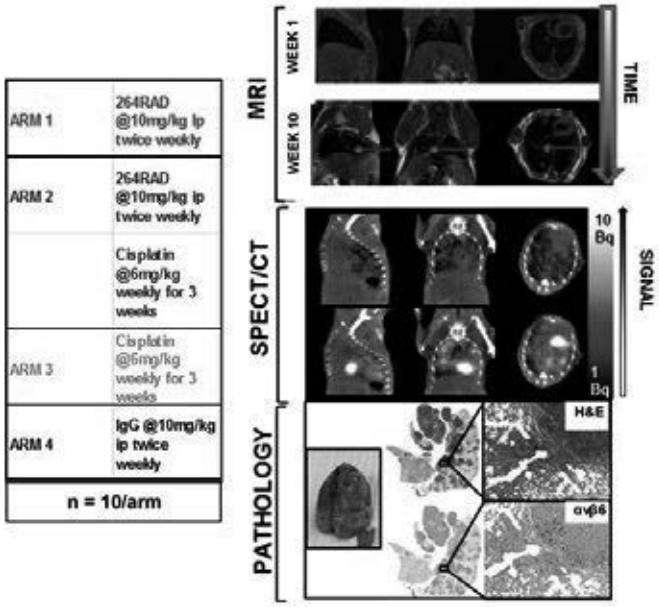
Background: Expression of integrin alpha-v-beta-6 (αvβ6) is restricted to epithelial cells. It is weak or absent on normal tissues unless tissue

re-modelling occurs in situations like fibrosis and cancer. It promotes multiple pro-tumorigenic processes, including cell migration, invasion and the activation of latent TGFβ[1]. Strong expression in multiple cancers is associated with poorer prognosis including a reported 54% of non-small cell lung cancers (NSCLC). Antibody blockade of αvβ6 with 264RAD antibody reduces tumour growth in breast and pancreatic cancer mouse models. The effect of αvβ6 blockade on NSCLC is unknown. Mutations in KRAS occur in approximately 30% of NSCLC. In the well described conditional transgenic *Kras*$^{LSLG12D+/-}$*; P53fl*$^{fl/fl}$ (KP) mouse model of lung cancer, adenocarcinomas develop due to adenoviral cre-recombinase activation of a K-RasG12D allele and loss of P53. Tumour sections from this model show β6 expression (evidenced by αvβ6-specific SPECT imaging and pathology). We investigated the effect of αvβ6 blockade in the KP mouse. **Method:** KP mice tumours were initiated by intra-tracheal instillation of adenoviral cre-recombinase. At 10 weeks, when significant disease was present (confirmed by MRI) treatment commenced. Four treatment groups of n=10 were allocated to either: 264RAD(10mg/kg, ip twice weekly); 264RAD (10mg/kg, ip twice weekly) + cisplatin(6mg/kg, weekly for 3 weeks); cisplatin(6mg/kg, weekly for 3 weeks); or IgG (10mg/kg, ip twice weekly). Progression (MRI) and survival was monitored.



Result: s support using MRI as the preferred method to monitor tumour growth. Survival, lung pathology studies and imaging data will be presented at the meeting. **Conclusion:** We have established a method to study the effects of αvβ6 blockade on lung tumour growth in vivo and are developing an imaging strategy using both MRI and SPECT to analyse mouse lung tumour growth in a manner that best mirrors human studies.

Keywords: integrin alpha-v-beta-6, treatment, Antibody

P1.03 BIOLOGY
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P1.03-20 THE NOVEL SFN INHIBITORS APREPITANT AND TICAGRELOR EXERT ANTI-TUMOR EFFECTS THROUGH BLOCKING OF ONCOPROTEIN UBIQUITINATION

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Background: We have previously shown that the gene encoding stratifin (SFN, 14-3-3 sigma) is differentially expressed during the course of progression from AIS to early invasive adenocarcinoma (eIA), inducing early tumor progression by binding to SKP1 and blocking the activity of SCF^{FBW7} ubiquitin ligase. As suppression of SFN significantly reduces cell growth and tumor formation or progression, we expected that inhibition of SFN could be a promising therapeutic strategy for lung adenocarcinoma. **Method:** To identify candidate compounds that bind specifically to SFN and block SFN-SKP1 binding, we carried out *in silico* library screening based on putative druggable sites of SFN around the SKP1 interaction interface using molecular docking against 7,133 bioactive compounds from the DrugBank database. Experimental validation was performed for 46 compounds that showed the highest docking scores. Cell growth and dissociation of SFN-SKP1 were examined by WST-8 assay and IP/western blotting after treatment with each compound. Finally, 4 candidate compounds were subjected to *in vivo* evaluation. Tumor-bearing mice that had received subcutaneous injection of A549 cells were subjected to two experimental schedules: 1) Daily oral administration of each compound starting at 1 day after injection until 21 days. 2) Same as 1) but starting when the tumors had reached 100 mm^3 in size. **Result:** Through *in silico* screening and experimental validation, we identified 4 compounds as SFN inhibitors: Aprepitant, Ticagrelor, Ezetimibe, and Chlorhexidine. All of them significantly and dose dependently reduced cell growth and SFN-SKP1 binding. Notably, Aprepitant completely blocked *in vivo* tumor formation, and Ticagrelor markedly reduced tumor progression when administered from the day after tumor cell injection. Furthermore, Aprepitant and Ticagrelor reduced tumor progression in a dose-dependent manner even when administration was started after tumors had grown to 100 mm^3. **Conclusion:** Here we have shown that inhibition of SFN-SKP1 binding results in an anti-tumor effect. Since SFN binding to SKP1 results in SCF^{FBW7} dysfunction and allows oncoproteins such as cyclin E1 and c-Jun to evade ubiquitination and subsequent degradation, it is considered that inhibition of SFN will lead to ubiquitination of these oncoproteins. Although Aprepitant is a NK-1R (neurokinin-1 receptor) antagonist which is already approved as an antiemetic drug, and Ticagrelor is a reversible P2Y12 inhibitor exerting an anti-platelet effect, our results suggest that these agents could be applicable for treatment of lung adenocarcinoma. As overexpression of SFN starts from eIA, we believe that SFN inhibitors will provide a novel chemotherapeutic strategy for early-stage lung adenocarcinoma.

Keywords: Early-stage, Adenocarcinoma, stratifin

P1.03 BIOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.03-21 HUAIER AQUEOUS EXTRACT INDUCES LUNG ADENOCARCINOMA CELL APOPTOSIS THROUGH EXCESSIVE ACTIVATION OF MEK/ERK SIGNALING PATHWAY

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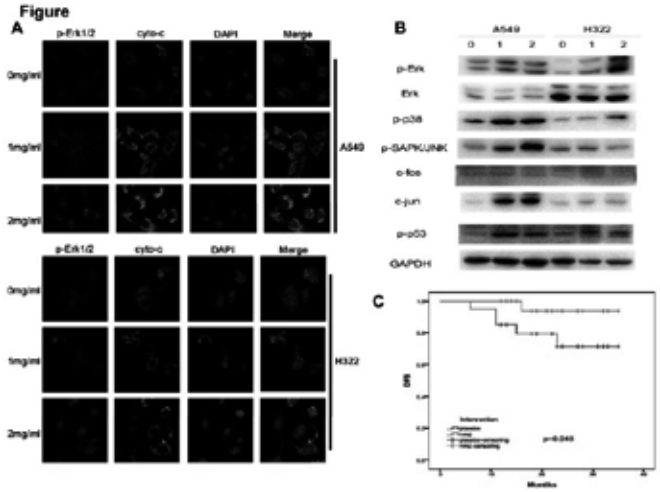
Background: As the most important pathological types of lung cancer, adenocarcinoma has poor prognosis due to the characteristics of early metastasis and recurrence even in effective surgery, radiotherapy and chemotherapy. In China, Traditional Chinese medicine "Huaier aqueous extract" (HAE) is widely used in antineoplastic treatment, but its molecular mechanism in lung adenocarcinoma remains unclear. This study aimed to explore the apoptotic mechanism of HAE in lung adenocarcinoma. **Method:** MTT assay and flow-cytometric analysis were measured to identify the cell viability and apoptosis rate affected by HAE in human lung adenocarcinoma A549, H322 cell. Immunofluorescence assay was applied to examine the effect of HAE on expression and distribution of Cytochrome C and ERK1/2 in A549, H322 cell. Further, A549 cell was respectively treated with HAE and subjected to western blotting for protein level of MEK/ERK signaling pathway. In human trials, a total of 40 patients with stage I lung adenocarcinoma after complete resection were enrolled from January 2015 to December 2016. 20 of them were given HAE and others were not, and then the patients' 3-year disease free survival was examined. **Result:** HAE significantly inhibited the cell viability of A549, H322 cell in dose-dependent and time--dependent manner. Further, HAE induced accumulation of Cytochrome C, an apoptosis core factor, in cytoplasm and promote the apoptosis of A549, H322 cells. Meanwhile, HAE launched the expression of ERK1/2 and the latter migrated more to the nucleus following with excessive activation of MEK/ERK signaling pathway. The patients treated with HAE showed fewer recurrences than the rest (3-year disease free survival: 93.8% vs 71.4%; P=0.048).

(See next page)



Conclusion: HAE could over-activate MEK/ERK signaling pathway and exert apoptosis-inducing effects in lung adenocarcinoma.

Keywords: Huaier aqueous extract, MEK/ERK signaling pathway, lung adenocarcinoma

P1.03-22 MIR-125B PLAYS A TUMOR SUPPRESSOR ROLE IN INFLAMMATION-RELATED NON-SMALL CELL LUNG CANCER VIA REPRESSING IGF-1 SIGNAL PATHWAY

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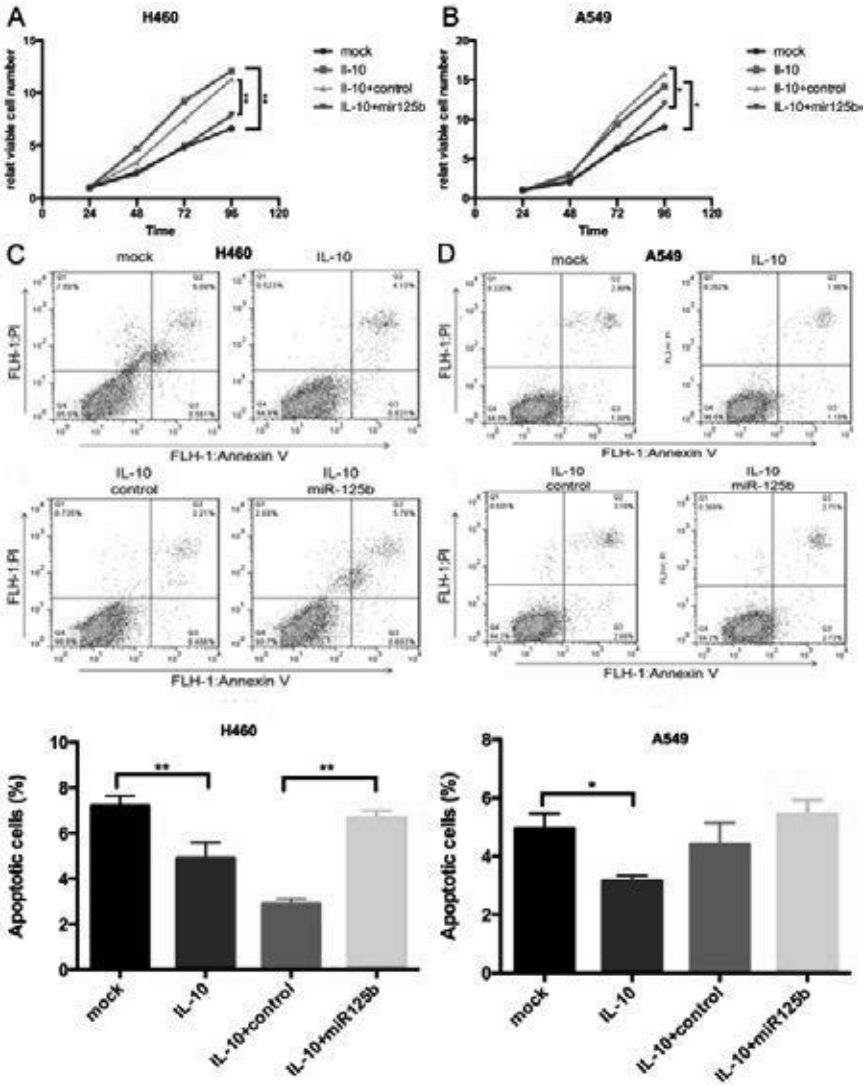
Background: Epidemiologic data have indicated that chronic inflammation was highly associated with the pathogenesis of lung cancer. However, the molecular relations between inflammation and lung cancer have not been well understood. MicroRNAs could connect the inflammatory response with tumorigenesis through regulating their cancer-related targets. The aim of the present study was to identify the core miRNA in inflammation-related lung cancer and its potential mechanisms. **Method:** RT-PCR was used to detect the expression of miRNAs and mRNAs. CKK8 and flow cytometry assays was performed for the function experiments. Microarray analysis and IPA analysis were used to predict the potential signal pathway. **Result:** Mir-125b was the most dramatically up-regulated miRNAs after treated with IFN-r, whereas after stimulated with IL-10, mir-125b was the most strikingly down-regulated ones. Restoration of mir-125b expression could completely overrode the impact of IL-10 on both cell proliferation and apoptosis in NSCLC cell lines(Figure1). And the level of mir-125b was significantly lower in 30 NSCLC tumor tissues compared with normal controls (P<0.0001). Microarray analysis found 69 up-regulated genes and 105 down-regulated genes after down-regulate mir-125b. And IPA analysis indicated that IGF-1 signaling pathway was dramatically activated. The results were validated by RT-PCR.



Conclusion: MiR-125b might play a tumor suppressor role via inhibiting IGF-1 signaling in inflammation-related lung cancer.

Keywords: lung cancer, miR-125b, IGF-1

P1.03 BIOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.03-23 THE MOLECULAR LANDSCAPE AND OUTCOME OF CHINESE PATIENTS WITH NON-SMALL CELL LUNG CANCER HARBORING NTRK1 POINT MUTATIONS: A RETROSPECTIVE STUDY

X. Chen[1], C. Xu[2], W. Wang[3], Q. Zhang[4], W. Zhuang[5], Y. Zhu[6], Y. Chen[4], M. Fang[3], G. Chen[7], T. Lv[8], Y. Song[8]

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Background: The identification and clinical validation of cancer driver genes are essential to accelerate the translational transition of cancer genomics, as well as to find clinically confident targets for the therapeutic intervention of cancers. While the genetic variability of neurotrophic receptor tyrosine kinase 1 (*NTRK1*) mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *NTRK1* mutations. **Method:** A total of 389 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *NTRK1* mutation and other genes were detected by next generation sequencing. **Result:** *NTRK1* gene mutation rate was 4.11% (16/389) in non-small cell lung cancer, including H268Q (1 patient), V181M (1 patient), Q459R (1 patient), G726C (1 patient), R89H (1 patient), M635I (1 patient), L126Q (1 patient), G138R (1 patient), E245A (1 patient), M530T (1 patient), L549Cfs*73 (1 patient), N293S (1 patient), E245A (1 patient), W236C (1 patient), E456K (1 patient) and F297L (1 patient), and median overall survival (OS) for these patients was 11.0 months. Among them, all patients were *NTRK1* gene with co-occurring mutation. Briefly, patients with (n=5) or without (n=11) co-occurring *EGFR* mutations had a median OS of 14.0 months and 11.0 months respectively (P=0.90); patients with (n=12) or without (n=4) co-occurring *TP53* mutations had a median OS of 11.0 months and 6.0 months respectively (P=0.67); patients with (n=3) or without (n=13) co-occurring *BRAF* mutations had a median OS of 14.0 months and 11.0 months respectively (P=0.43); patients with (n=4) or without (n=16) co-occurring *CDKN2A* mutations had a median OS of 3.5 months and 14.0 months respectively (P<0.01). **Conclusion:** *NTRK1* oncogenic activation through gene fusion defines a novel and distinct subset of NSCLC. *EGFR*, *TP53* and *BRAF* gene accompanied may have less correlation with *KIT* mutation in NSCLC patients. *CDKN2A* accompanied mutations might play a worse prognosis in *NTRK1* gene mutation non-small cell lung cancer.

Keywords: Non-small-cell lung cancer, NTRK1 mutation, Prognosis

P1.03 BIOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.03-24 TMPRSS4: A NOVEL PROGNOSTIC BIOMARKER AND THERAPEUTIC TARGET IN NSCLC

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Background: Genomic analyses are identifying novel genes involved in the pathogenesis of non-small cell lung cancer (NSCLC). TMPRSS4, a membrane-anchored serine protease, was previously found as highly overexpressed in NSCLC. Since proteases have been functionally related to cancer growth and metastasis, we sought to study the prognostic value and role of TMPRSS4 in NSCLC. **Method:** TMPRSS4 expression was evaluated by immunohistochemistry and H-score calculation in TMAs containing a total number of 455 cases. Kaplan-Meier, log-rank and Cox analyses were used to study the prognostic value. In addition, functional assays using NSCLC cell lines and in vivo models were used to assess the possible role of this protease in NSCLC. **Result:** High expression of TMPRSS4 was associated with reduced relapse-free survival (RFS, p=0.003) and overall survival (OS, p=0.007) in NSCLC patients. The prognostic value was also found in patients with stages I-II. Multivariant Cox regression analysis identified TMPRSS4 as an independent prognostic factor in NSCLC for both RFS (HR 1.61 [1.16-2.23], p<0.004) and OS (HR 1.52 [1.14-2.03], p<0.005). In functional studies we developed genetic systems to overexpress or reduce TMPRSS4 levels in lung cancer cells lines. Overexpression in LKR13 cells led to increased clonogenicity, migration and multiorganic metastasis in liver, bone and suprarenal gland. Abrogation of TMPRSS4 in H358 and H2170 cell lines caused a very strong reduction in proliferation (>70%, 96h after plating), clonocenicity (>90%, after 15 days in culture) and subcutaneous tumor growth. Reduction in S and G2/M phases of the cell cycle, increased apoptosis, and changes in gene expression of cell replication- and migration-promoting genes (i.e. MCM6, TYMS and CDKN1A(p21)) were also found. Cells lacking TMPRSS4 were highly sensitized to chemotherapy, including cisplatin, paclitaxel and gemcitabine, which significantly enhanced the antiproliferative, antitumor and proapoptotic effect of these drugs. **Conclusion:** Our results show that TMPRSS4 is a biomarker of poor prognosis in NSCLC and plays an important role in tumor growth and metastasis, and suggest that its blockade may enhance sensitivity to chemotherapy.

Keywords: Prognosis, TMPRSS4, Chemosensitization

P1.03 BIOLOGY
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P1.03-25 THE FREQUENCY AND PROGNOSIS OF ATM MUTATIONS IN CHINESE NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: The ataxia-telangiectasia mutated kinase protein (*ATM*) plays a critical role in the cellular response to double strand DNA damage. While the genetic locus of *ATM* mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *ATM* mutations. **Method:** A total of 389 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *ATM* mutation and other genes were detected by next generation sequencing. **Result:** *ATM* gene mutation rate was 6.17% (24/389) in non-small cell lung cancer, including L229V (1 patient), V2298E (1 patient), M2041V (1 patient), D126N (1 patient), S2123N (1 patient), Q95L (1 patient), R337H (1 patient), H1474R (1 patient), R772Sfs*25 (1 patient), W488L (1 patient), M1064T (1 patient), E347A (1 patient), K1192R (1 patient), P1374S (1 patient) R248* (1 patient), M1321I (1 patient), I346N (1 patient), H2430R (1 patient), G494D (1 patient), N2282S (1 patient), A1945S (1 patient), E518* plus D1616V (1 patient), Q161* plus E699Q (1 patient) and D2448G plus L2261Tfs*12 (1 patient), and median overall survival (OS) for these patients was 18.0 months. Among them, all patients were *ATM* gene with co-occurring mutation. Briefly, patients with (n=8) or without (n=16) co-occurring *EGFR* mutations had a median OS of 21.0 months and 11.0 months respectively (P=0.19); patients with (n=13) or without (n=11) co-occurring *TP53* mutations had a median OS of 21.0 months and 14.0 months respectively (P=0.44). **Conclusion:** Although *EGFR* and *TP53* gene accompanied may have less correlation with *ATM* mutation in NSCLC patients, predict which patients may harbor *ATM* mutations, could have implications in triaging toward *ATM* variant identification for potential future targeted therapy. These data have implications for the identification of therapeutic target candidates.

Keywords: Non-small-cell lung cancer, Prognosis, ATM mutation

P1.03 BIOLOGY
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P1.03-26 ANALYSIS OF DDR2 GENE ABERRATIONS IN CHINESE NON-SMALL-CELL LUNG CANCER PATIENTS AND EVALUATION OF THEIR PROGNOSIS

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Background: Recently, Mutations in discoidin domain receptor 2 (*DDR2*) gene were recently identified as promising molecular targets in non-small-cell lung cancer. While the genetic spectrum of *DDR2* mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *DDR2* mutations. **Method:** A total of 283 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *DDR2* mutation and other genes were detected by next generation sequencing. **Result:** *DDR2* gene mutation rate was 3.18% (9/283) in non-small cell lung cancer, including S311N (3 patients), E44K (1 patient), R709Q (1 patient),

T564I (1 patient), R742Q (1 patient), G206* (1 patient) and M117I (1 patient), and median overall survival (OS) for these patients was 20.0 months. Among them, all patients were *DDR2* gene with co-occurring mutation. Briefly, patients with (n=6) or without (n=3) co-occurring *EGFR* mutations had a median OS of 20.0 months and 9.0 months respectively (P=0.29); patients with (n=4) or without (n=5) co-occurring *TP53* mutations had a median OS of 17.0 months and 21.5 months respectively (P=0.63); patients with (n=2) or without (n=7) co-occurring *KRAS* mutations had a median OS of 13.5 months and 20.0 months respectively (P=0.82); patients with (n=2) or without (n=7) co-occurring *PTPRD* mutations had a median OS of 15.0 months and 20.0 months respectively (P=0.96). **Conclusion:** *DDR2* mutations were observed in 3.18 % of cases of NSCLC. *DDR2*-mutated NSCLC can exhibit other driver gene alterations. No clinical characteristics were significantly associated with *DDR2* mutation.

Keywords: Non-small-cell lung cancer, Prognosis, DDR2 mutation

P1.03 BIOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.03-27 SOMATIC MUTATIONS IN BRCA2 GENES ARE ASSOCIATED WITH PROGNOSIS IN CHINESE NON-SMALL-CELL LUNG CANCER PATIENTS

J. Lai[1], C. Xu[2], W. Wang[3], Q. Zhang[4], W. Zhuang[2], Y. Zhu[5], Y. Huang[2], Y. Chen[2], G. Chen[2], M. Fang[3], T. Lv[6], Y. Song[7]

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Background: The role of *BRCA2* gene somatic mutations are mainly to maintain genome integrity in response to DNA damage through different mechanisms. Deregulation of *BRCA2* is associated with the development of tumor and altered sensitivity to chemotherapeutic agents, but the genetic variability of *BRCA2* somatic mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *BRCA2* somatic mutations. **Method:** A total of 362 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *BRCA2* somatic mutation and other genes were detected by next generation sequencing. **Result:** *BRCA2* gene somatic mutation rate was 4.97% (18/362) in non-small cell lung cancer, including S547P (2 patients), G1433W (2 patients), I488V (1 patient), C315S (1 patient), T2007S (1 patient), I1929V (1 patient), H3117Y (1 patient), G1370V (1 patient), T768S (1 patient), E2260Q (1 patient), R2087K (1 patient), E3167Q (1 patient), S163T (1 patient), T152I (1 patient), E2275Q (1 patient) and S163T (1 patient) , and median overall survival (OS) for these patients was 18.0 months. Among them, all patients were *BRCA2* gene with co-occurring somatic mutation. Briefly, patients with (n=3) or without (n=15) co-occurring *EGFR* mutations had a median OS of 21.0 months and 18.0 months respectively (P=0.22); patients with (n=11) or without (n=7) co-occurring *TP53* mutations had a median OS of 7.5 months and 18.0 months respectively (P=0.15); patients with (n=2) or without (n=16) co-occurring HER2 mutations had a median OS of 11.0 months and 20.0 months respectively (P=0.24). **Conclusion:** *BRCA2* mutations represent a distinct subset of NSCLC. NGS might be useful for evaluation of *BRCA2* unclassified variants. Our results show that *BRCA2* mutations delineate an aggressive subtype of lung cancer for which a targeted treatment through BRCA2 inhibition might offer new opportunities.

Keywords: Prognosis, BRCA2 somatic mutation, Non-small-cell lung cancer

P1.03 BIOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.03-28 ASSOCIATION BETWEEN MOLECULAR CHARACTERISTICS OF CTNNB1 MUTATIONS AND PROGNOSIS IN PATIENTS WITH NSCLC IN CHINESE PATIENTS

J. Lai[1], C. Xu[2], W. Wang[3], Q. Zhang[4], W. Zhuang[5], Y. Huang[4], Y. Zhu[6], Y. Chen[4], G. Chen[5], M. Fang[7], T. Lv[8], Y. Song[9]

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Background: Recently, *CTNNB1*, encoding beta-catenin, is a well-known tumor-related gene in the wnt signaling pathway. While the genetic variability of *CTNNB1* mutation NSCLC patients is unclear.The aim of this study is to investigate mutations and prognosis of NSCLC harboring *CTNNB1* mutations. **Method:** A total of 677 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *CTNNB1* mutation and other genes were detected by next generation sequencing. **Result:** *CTNNB1* gene mutation rate was 1.92% (13/677) in non-small cell lung cancer, including S33F (4 patients), S33C (1 patient), D32H (1 patient), G34R (1 patient), G34V (1 patient), G34del (1 patient), D11G (1 patient), S45P (1 patient), S45F (1 patient) and S45del plus S33Y (1 patient), and median overall survival (OS) for these patients was 12.0 months. Among them, all patients were *CTNNB1* gene with co-occurring mutations. Briefly, patients with (n=7) or without (n=6) co-occurring *EGFR* mutations had a median OS of 25.8 months and 8.5 months respectively (P=0.18); patients with (n=10) or without (n=3) co-occurring *TP53* mutations had a median OS of 10.0 months and 17.5 months respectively (P=0.35); patients with (n=2) or without (n=11) co-occurring *BRAF* mutations had a median OS of 7.5 months and 13.0 months respectively (P=0.14); patients with (n=2) or without (n=11) co-occurring *ATM* mutations had a median OS of 17.5 months and 11.0 months respectively (P=0.53). **Conclusion:** Accompanied gene has not well been connected with *CTNNB1* gene mutations. Our finding expands the mutant spectrum of *CTNNB1* gene and adds new understanding of the phenotype.

Keywords: CTNNB1 mutation, Non-small-cell lung cancer, Prognosis

P1.03 BIOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.03-29 AN INTRONIC VARIANT IN EGFR REGULATES GBAS EXPRESSION AND PREDICTS SURVIVAL IN EARLY-STAGE NON-SMALL CELL LUNG CANCER

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Background: Genome-wide association studies (GWAS) have indicated that most of the currently identified disease- and trait-associated single nucleotide polymorphisms (SNPs) are *intronic* or intergenic. RegulomeDB is a recently developed database that provides functional annotations for regulatory features of SNPs located in non-coding regions. **Method:** We evaluated the potential regulatory SNPs in the *EGFR* gene region using RegulomeDB and their associations with prognosis after surgery in non-small cell lung cancer (NSCLC) patients. A total of 698 patients with surgically resected NSCLC were enrolled and seven SNPs were selected based on RegulomeDB database. All SNPs were genotyped using SEQUENOM's MassARRAY® iPLEX assay. **Result:** Among the seven SNPs evaluated, the rs9642391 (*EGFR* ivs19+2851C>G) was found to be significantly associated with survival outcomes (adjusted HR for overall survival = 0.70, 95% CI = 0.56-0.87, *P* = 0.001; and adjusted HR for disease free survival = 0.82, 95% CI = 0.70-0.97, *P* = 0.02; under codominant model). According to RegulomeDB, the rs9642391C>G, which is located in intron 19 of *EGFR*, was predicted to influence the expression of *glioblastoma amplified sequence* (*GBAS*), but not *EGFR*. As predicted, the rs9642391C>G was associated with *GBAS* mRNA expression (*P*=0.024), but not *EGFR* mRNA expression in tumor tissues. **Conclusion:** In conclusion, our study provided evidence that the rs9642391C>G in the intron of *EGFR* is associated with *GBAS* expression and survival outcomes of patients with surgically resected early-stage NSCLC.

Keywords: EGFR, RegulomeDB, survival

P1.03 BIOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.03-30 THE NUMBER OF MUTATED REPAIR GENES AS PREDICTOR FOR TUMOR MUTATION BURDEN OF LUNG ADENOCARCINOMA

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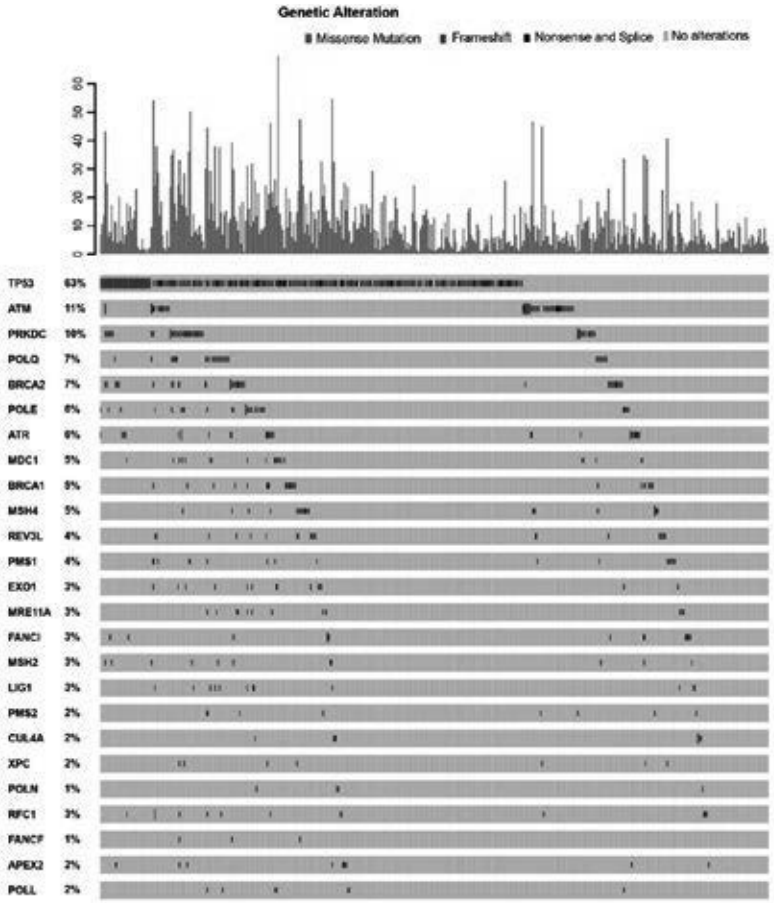
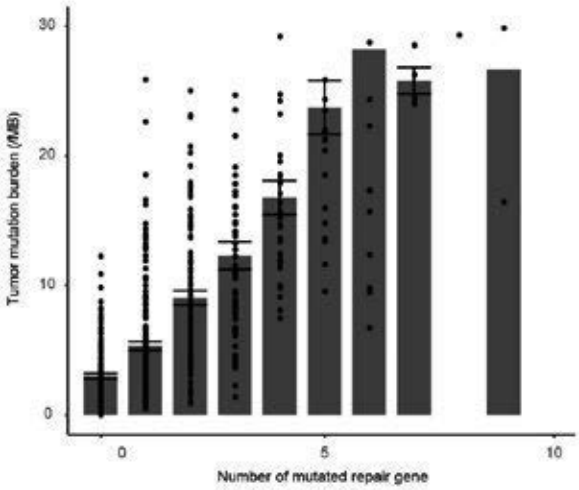
Background: Disruption of repair gene products will result in higher risk of mutation events and genetic instability. Despite some repair genes such as BRCA1 and FANCA being intensively reported in breast cancer, ovarian cancer, and the predisposition to cancers, the effects of protein dysfunction of repair genes on mutation events have not been quantified. The established repair pathways are responsible for different

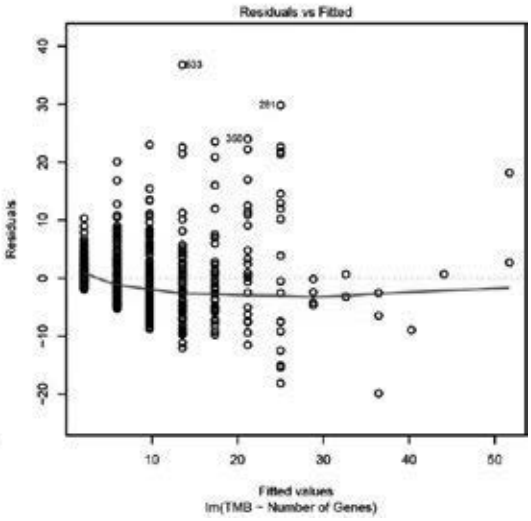
mutation events and may account for respective mutation patterns. Therefore, we conducted an in-depth investigation of effect of individual repair pathways or individual repair genes on tumor mutation burden (TMB). **Method:** We obtained level 4 variant datasets from The Cancer Genome Atlas (TCGA) which comprises of 568 samples. The TMB of each individual was calculated and the population was divided into subgroups as per the status of harboring mutations in repair genes as well as the specific repair pathways. **Result:** In the 568 lung adenocarcinoma patients, 434 patients have somatic mutations in any of the 112 DNA repair genes. The individuals harboring mutations in repair genes have significantly higher TMB (Mean=3.019, S.E.=0.206) than those do not (Mean=11.085, S.E.=0.493), and we derived a 3.81-fold increase in TMB for mutations occuring in an additional repair gene. Those that harbor mutations in TP53 account for 63% of the population, and ATM and PRKDC account for 11% and 10, respectively.

Conclusion: We identified most highly mutated repair genes and quantified the increase in risk for each additional mutated repair gene. Although the TMB of individuals with mutations in specific repair gene or pathway show no significant difference, a larger dataset that comprises adequate number of samples within each explanatory variables such as incidence of cell division, tumor stages to be taken into model, can be expected to derive a more robust predictor.

Keywords: TCGA, DNA repair gene, Tumor mutation burden







POSTER SESSION 1
MONDAY, SEPTEMBER 24, 2018

P1.03-31 PERIOSTIN IS A NEGATIVE PROGNOSTIC FACTOR AND PROMOTES CANCER CELL PROLIFERATION IN NON-SMALL CELL LUNG CANCER

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Background: Periostin is a matricellular protein that is secreted by fibroblasts and interacts with various cell-surface integrin molecules. Although periostin is known to support tumor development in human malignancies, little is known about its effect on lungcancer progression. **Method:** We classified 189 clinical specimens from patients with nonsmall cell lungcancer according to high or low periostin expression. In a syngenic implantation model, Ex3LL cells (mouse lung cancer cell line, 1×106 in 100μL PBS) were implanted into the left thigh muscle of periostin−/− or periostin+/+ mice. Tumor formation was monitored weekly. Four weeks after implantation, the mice were then euthanized. The primary tumors and metastatic lung nodules were assessed. **Result:** We found a better prognosis for patients with low rather than high periostin, even in cases of advancedstage cancer. In a syngenic implantation model, murine Ex3LL lungcancer cells formed smaller tumor nodules in periostin−/− mice than in periostin+/+ mice, both at the primary site and at metastatic lung sites. An in vitro proliferation assay showed that stimulation with recombinant periostin increased Ex3LL-cell proliferation. We also found that periostin promotes ERK phosphorylation. **Conclusion:** Our results demonstrated that high periostin expression is a strong prognostic factor in lung cancer, and that periostin secreted by adjacent fibroblasts may promote lung cancer proliferation and invasion. We believe that periostin represents a potential target in lungcancer tumor progression.

Keywords: ERK, periostin, lung cancer

P1.03-32 MOLECULAR CHARACTERISTICS AND PROGNOSIS FBXW7 MUTATIONS IN CHINESE NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: *FBXW7* (F-box and WD repeat domain containing-7) is a tumor suppressor protein that regulates the degradation of various oncoproteins in several malignancies. However, limited information is available regarding *FBXW7* mutations in non-small-cell lung cancer. While the genetic variability of *FBXW7* mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *FBXW7* mutations. **Method:** A total of 229 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *FBXW7* mutation and other genes were detected by next generation sequencing. **Result:** *FBXW7* gene mutation rate was 3.06% (7/229) in non-small cell lung cancer, including G66Efs*55 (1 patient), I487Sfs*23 (1 patient), S668Vfs*39 (1 patient), G493E (1 patient), R49W(1 patient), S550Efs*26 (1 patient) and R505L (1 patient), and median overall survival (OS) for these patients was 10.0 months. Among them, all patients were *FBXW7* gene with co-occurring mutation. Briefly, patients with (n=2) or without (n=5) co-occurring *EGFR* mutations had a median OS of 13.5 months and 10.0 months respectively (P=0.56); patients with (n=5) or without (n=2) co-occurring *TP53* mutations had a median OS of 6.0 months and 17.5 months respectively (P=0.27); patients with (n=2) or without (n=5) co-occurring *PIK3CA* mutations had a median OS of 8.0 months and 14.0 months respectively (P=0.43); patients with (n=3) or without (n=4) co-occurring *STK11* mutations had a median OS of 4.0 months and 17.5 months respectively (P=0.06). **Conclusion:** *FBXW7*, normally a tumor suppressor, can act as an oncogene when mutated and may play an important role in the pathogenesis of NSCLC. *EGFR*, *TP53* and *PIK3CA* gene accompanied may have less correlation with *FBXW7* mutation in NSCLC patients. Everolimus may displayed moderated efficacy in patients with *FBXW7* mutation. *STK11* accompanied mutations might play a worse prognosis in *FBXW7* gene mutation NSCLC.

Keywords: FBXW7 mutation, Non-small-cell lung cancer, Prognosis

P1.03-33 MUTATIONAL SPECTRUM AND PROGNOSIS OF NON-SMALL-CELL LUNG CANCER HARBORING MTOR MUTATIONS IN CHINESE POPULATION

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Background: Mammalian Target of Rapamycin (mTOR) is a validated target in cancer. It remains to be determined whether non-small-cell lung cancer patients bearing mTOR mutation could be selected for treatment with PI3K-AKT-mTOR pathway inhibitors. While the genetic spectrum of *MTOR* mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *MTOR* mutations. **Method:** A total of 639 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *MTOR* mutation and other genes were detected by next generation sequencing. **Result:** *MTOR* gene mutation rate was 3.60% (23/639) in non-small cell lung cancer, including T1830_T1833[2>1] (3 patients), S221N (1 patient), C1483F (1 patient), D1527H (1 patient), I1964V (1 patient), E1799K (1 patient), L88F (1 patient), P2273L (1 patient), E97K (1 patient), L565Q (1 patient), M1038I (1 patient), A1792V (1 patient), R1896Q (1 patient), G1678E (1 patient), M2327I (1 patient), E2419K (1 patient), A2248S (1 patient), T1870S (1 patient), V2198A (1 patient), R1482P (1 patient) and E1362K (1 patient), and median overall survival (OS) for these patients was 13.0 months. Among them, all patients were *MTOR* gene with co-occurring mutation. Briefly, patients with (n=5) or without (n=18) co-occurring *EGFR* mutations had a median OS of 17.0 months and 11.0 months respectively (P=0.33); patients with (n=15) or without (n=8) co-occurring *TP53* mutations had a median OS of 11.0 months and 13.0 months respectively (P=0.42). **Conclusion:** *MTOR* mutation may predict a worse prognosis of NSCLC. MTOR pathway inhibitors everolimus may be beneficial for NSCLC patients with specific *MTOR* mutations. *EGFR* and *TP53* gene accompanied may have less correlation with *MTOR* mutation in NSCLC patients. The findings of this study could facilitate both clinical trial design and therapeutic strategies.

Keywords: MTOR mutation, Non-small-cell lung cancer, Prognosis

P1.03-34 COMBINED MOLECULAR AND RADIOLOGICAL EVALUATION UNVEILS THREE SUBTYPES OF DISEASE PROGRESSION TO A THIRD GENERATION EGFR TKI

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Background: The definition of disease progression (PD) to EGFR TKIs has evolved from RECIST to a combination of clinical and RECIST evaluation. Patients with dramatic, local or gradual progression to third generation EGFR TKIs have been tailored to different subsequent treatment strategies. However, little is known about progression to third generation EGFR TKIs from molecular perspective. **Method:** Longitudinal plasma samples were collected from T790M-positive patients who progressed on a third generation EGFR TKI AC0010 in a phase I/II study in Guangdong Lung Cancer Institute. A pre-defined and unified molecular and radiological evaluation of PD were performed. Ultra-deep sequencing capturing 295 cancer-related genes was performed to track the changes in ctDNA to depict molecular PD, which was defined by acquired SNV/SCNV, or ≥20% increase in allelic fraction/copy number of pre-existing SNV /SCNV or both. Radiological PD was defined by RECIST. **Result:** As of October 2016, 102 serial plasma samples from 23 patients with clinical PD were included. Three subtypes of PD to AC0010 were revealed (Fig1). Molecular PD occurred prior to radiological PD in 43.5% of patients (10/23), with an average lead time of 3.0 months. Molecular PD occurred concurrently with radiological PD in 39.1% of patients (9/23). Interestingly, 17.4% of patients (4/23) experienced radiological PD prior to molecular PD, with molecular PD occurred during AC0010 continuation beyond progression (CBPD) in 3 patients. Of patients experienced clinical stable PD in extracranial lesions, radiological PD occurring prior to molecular PD group (n=2) demonstrated longer duration of AC0010 CBPD than molecular PD occurring prior to (n=3) or concurrently with radiological PD groups (n=4) (Median, 5.6 months vs. 1.9 months vs. 1.8 months).

Fig 1A: Combined molecular and radiological evaluation unveils 3 subtypes of PD

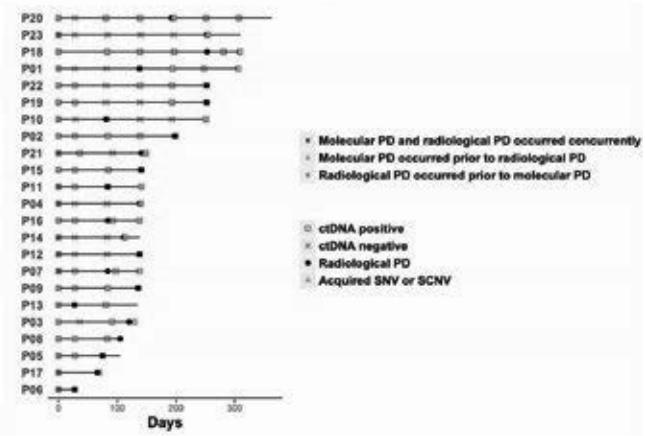
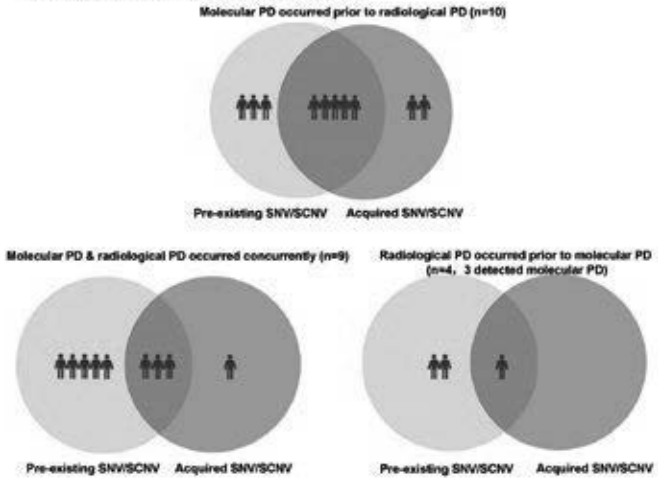


Fig 1B: Genetic characteristics of 3 subtypes of PD



Conclusion: Our study revealed 3 distinct subtypes of PD to AC0010, providing insights into PD by combining molecular and radiological evaluation and might guide the optimal time for treatment switch and personalized subsequent treatments.

Keywords: Third generation EGFR TKI, molecular PD, radiological PD

P1.04 IMMUNOONCOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.04-01 IMPACT OF CHROMATIN REMODELING GENES INCLUDING SMARCA2 AND PBRM1 ON NEOANTIGEN AND IMMUNE LANDSCAPE OF NSCLC

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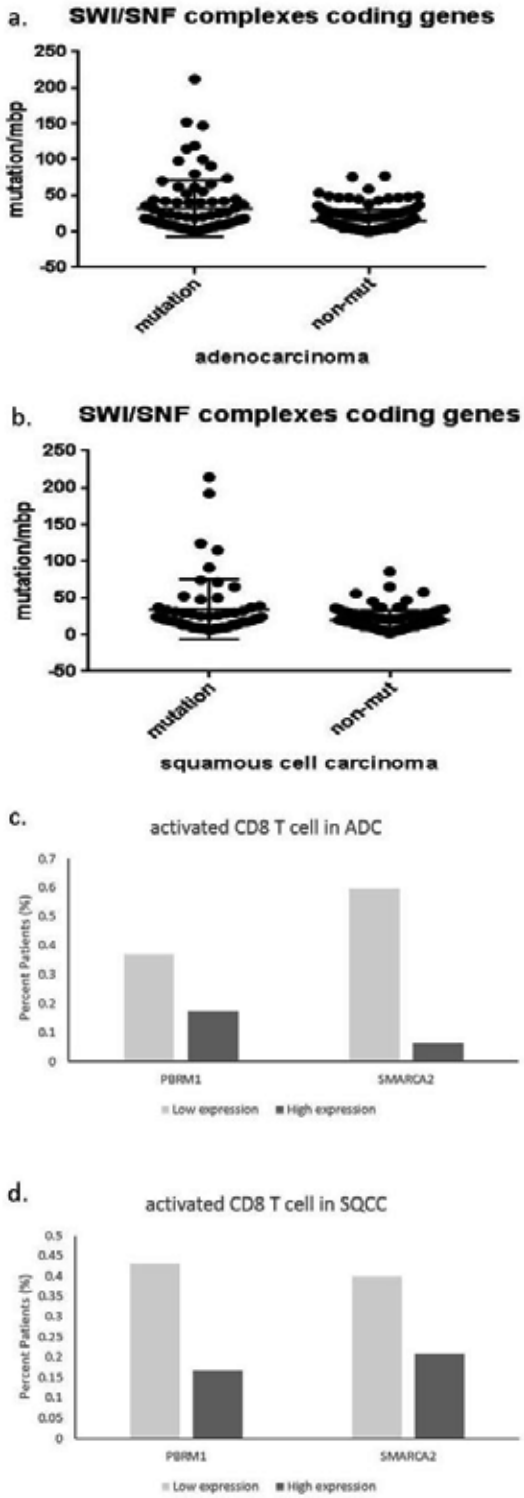
Background: Epigenetic changes in tumors and their microenvironment immune cells have been the recent focus of cancer research. Aberrations in SWI/SNF complexes within the chromatin remodeling machine may play a major role in carcinogenesis. However, little is known about their impact on neoantigen and the immune landscape of NSCLC. **Method:** Patients were divided into two groups; Mut group (at least one mutation in 27 SWI/SNF complex subunit genes including SMARCA2 and PBRM1) and NoMut group (no SWI/SNF mutations). We analyzed genomic, transcriptomic data from the TCGA database including patients with adenocarcinoma (ADC, n=515) and squamous cell carcinoma (SQCC, n=501) of lung cancer. The tumor immune landscape was analyzed using the signatures derived from 812 'immune metagenes' (Angelova, M. *et al*, 2015). We analyzed neoantigen burden and immune landscape between two groups. RNA expression of the above genes were compared. Patients were also divided by the expression levels of the above genes (1st quartile vs 4th quartile). **Result:** Mut group (142 samples, 14%) showed significant higher neoantigen burden compared with NoMut group in ADC and SQCC (mean 32.17/15.22 and 34.75/19.83 mutation/mbp, respectively, both $P<0.01$). In addition, the Mut group demonstrated higher infiltration of activated CD8 T cells compared with the NoMut group in ADC (39%/25%, $P<0.01$). However, there was no significant difference between two groups in SQCC (32%/27%, $P=0.42$). For two representative genes (SMARCA2 and PBRM1), lower expression of the two genes were associated with higher infiltration of activate CD8 T-cells in ADC (60%/6% and 37%/17%, respectively, both $P<0.01$) and SQCC (40%/21% and 43%/17%, respectively, both $P<0.01$). However, there was no difference in neoantigen burden with respect to gene expression in either ADC or SQCC.



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Conclusion: Mutation or low expression of chromatin remodeling genes including SMARCA2 and PBRM1 were associated with higher neoantigen burden and higher tumor infiltration of activated CD8 T-cells in human NSCLC.

Keywords: NSCLC, chromatin remodeling, SWI/SNF complexes, SMARCA2, PBRM1

P1.04 IMMUNOONCOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.04-02 TARGETING ESTABLISHED LUNG CANCER THROUGH COMBINATION OF DNT CELLULAR THERAPY WITH PD1 CHECKPOINT BLOCKADE

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Background: Lung cancer is the leading cause of cancer-related deaths worldwide. Immune-checkpoint blockade such as anti-PD1 therapies achieved clinical benefit which correlated with presence of immune cells in tumors. Adoptive T cell therapies is another form of immunotherapy with therapeutic-potentials, but obtaining sufficient tumor-antigen specific T cells and discovery of high-expressing tumor-specific antigens remain as challenge. Recently, we have demonstrated that a population of cytotoxic T cells (CD3+CD4-CD8-), termed double negative T (DNT) cells, has potent anti-cancer effect in vitro and in patient-derived xenograft models, can be expanded ex vivo to a therapeutic quantity and quality. In this study, whether DNT cell can target established lung cancer either alone or in combination with anti-PD1 is investigated. **Method:** Infiltrating T cell populations from 12 resected lung tumors were characterized and compared to resected adjacent and normal tissues using Flow-cytomtery. To determine the efficacy of ex vivo DNT cell therapy on lung cancer, NSG mice subcutaneously engrafted with H460 were systemically infused with DNT cells or DNT cell with Nivolumab in three doses when tumor size reached 100mm3, the tumor size and DNT cell infiltration level were monitored. **Result:** The frequency of DNT cell was reduced in lung tumor when compared to the adjacent and non-tumoral tissues of the same patient. Like conventional CD4 and CD8 T cells, 36%-52% of DNT cells within tumor expressed elevated levels of PD1, suggesting that DNT cells function may be suppressed by PD-1 pathway in patients. Using xenograft mice, we show that treatment with DNT cell alone reduced tumor growth by 14%-38%. A greater reduction (30%-68%) was observed when DNT cell treatment was combined with PD1 blockade, where PD1 blockade alone had no significant effect. Compared to DNT cell transfer alone, DNT cells with PD1 blockade led to a greater infiltration of cells with higher expression of cytotoxicity markers NKG2D and IFN-y and reduced inhibitory markers TIM3 and LAG3. **Conclusion:** These studies indicate the potential of DNT cell for the treatment of established lung cancer and that combination of DNT cell with PD1 blockade may further enhance the treatment efficacy by increasing DNT cell infiltrating to solid tumor.

Keywords: adoptive cellular therapy, lung cancer, PD1 checkpoint blockade

P1.04 IMMUNOONCOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.04-03 SUPPRESSIVE IMMUNE CELL PROFILING IN PATIENTS WITH NON-SMALL CELL LUNG CANCER.

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Background: The factors in tumor microenvironment hinder T cell activities against tumor cells. The major immunosuppressive cells in tumor sites are myeloid derived suppressor cell (MDSC), tumor associated macrophage (TAM), and regulatory T (Treg) cell, and the effector molecules released by those immunosuppressive cells also regulate T cell activities. Therefore, in this study we examined the pattern of immunosuppressive cells in patients with non-small cell lung cancer depending on their stages and we compared those immunosuppressive cells in healthy donor blood PBMC as well. Then, we tested T cell activities to verify whether suppressive immune cell populations can influence T cell activity. **Method:** Granulocytic-MDSC, Monocytic-MDSC, TAM, and Treg population from patients' PBMC (n=59) and healthy donors' PBMC (n=20) were analyzed by FACS Verse with appropriate antibodies. For suppressive assay, isolated T cells were activated with anti-CD3 and anti-CD28 for an hour and then MDSC was co-cultured with T cells for a week followed by Ki-67 level analysis by FACS Verse. T cell activity and suppression were tested by FACS analysis with identified cell surface markers. **Result:** G-MDSC (p-value=0.0023) and M-MDSC (p-value=0.0032) population were higher in advanced non-small cell lung cancer patients (stage III&IV) compared with stage I&II patients or healthy donor. G-MDSC isolated from patient's blood was co-cultured with activated T cells from the same patient. After one week, T cell activity was dramatically inhibited compared with T cell alone ($p < 0.001$, E:T = 5:1, 10:1) confirming suppressive activity of MDSC against T cells. TAM population was increased as disease progressed ($p<0.001$), and Treg also slightly increased (p-value=0.0373) in stage III&IV. Activated T cells were higher in stage III&IV, but suppressed T cells were also higher in stage III&IV compared with stage I&II. **Conclusion:** G-MDSC and M-MDSC population increased as disease progressed and G-MDSC effectively suppressed T cell activities. TAM population increased in advanced non-small cell lung cancer patients, and Treg population also slightly increased in stage III&IV. Both activated and suppressed T cells were higher in stage III&IV compared with stage I&II.

Keywords: Myeloid Derived Suppressor Cell, Tumor Associated Macrophage, Immunotherapy

P1.04 IMMUNOONCOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.04-04 EFFICIENT UPTAKE OF RECOMBINANT LIPIDATED SURVIVIN BY ANTIGEN-PRESENTING CELLS INITIATES ANTIGEN CROSS-PRESENTATION AND ANTITUMOR IMMUNITY

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Background: Survivin is over-expressed in various types of human cancer, but rarely expressed in terminally differentiated adult tissues. Thus, survivin is a potential target antigen for a cancer vaccine. However, self-tumor associated antigens are not highly immunogenic. Bacteria derived lipoproteins can activate antigen-presenting cells through their toll-like receptors to enhance immune responses. In this context, lipidated survivin is an attractive candidate for cancer immunotherapy. **Method:** In the present study, recombinant lipidated human survivin (LSur) was prepared from an Escherichia coli-based system. We investigated whether LSur is efficiently captured by antigen presenting cells then facilitating effective induction of survivin cross-presentation and generation of immunity against cancer cells. **Result:** Our results demonstrate that LSur, but not its non-lipidated counterpart, can activate mouse bone marrow derived-dendritic cells (BMDCs) to enhance cytokine (IL-6, TNF-α, and IL-12) secretion and co-stimulatory molecules (CD40, CD80, CD86 and MHC II) expression. However, the pathways involved in the capture of the recombinant lipidated antigen by antigen-presenting cells have not yet been elucidated. To this end, we employ various endocytosis inhibitors to study the effect on LSur internalization. We show that the internalization of LSur is suppressed by the inhibition of various routes of endocytosis. These results suggest that endocytosis of LSur by BMDCs can be mediated by multiple mechanisms. Furthermore, LSur is trafficked to the early endosome after internalization by BMDCs. These features of LSur are advantageous for cross-presentation and the induction of antitumor immunity. **Conclusion:** We demonstrate that immunization of C57BL/6 mice with LSur under treatment with exogenous adjuvant-free formulation induce survivin-specific CD8+ T-cell responses and suppress tumor growth. The antitumor responses are mediated by CD8+ cells. Our findings indicate that LSur is a potential candidate for stimulating protective antitumor immunity. This study suggests that lipidated tumor antigens may be a promising approach for raising a robust antitumor response in cancer immunotherapy.

Keywords: cross-presentation, Recombinant lipoprotein, cancer immunotherapy

P1.04-05 ELUCIDATING THE ROLE OF LEUKOCYTE-ASSOCIATED IMMUNOGLOBIN-LIKE RECEPTOR 2 (LAIR2) IN LUNG CANCER DEVELOPMENT

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Background: The tumor microenvironment play an important role in shaping cancer development. The contexture of stromal infiltrates have been shown promote or inhibit tumor growth and patient prognosis. In attempts to gain insight into the immune networks that regulate tumorigenesis, we used genome wide expression datasets from patients with resected early stage non-small cell lung cancer (NSCLC) to identify immune-related genes associated with patient survival. **Method:** Gene expression analysis was conducted on microarray datasets from 128 early-stage NSCLC adenocarcinoma resected tumor samples. Limiting analysis to immune-related genes, we identified a minimum gene set containing LAIR2 that was prognostic for lung adenocarcinoma. Immunohistochemistry and gene ontology analysis were used to determine the function of LAIR2. **Result:** From the gene signature, the gene encoding the immune collagen receptor LAIR2, was highly expressed within the high-risk patient subgroup (HR = 2.71, 95% CI = 1.49 to 4.90, *P* = 0.001). Gene ontology analysis revealed that LAIR2 expression correlated with negative immune regulation and associated immune signatures. Immunohistochemistry of resected lung adenocarcinoma revealed heterogeneous expression of LAIR2 within tumor epithelium and stromal immune cells, suggesting specificity and localization. ELISA for LAIR2 suggest that CD4+ Th2 cells maybe a major source of LAIR2 secretion and that recombinant LAIR2 may promote T cell exhaustion by activation of CD8+ T cells and upregulation of PD1 and LAG3. **Conclusion:** Our results suggest that expression of LAIR2 result in poor patient prognosis and is associated with negative immune regulation. An understanding of LAIR2 function will provide insight into factors required during lung cancer progression and targets for intervention.

Keywords: T cells, Prognosis, Immunology

P1.04-06 CLINICOPATHOLOGICAL ANALYSIS OF PULMONARY PLEOMORPHIC CARCINOMA

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Background: Pulmonary pleomorphic carcinoma (PC) is a histological type of poorly differentiated non-small cell lung carcinoma (NSCLC) which consists of both sarcomatous and carcinomatous components. Except for its aggressive behavior and resistance to chemoradiotherapy, clinicopathological characteristics remain elusive due to its rarity. Recently, immunotherapy targeting the programmed death-1 (PD-1)/PD ligand 1 (PD-L1) pathway has demonstrated favorable clinical outcomes in NSCLC. However, the expression patterns of PD-L1 in pulmonary PC are still unknown. We reviewed the results of clinicopathological characteristics and PD-L1 expression of 46 cases of pulmonary PC resected in our institution. **Method:** Forty-six patients with pulmonary PC consecutively underwent lung resections for the treatment in our institution between 2002 and 2017. Various clinical and pathological data were reviewed retrospectively to analyze prognostic factors for overall survival (OS) after surgery. OS was compared among patient groups by log-rank tests. For multivariate analyses, Cox hazard models were applied. P-value less than 0.05 was considered significant. Tissue samples were collected from the paraffine-embedded tumor blocks of these patients. Then, PD-L1 expression levels of the tumor were examined by immunohistochemical staining method using anti PD-L1 antibody (clone 28-8). **Result:** Patients were 40 male and 6 female, and their median age was 68 years (range: 36 to 83 years). The majority of patients with pulmonary PC were smokers (87.0%, 40/46). Forty-five tumors contained identifiable carcinomatous components, and the other 1 consisted of only spindle cell component. An adenocarcinoma component was found in 27 cases, a squamous cell carcinoma component in 5, and the other components in 14. OS rate was 50.8% at 5 years. Univariate analysis revealed that tumor size over 3 cm, the presence of necrosis and pathological T factor were significantly associated with poorer overall survival. Lymphatic invasion was not statistically significant, but tended to be associated with poorer overall survival. Multivariate analysis showed that lymphatic invasion tended to be associated with poorer overall survival. PD-L1 was highly expressed in pulmonary PC (62.5%, 10/16). The proportion of PD-L1 expression was significantly higher in the sarcomatous component than in the carcinomatous component. **Conclusion:** We found that lymphatic invasion suggested a worse prognosis for resection of pulmonary PC. Moreover, our study demonstrates that pulmonary PCs very frequently express PD-L1. Thus, targeting the PD-1/PD-L1 pathway may represent a potential therapeutic candidate for this aggressive tumor especially in its sarcomatous component.

Keywords: Pulmonary pleomorphic carcinoma, the programmed death-1 (PD-1)/PD ligand 1 (PD-L1) pathway, Immunotherapy

P1.04-07 PEMETREXED ENHANCES ANTI-TUMOR EFFICACY OF PD-L1 BLOCKADE BY PROMOTING INTRA-TUMOR IMMUNE RESPONSE VIA TUMOR AND T CELL-INTRINSIC MECHANISMS

D. Schaer[1], S. Geeganage[2], N. Amaladas[1], Z.H. Lu[2], E. Rasmussen[1], A. Sonyi[1], D. Chin[1], A. Capen[2], Y. Li[1], C. Meyer[2], B. Jones[2], X. Huang[1], S. Luo[2], C. Carpenito[1], K. Roth[2], A. Nikolayev[2], B. Tan[2], M. Brahmachary[1], K. Chodavarapu[1], F. Dorsey[2], J. Manro[2], T. Doman[2], G. Donoho[2], G. Hall[1], M. Kalos[1], R. Novosiadly[1]

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Background: The combination of pemetrexed/carboplatin with the PD-1 antibody pembrolizumab demonstrates a substantial increase in overall survival in NSCLC patients (hazard ratio 0.49) based on KEYNOTE-189 Phase III data (Gandhi et al., 2018), and represents the first chemoimmunotherapy combination ever approved in Oncology. However, the mechanisms underlying the efficacy of this combination remain largely unknown. Many chemotherapies in general and antifolates in particular have detrimental effects on immune homeostasis, and differ in their ability to induce immunogenic tumor cell death. Nevertheless, KEYNOTE-189 results suggest a positive interaction between pemetrexed-based chemotherapy and immunotherapy highlighting the importance to understand the role of pemetrexed in modulating antitumor immune response to assure rational application of this therapy to the appropriate patients. **Method:** To characterize the effects of pemetrexed on intra-tumor immune response, murine syngeneic tumor models (MC38 and Colon 26) were treated with pemetrexed, paclitaxel with or without carboplatin, or anti-mouse PD-L1. Immune cell subsets and immune-related changes in tumor tissue and T cells were assessed by flow cytometry and gene expression analysis. Tumor and T cell-intrinsic effects of pemetrexed including ability to induce immunogenic cell death of tumor cells and enhance immune function through changes in mitochondrial respiration and gene expression in T cells were also evaluated. **Result:** In MC38 syngeneic mouse tumor model, pemetrexed increases frequency of intratumor leukocytes and cycling (Ki67+) T cells accompanied by gene expression changes indicative of T cell inflamed phenotype. In contrast, paclitaxel exerts quantitatively and qualitatively different immune effects mainly associated with modest upregulation of myeloid cell-related genes whereas carboplatin barely exhibits any immune-related changes in monotherapy and appears to attenuate immunomodulatory effects induced by pemetrexed in MC38 tumors. Pemetrexed in combination with PD-L1 antibody demonstrates enhanced antitumor efficacy and pronounced inflamed/immune activation phenotype in Colon26 syngeneic mouse tumor model. *In vitro* data indicate that pemetrexed is a potent inducer of immunogenic tumor cell death as exemplified by marked release of HMGB1 in MC38 and Colon26 tumor cells and suggest T cell-intrinsic effects exemplified by enhanced mitochondrial content, oxidative respiration and increased expression of cell surface molecules and immune-related genes indicative of T cell activation. **Conclusion:** Pemetrexed promotes intra-tumor T cell-mediated immune response through immunogenic tumor cell death and increased activation and metabolic fitness of T cells leading to an enhanced anti-tumor efficacy in combination with PD-L1 antibody.

Keywords: pemetrexed, PD-(L)1, chemoimmunotherapy

P1.04-08 CO-RESIDENCE OF PATIENT-DERIVED IMMUNE CELLS IN PATIENT-DERIVED XENOGRAFTS FROM LUNG CANCER PATIENTS

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Background: Patient-derived xenograft (PDX) models have been shown to recapitulate many characteristics of human tumors and have been increasingly used for anticancer drug development, molecular characterization of cancer biology, and development of precision therapies. However, because PDXs are grown in immunodeficient mouse strains, they are regarded as inappropriate for preclinical evaluation of anticancer immunotherapy. Here we evaluated whether patient-derived immune cells co-exist in PDXs derived from lung cancer patients. **Method:** First-generation PDX (F1) was established by subcutaneously implanting human tumor tissue into non-obese diabetic-severe combined immunodeficiency (NOD-SCID) mice with a null mutation of the gene encoding for interleukin-2 receptor g (NSG). When the resulting tumors in these mice grew to about 1.5 cm in diameter, we passaged the tumors in NSG or nude mice for subsequent generations. A small piece of these PDX tissues (about 2-3 mm^3) were minced into fragments and cultured in media containing human interleukin-2 (IL-2) (2000 -6000 units/ml) for up to 6 weeks. The proliferated lymphocytes for analyzed by fluorescence-activated cell sorting (FACS) with antibodies specific for human immune cell surface markers. The provenance of cultured cells was determined by DNA fingerprinting assay together with patients' DNA samples from primary tumors and/or peripheral blood mononuclear cells (PBMC). **Result:** The mean time of PDX growth in NSG mice before harvesting for culturing tumor-infiltrating lymphocytes (TILs) was 120 days (ranging from 63-292 days). TILs were successfully cultured from 8 of 25 PDXs samples (about 32%), with one from F2 PDXs and 7 from F1 PDXs. TILs from five of those PDXs were predominantly human $CD3^+CD8^+$ T cells (72% -99%), while the remaining three were predominantly human $CD19^+$ B cells (77% - 95%). DNA fingerprint analysis showed that genotypes of TILs were identical to patients' primary tumors and/or PBMC, demonstrating that the TILs were from the same patients as the PDXs. Further analysis showed that $CD8^+$ T cells from PDXs were $CD45RO^+$, with either $CD62L^+$ or $CD62L^-$. **Conclusion:** Patient-derived immune cells co-exist with PDXs in some lung cancer PDX models. Most of those immune cells were $CD3^+CD8^+$ and could be memory T cells. These results suggest that some PDXs might be used for evaluating functions of tumor resident immune cells and/or for evaluating anticancer immunotherapies.

Keywords: Lung cancer, patient-derived xenografts (PDX), Tumor infiltrating lymphocytes (TIL), immunotherapy

P1.04-09 IMMUNOMODULATORY EFFECTS OF AFATINIB AND PEMBROLIZUMAB IN EGFR-MUTANT NSCLC WITH PROGRESSION ON PRIOR EGFR-TKI

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Background: EGFR-mutant NSCLC is less responsive to single agent PD-1 blockade than smoking associated NSCLC. Preclinical models suggest EGFR-TKI can render a more immunocompetent tumor microenvironment. This study examined the immunomodulatory effects of combination second generation EGFR-TKI and PD-1 antibody. **Method:** In this phase 1 dose de-escalation study, patients were treated with afatinib 40 mg oral daily and pembrolizumab 200 mg IV q21day. Key Eligibility: advanced EGFR-mutant NSCLC with progression (PD) on prior EGFR-TKI, age≥18, ECOG PS≤1, acceptable organ function, no significant autoimmune diseases, measurable disease and controlled brain metastases. Tissue biopsy performed baseline and week 5-6 on treatment for PD-L1 IHC (22C3) and quantitative immunofluorescence for immune cell subsets and next-generation sequencing. Blood at baseline and at serial on-treatment timepoints were collected for ctRNA of PD-L1, EGFR, HER2 and MET; changes in circulating immune cell subsets, T-Cell repertoire and cytokine levels were evaluated by flow cytometry and Luminex. **Result:** No DLTs were observed in the first 6 patients and the 10 patient expansion cohort proceeded at afatinib 40 mg daily and pembrolizumab 200 mg IV q21day. Eleven patients enrolled to date. Key molecular and pathologic characteristics: adenocarcinoma 9, neuroendocrine 1, squamous 1. EGFR-TKI resistance mechanism: EGFR-T790M 4, EGFR-T790M/C797S 1, HER2 amp 1, MET 2, Her2 amp+neuroendocrine differentiation 1, unknown 2. Five patients had prior second line osimertinib. Three (27%) patients had immune related AEs (G2 adrenal insufficiency, G2 nephritis, G3 colitis). Nine patients were evaluable for response: (1 PR, 7 SD ((6/7) with tumor reduction <30%)). The responding patient had squamous histology tumor, prior PD on erlotinib, and PFS of 11 months with PD-L1 (22C3) TPS 40% and PD-L1 and PD-L2 amplification. Treatment with afatinib and pembrolizumab induced systemic immune changes including trend for increased soluble IDO, MIG, TIM3, IP-10, LAG3, PD-L1 and PD-L2 and decreased IFN-gamma. ctRNA for EGFR and PD-L1 were detected in 7/7 and 6/7 patients, respectively, with dynamic changes in allele frequency of EGFR and PD-L1 observed. Baseline PD-L1 (22C3) TPS ranged from 0% to 75% expression. Four patients had repeat biopsy and in paired samples analyzed PD-L1 (22C3) expression decreased in the stroma. **Conclusion:** Immunomodulatory effects of afatinib with pembrolizumab were noted in the tumor microenvironment and peripheral blood. Only modest clinical activity has been observed thus far in patients with PD on prior EGFR-TKI. Genomic and immune-profiling is feasible in EGFR-mutant NSCLC and may identify EGFR-mutant NSCLC patients who may respond or lack benefit to PD-1 blockade.

Keywords: immune microenvironment, EGFR-mutant NSCLC, Immunotherapy

P1.04-10 THE IMPORTANCE OF SUPPRESSOR AND CYTOTOXIC T LYMPHOCYTE SUBSETS AND CYTOTOXIC MECHANISMS IN NON-SMALL CELL LUNG CANCER

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Background: Lung cancer represents the second most frequent cause of death worldwide, and most common subtype of lung cancer is non-small cell lung cancer (NSCLC). Recent trials showed that deficiencies in anti-tumor immunity play a major role in carcinogenesis of NSCLC. $CD8^+CD28^-$ cytotoxic T (Tc) cells and $CD4^+CD25^+FoxP3^+$ regulatory T (Treg) cells known as suppresor CD4+ T cells, have been shown to exist in tumor tissues and inhibits the anti-tumoral immune responses. Natural killer (NK) cells are cytokine producing innate lymphoid cells having cytotoxic capacity to kill tumor cells. In this study the prevalence of Treg cells and CD28 expressing Tc cells and cytotoxic functions were analyzed. **Method:** The study groups comprised patients with newly-diagnosed non-small cell lung cancer (NSCLC) (n=46) with T1-3N0M0 NSCLC, none of whom had received preoperative chemotherapy and/or radiotherapy, and healthy subjects (n=46). The prevalence of $CD3^-CD16^+CD56^+$ NK cells, $CD4^+CD25^+Foxp3^+$ regulatory (Treg) and $CD8^+CD28^-$ T cells were analyzed by flow cytometry. Cytotoxic capacity of NK and $CD8^+$ T cells were analyzed by CD107a degranulation assay. **Result:** NK and $CD8^+CD28^-$ suppressor T cells were increased however percentage of activator $CD8^+CD28^+$T lymphocytes were significantly decreased in patients with NSCLC compared to healthy subjects (p=0.002, p=0.005, p=0.000, p=0.001, p=0.001, p=0.02 and p=0.02, respectively). Although the cytotoxic activity of NK cells did not differ between the groups, CD107a expression was found increased in total $CD8^+$ T cells in unstimulated and K562 stimulation (p=0.001). Although the number of Treg cells are decreased in the NSCLC group but this is not statistically significant. No statistically signficant difference was found in terms of lymphocyte subsets and NK cells between the patients with early(T1) and late stages(T2-3). **Conclusion:** Our findings showed that suppressor $CD8^+CD28^-$ T cell subset as well as NK cells were increased in patients with operable NSCLC. Increased $CD8^+CD28^-$ T cells might cause supression of antitumour immunity and their prevalence might be useful to assess immunotherapy outcomes in patients. Although the number of NK cells increased significantly, the activity of NK cells did not show difference. Functional evaluation of cells has been found to be more important than cell populations.

Keywords: non-small cell lung cancer, anti-tumor immunity, Treg cells

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P1.04-11 EXPLORING THE GERM-LINE CONTRIBUTION TO EXCEPTIONAL RESPONSE TO PD-1/PD-L1 INHIBITION IN PATIENTS WITH NSCLC BY WHOLE GENOME SEQUENCING

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Background: Responses to immune checkpoint inhibitors (CPI) may vary between individuals because of somatic mutation differences in the tumour and/or germ-line differences in immunological tolerance. To explore the latter, this ongoing study evaluates patients with metastatic non-small cell lung cancer (NSCLC) treated with single agent PD-1 or PD-L1 inhibitors recruited from a treatment pool of 420 patients (total) / 137 (active since 1 August 2017). **Method:** Rare and common germ-line DNA variants are analysed in exceptional responders and non-responders by whole genome sequencing (WGS) (Illumina HiSeqX Ten). Exceptional responders are defined as patients with complete or partial response of more than 12 months or stable disease of more than 24 months (per RECIST), and a concurrent immune-related adverse event of any grade. Non-responders are defined as patients with best response of progressive disease, having received at least 4 cycles or 2 months of treatment. In these individuals, the burden of rare and common variants in immune tolerance genes is analysed and compared to the Medical Genome Reference Bank (MGRB), comprising WGS of 1144 well-elderly individuals. Comparisons are made with Fisher Exact test. Genetic risk scores for auto-immune conditions are calculated for these cohorts, MGRB and NSCLC patients included in The Cancer Genome Atlas. Scores are calculated using curated risk alleles and OR weightings derived from the NHGRI-EBI GWAS catalogue. **Result:** Recurrent rare variants (Exome Aggregation Consortium (ExAC) frequency < 1%) were found within responders sequenced to date (n=20), including variant A, a frameshift mutation in a protein kinase not present in ExAC, with allelic frequency (AF) of 1.27% in MGRB and 17.5% of our cohort (p<0.0001). Multiple common variants (ExAC ≥1%) were more frequent within the cohort compared with population standard. Among these, three functional variants within gene B, encoding a protein involved in modulating immune-responsiveness, (variant B.1, B.2 and B.3, ExAC AF: 1.3%, 0.99% and 2.3%), were found seven times (total) across six individuals (one compound heterozygous B.2/B.3). The exceptional responders cohort was enriched for subjects with higher genetic risk for Disease A, psoriasis and psoriatic arthritis compared with control groups. **Conclusion:** Preliminary findings suggest individuals harbouring functional variants in genes promoting immune tolerance may be more responsive to PD-1/PD-L1 inhibitors. This may be due to higher basal immune activation, requiring greater reliance on inhibitory checkpoints to maintain homeostasis. Ordinarily, this would be clinically undetectable, however the addition of a pharmacological CPI may more effectively break immune tolerance in this primed environment.

Keywords: Immunogenomics, Immunotherapy, whole genome sequencing

P1.04 IMMUNOONCOLOGY
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P1.04-12 MASS SPECTROMETRY-BASED SERUM PROTEOMIC SIGNATURE AS A POTENTIAL BIOMARKER FOR SURVIVAL IN NSCLC PATIENTS WITH IMMUNOTHERAPY

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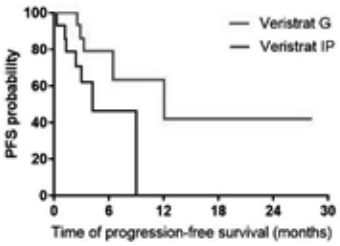
Background: The Veristrat test is a serum biomarker using a mass spectrometry (MS)-based proteomic signature derived from machine learning. It is used as a prognostic marker for patients with NSCLC undergoing platinum-based chemotherapy. However, its role in patients undergoing immunotherapy has not been investigated. **Method:** 47 patients with advanced stage NSCLC and no activating EGFR mutation underwent VeriStrat testing from 2016 to 2017. Patients were grouped into Veristrat 'Good' risk group (VS-G) or Veristrat 'Indeterminate' & Veristrat 'Poor' risk group (VS-IP). Kaplan-Meier survival analyses with log rank test were performed to compare the progression-free survival (PFS) and overall survival (OS) between the two groups. PFS of NSCLC patients treated with immunotherapy was derived from the time of the immunotherapy to disease progression or death. **Result:** 47 patients had a mean age of 65.6 (range: 30 to 91). 26 patients were female (55%). 26 patients had diagnosis of adenocarcinoma (55%), while 18 patients had squamous cell carcinoma (38%). 32 patients (68%) underwent treatment with a PD-1 inhibitor (pembrolizumab or nivolumab), whereas 15 patients (32%) did not. 32 patients (68%) demonstrated VS-G trait while 15 patients (32%) demonstrated VS-IP trait (intermediate: 1, poor: 14). Overall, VS-G demonstrated significantly prolonged PFS compared to VS-IP for all NSCLC patients regardless of treatment (median PFS, 12.0 months vs. 6 months, p<0.05), though there was not a significant different in OS between VS-G and VS-IP. Among NSCLC patients treated with immunotherapy, VS-G classification trended towards increased PFS when compared to VS-IP (Figure 1, median PFS, 12.0 vs 4.2 months, p=0.054), while OS was not statistically different. Multivariate analysis revealed that Veristrat was an independent predictor of PFS in this patients, regardless of various clinical factors.

Figure 1
Progression-free survival by NSCLC population treated with immunotherapy



Conclusion: MS-based serum proteomic signature may serve as a biomarker for survival outcome in patients with NSCLC, including patients undergoing immunotherapy.

Keywords: NSCLC, Veristrat, immunotherapy, biomarker, survival outcome

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P1.04-13 COMBINING CLINICAL AND GENOMIC DATA FOR PREDICTING RESPONSE TO CHECKPOINT INHIBITORS IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Programmed death receptor (PD-1) inhibitors have emerged as a viable option for several cancers including advanced non-small cell lung cancer (NSCLC) by demonstrating good response rates, increased long-term survival, and a favorable safety profile. Although PD-L1 expression and tumor mutational burden have some role in determining response, these are not always predictive. Therefore identification of other characteristics to predict response to immunotherapy remains of interest and is the focus of this study. **Method:** Information from patients with NSCLC treated at UH Cleveland Medical Center has been compiled into a large single institution database. From this prospective database, 116 patients treated with PD-1 inhibitors were identified and their pathological, clinical, and genomic characteristics were gathered.

Parameters such as sex, race, smoking status (current vs. former vs. never smoker, years smoking and pack years), and tumor mutational status were statistically analyzed to determine association with response to immunotherapy. **Result:** In this study, 116 patients were treated with PD-1 inhibitors. Overall the response rate to therapy was 22%. Among the 116 patients, 78 had genomic data, which was analyzed and yielded four tumor mutations associated with a clinical response. Of the 6 patients with an NF1 mutation and 6 with an RB1 mutation, none showed a response to treatment (p=0.178). Conversely our analysis showed a positive response to immunotherapy with KRAS and MYC mutations at p-values of 0.098 and 0.018, respectively. MYC mutation remains statistically significant at predicting response when controlling for the effects of age and smoking history. Of significant interest we found that a positive response to immunotherapy is associated with positive smoking history and current smoking status. The response rate to immunotherapy was 0% for never smokers, 21.6% for former smokers, and 29.4% for current smokers (p=0.193). Both years smoking and pack years are positively associated with response to immunotherapy with a response increase of 3% per each year smoking (p=0.062). **Conclusion:** This study found a positive correlation between response to immunotherapy in patients with NSCLC and ongoing smoking habits as well as overall pack years smoked. It also demonstrated that positive response to therapy is associated with tumor mutations in KRAS and MYC while a lack of response is associated with tumor mutations in NF1 and RB1.

Keywords: next generation sequencing, smoking, Checkpoint inhibitors

P1.04 IMMUNOONCOLOGY
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P1.04-14 HLA B44 SUPERTYPE ASSOCIATED WITH LESS FAVORABLE NEOANTIGEN BINDING IN NON-SMALL CELL LUNG CANCER TREATED WITH IMMUNOTHERAPY

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Background: Human leukocyte antigen (HLA) supertypes may influence immunotherapy efficacy, particularly HLA class 1 B44 supertype (B44), which is found in 35-55% of the population irrespective of race (Sidney, BMC Immunol). In melanoma patients treated with immune checkpoint inhibitors, presence of B44 correlated with improved survival (Chowell, Science), but in a cohort of 58 non-small cell lung cancer (NSCLC) patients treated with single-agent pembrolizumab, B44 was associated with poorer outcomes (Lu, ASCO 2018). Given B44's small electropositive binding pocket, it was hypothesized that the transversions that predominate in NSCLC result in more positive tumor variant amino acids (vAAs) and that these neoantigens would have decreased binding affinity and/or HLA B44:peptide stability. **Method:** 58 advanced NSCLC patients treated with pembrolizumab had germline and tumor multiplexed paired-end Illumina WES performed. HLA typing used BWA-ALN and Athlates software; supertype was determined by 2008 criteria (Sidney, BMC Immunol). Six subjects with at least one strong HLA B44 supertype allele had nonsynonymous coding mutations identified with Genome Toolkit Analysis (GATK) best practices utilizing the Hg38 genome reference. PvacSeq software used NetMHC algorithms to identify tumor neoantigens 9 base pairs in length matched to their corresponding HLA B44 allele (B44-specific neoantigens, BSNs). Missense BSNs were classified by transition (Ti) transversion (Tv) ratios and vAA charge change. TiTv was compared with matched pairs analysis. Predicted NetMHC IC50 binding affinities were compared with student's t-tests. All statistical analyses were performed with SAS JMP, Version 13.0 (Cary, NC). **Result:** Among the 6 subjects, 3073 BSNs were identified; 1090 were unique. There were no common BSNs among subjects. Subject tumor TiTv median was 1.58 (95% CI 1.09-1.94), mean difference compared to germline was -0.62 (95% CI -1.11 to -0.12, p=0.02). BSNs with vAAs that changed charge represented 13.5% of all BSNs. Positive vAA charge changes were as expected based on theoretical distribution (12.5% Tv vs 6.3% Ti, p=0.02). In aggregate, there were 205 BSNs with negative charge change (-BSN) and 204 with positive charge change (+BSN). The anticipated HLA B44 binding affinity was lower for +BSN, with median NetMHC IC50 binding 176.2 (95% CI 178.0-217.9) vs 258.6 (95% CI 216.9-257.7) for -BSN, p<0.01. **Conclusion:** A potential mechanism for decreased survival in B44 NSCLC subjects treated with immunotherapy is unfavorable neoantigen binding related to increased transversions leading to tumor vAAs with positive charge changes and poorer HLA B44 binding. All subjects from this cohort will be evaluated for BSNs 8-12 base-pairs long to confirm these findings.

Keywords: NSCLC, Neoantigens, Immunotherapy

P1.04 IMMUNOONCOLOGY
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P1.04-15 COMPUTERIZED TOMOGRAPHY TEXTURE ANALYSIS AS BIOMARKER OF BENEFIT FROM NIVOLUMAB IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: While immune checkpoint inhibitors (ICIs) have revolutionized the management of advanced non-small cell lung cancer (NSCLC), response assessment is a challenging task. Indeed, due to the peculiar mechanism of action of ICIs, the currently employed response evaluation criteria based on dimensional assessment might underestimate their activity. Computerized tomography texture analysis (CTTA) is an emerging approach belonging to the field of "radiomics" and based on the analysis of quantitative data extracted from imaging features; recently, correlations between CTTA and histopathologic as well as molecular characteristics of solid tumors were observed. Our aim is to determine whether parameters derived from CTTA might be used to assess the benefit from ICIs in advanced NSCLC. **Method:** Among 74 patients (Pts) treated with nivolumab for advanced NSCLC, 35 had CT scans evaluable for CTTA and had undergone at least two assessments (at baseline and after 4 cycles). Each pulmonary lesion was evaluated by a radiologist experienced in CTTA, blinded to clinical and temporal data; 295 texture analysis parameters were obtained from each image using an open source software (MaZda, version 4.6). The variations of parameters derived from pre-set gray-level co-occurrence matrices (GLCM) before and after 4 cycles of nivolumab were determined and compared with clinical outcomes. Statistical analyses were performed using MedCalc Statistical Software (version 18). **Result:** After a median follow up of 9.9 months, variations of GLCM features describing entropy were directly associated with overall survival (OS). Most notably, Pts with increase of entropy above the median value between baseline and the subsequent CT scan identified with a specific GLCM combination had longer OS (15.3 vs. 6.2 months; p= 0.044). This finding suggests that increased tissue heterogeneity during treatment, possibly caused by immune cells infiltration, might be associated with improved outcomes. **Conclusion:** CTTA might have a prognostic/predictive role during treatment with ICIs for NSCLC. Further analyses including clinical and histopathologic features are currently ongoing, in order to enlighten the biological mechanisms at the basis of our observations.

Keywords: Nivolumab, Prognosis, Radiomics

P1.04 IMMUNOONCOLOGY
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P1.04-16 COMPARISON OF CLINICAL RESPONSE TO CHECKPOINT INHIBITORS IN ADVANCED NSCLC WITH HIGH PD-L1 EXPRESSION TESTED ON CYTOLOGY VERSUS BIOPSY SAMPLES

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Background: PD-L1 immunohistochemistry (IHC) expression correlates with clinical response to checkpoint inhibitors in advanced-stage NSCLC. PD-L1 IHC testing is usually performed on tissue blocks from core needle biopsy or surgical resection, but appears to be feasible on cytology cell blocks as well. In this retrospective study, we assessed the clinical response to checkpoint inhibitors in patients with NSCLC and high PDL1 IHC expression on cytology specimens in comparison with tissue biopsy specimens. **Method:** Between August 2015 and April 2018, 116 patients with NSCLC received immunotherapy at our institution. Only cases with known PD-L1 expression from IHC testing performed on small biopsies or cytology cell blocks were included. A total of 65 consecutive cases were reviewed, including 40 small biopsies and 25 cytology samples. A Tumor Proportion Score (TPS) was categorized as high (≥ 50% tumor cell staining) or low (<50%). Response to treatment was categorized as disease control (DC, including complete and partial response and stable disease) or progression (PD). The primary outcome was the rate of disease control. **Result:** Patients were mostly current or ex-smokers (91%), Caucasians (82%) and non-squamous carcinomas (85 %). High TPS

was seen in 44 (68%) cases. Immunotherapy was given in the first line setting in 20 (31%) patients, the second line in 36 (55%), and the third line in 9 (14%). 50 (77%) patients received Pembrolizumab, 10 (15%) Nivolumab and 5 (8%) others received immunotherapies on RCTs. Overall, there was DC in 40 (62%) patients and PD in 17 (26%). There was no significant difference in DC rate between the cytology and the small biopsy groups in high TPS group.

Table 1: Response to treatment according to the type of sample used to perform PD-L1 IHC

	Sample type	Response to Treatment		Total	P-value
		DC	PD		
Overall*	Small biopsy	28 (76%)	9 (24%)	37	0.22
N=57	Cytology cell block	12 (60%)	8 (40%)	20	
High TPS	Small biopsy	17 (68%)	8 (32%)	25	0.93
N=38	Cytology cell block	9 (69%)	4 (31%)	13	

* 8/65 patients who discontinued treatment or died prior to response evaluation were not included in this analysis

Conclusion: PD-L1 expression on cytology cell blocks and on small biopsies appears to have similar clinical significance. Further prospective trials are needed to confirm these findings.

Keywords: PD-L1 expression, advanced NSCLC, cytology

P1.04 IMMUNOONCOLOGY
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P1.04-17 TUMOUR BURDEN AS A PREDICTIVE TOOL OF RESPONSE TO IMMUNE CHECKPOINT INHIBITORS (ICI) IN PATIENTS WITH METASTATIC NON-SMALL-CELL LUNG CANCER

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Background: ICI are a novel class of agents that have revolutionized treatment for patients with metastatic non-small-cell lung cancer (NSCLC). Still, most patients do not benefit from PD-1 axis inhibitors, emphasizing the need for additional markers beyond PDL-1 expression for better selection of patients. **Method:** This retrospective, single centre study included all consecutive patients with advanced NSCLC who were evaluated with a FDG-PET scan prior to first administration of an ICI (nivolumab or pembrolizumab) between 1/2016 and 6/2017. Tumour burden was calculated using the total body Metabolic Tumour Volume (MTV) and the sum of all measurable lesions (SOML) with accordance to the RECIST criteria. This study received IRB approval. **Result:** A total of 58 patients with histologically proven NSCLC were included. Patients had a median age of 65 years (43-84), 59% were male, 62% had adenocarcinoma and 83% were previously treated with chemotherapy. The median PFS for the entire cohort was 5.7 (1-15.8) months, and the ORR for ICI was 44.8%. The median MTV was 12.95 (0-236) millimeter^3 and was significantly and inversely associated with longer PFS (p=0.036, 95%CI 1-1.015). The median SOML was 88 (13-305) centimetres, and was significantly and inversely associated with a longer PFS and higher ORR (PFS: P=0.004, 95% CI 1.002-1.011, ORR: OR 0.993 p=0.0067(. Additionally, patients with a SOML under 56 CM (first quartile) had a longer PFS compared to patients with a higher disease volume (Table1).

	SOML (CM)	Median PFS (months)	P value (compared to 1st quartile)
1st quartile	56	12.1	-
2nd quartile	88	5.1	0.017
3rd quartile	115	4.23	0.036
4th quartile	305	3.15	0.01

Table 1: some of measurable lesions (in centimeters) and PFS in metastatic NSCLC pateints recieving ICI **Conclusion:** In our study, a high tumour burden in patients with advanced NSCLC treated with ICI was associated with a shorter PFS and a lower ORR. This association warrants further prospective evaluation in order to optimize treatment.

Keywords: tumor burden, Immunotherapy, Immune checkpoint inhibitors

P1.04 IMMUNOONCOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.04-18 PD-L1 EXPRESSION AND ITS CORRELATION WITH TUMOR TNM STAGE IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Immunotherapy has now become a standard therapy of lung cancer treatment. Programmed death ligand (PD-L) 1 expression has provided a predictive biomarker for anti-PD-1/PD-L1 therapy. However, the relationship between the expression of PD-L1 and the clinical and pathologic features were still unclear. The purpose of this study was to investigate the clinical factors affecting the expression of PD-L1 and the concordance of the DAKO assay with the Ventana assay. **Method:** We evaluated in 178 non-small-cell lung cancer patients and assessed PD-L1 expression by immunohistochemistry after staining them with antibody 22C3 (Dako) or SP263 (Ventana). Clinical features were acquired from the electrical medical records, retrospectively. We analyzed the relationship between PD-L1 expression and clinicopathological characteristics. **Result:** One hundred fifty four patients were available for analysis. There were 130 cases which both tests were performed. Mean age was 66.7 years-old. Male patients were 70%, and adenocarcinoma was 68%. Stages were stage I 15.6%, II 7.1%, III 28.6%, and IV 48.7% respectively. In using the 22C3 antibody, PD-L1 expression in Tumor proportion score (TPS) ≥ 50% was 27.7%, and 52.3% in TPS ≥ 1%. PD-L1 expression rate in man was higher than woman (37,6 % vs 16,7%, P=0.028). In the sp263 antibody, PD-L1 expression rate (TPS ≥10%) was 52.9%, and 68.8% in TPS ≥ 1%. Age, primary tumor, regional lymph node, distant metastasis and stage grouping were not statistical different between patients with and without PD-L1 expression. All patients (n=36) with TPS ≥ 50% in the 22c3 test were found to have TPS ≥ 10% in the sp263 test. **Conclusion:** There were no specific predictable factor in PD-L1 expression except male factor. But, we suggest that further study will be needed by adding other factors and more patients.

Keywords: PD-L1 expression, non-small cell lung cancer, TNM stage

P1.04 IMMUNOONCOLOGY
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P1.04-19 NEUTROPHIL-TO-LYMPHOCYTE AND PLATELET-TO-LYMPHOCYTE RATIOS PREDICT SURVIVAL AFTER IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER

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Background: Effective use of immune checkpoint inhibitors in non-small cell lung cancer (NSCLC) may be improved by identifying biomarkers that are easily measured and predictive of clinical outcomes. Peripheral complete blood counts are commonly obtained and can be indicative of systemic inflammatory response, which has been associated with poor prognosis in multiple cancer types. Here, we investigated the ability of peripheral cell counts to predict patient survival after treatment with immunotherapy for NSCLC. **Method:** Complete blood counts were retrospectively collected for 274 patients and analyzed for absolute neutrophil count (ANC), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR). Values were obtained immediately prior to treatment initiation. Overall survival (OS) and progression-free survival (PFS) was assessed using Kaplan-Meier analyses with log-rank test and Cox regression analysis. **Result:** OS was significantly associated with ANC (HR 1.63, p<0.0001) and NLR>5 (HR 1.62, p<0.0001), as was PFS (HR 1.48, p=0.0008 and HR 1.48, p=0.0012, respectively). PLR>400 was not associated with OS but did have a significant association with PFS (HR 1.39, p=0.0388). Baseline elevation of both NLR and PLR identified a particularly high-risk population, with worse OS (HR 1.69, p=0.0020) and PFS (HR 1.58, p=0.0069) when compared to the patient group with low baseline NLR and PLR (Figure 1). High NLR and PLR as a combined marker remained an independent predictor of OS in multivariate analysis after adjusting for multiple clinical variables (HR 1.91, p=0.008).

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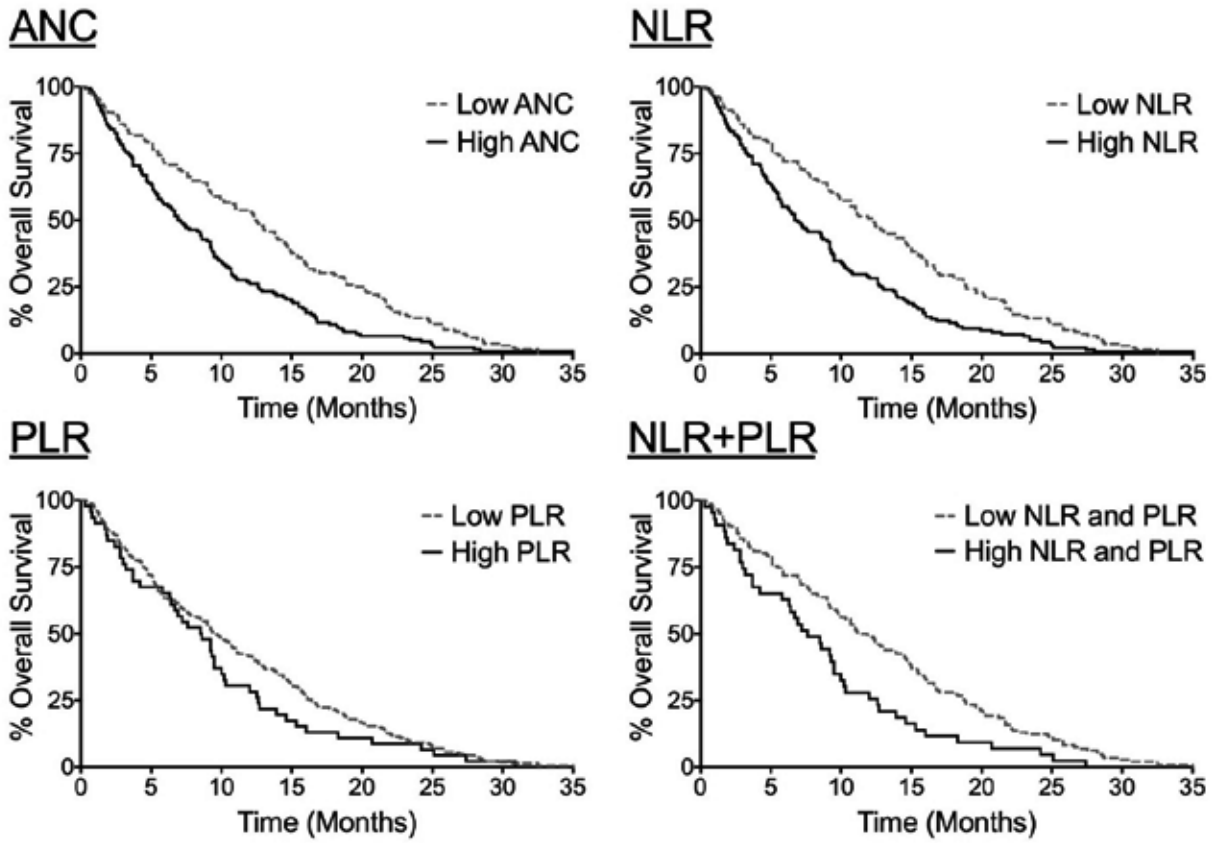

Conclusion: Increased baseline ANC, NLR, and PLR were associated with worse overall and progression-free survival, and the combination of both high NLR and PLR denoted a subgroup with especially poor outcomes. These findings will need to be validated in larger prospective studies to further assess their clinical utility.

Keywords: Immunotherapy, ANC, platelet

P1.04 IMMUNOONCOLOGY
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P1.04-20 COMPUTATIONAL BIOLOGICAL MODEL PREDICTION OF PD-L1 EXPRESSION AND IMMUNOTHERAPY RESPONSE FOR KRAS MUTATED LUNG CANCER BASED ON CO-MUTATIONS

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Background: Emerging data suggest that *KRAS* mutated non-small cell lung cancer (NSCLC) is a heterogeneous disease based on the presence of co-mutations. These co-mutations may impact PD-L1 expression, a predictive biomarker for PD-1/PD-L1 immunotherapy, and may result in differential responses to immunotherapy. **Method:** Genomic information of NSCLC patients, including 2888 from publically available datasets and 86 from Stanford University, was input into computational biological model (CBM) software (Cellworks Group, San Jose, CA). Customized computational protein network maps of disease characteristics were generated for each patient. CBM was used to predict PD-L1 protein expression and also response to PD-1/PD-L1 immunotherapy in *KRAS* co-mutation subsets using 3 key metrics: PD-L1 expression; Dendritic Cell Infiltration Index (9 chemokine markers); and Immunosuppressive Biomarker Expression (14 markers). **Result:** The major co-mutations observed with the *KRAS* mutation were in tumor suppressor genes (*TP53, STK11, CDKN2A, KEAP1*) and a downstream effector (*PIK3CA*). Using the CBM approach, *KRAS* mutated NSCLC tumors with *TP53* co-mutations had the highest prevalence of PD-L1 protein expression whereas tumors with *KRAS/KEAP1* and *KRAS/STK11/KEAP1* co-mutations were associated with the lowest expression. Expression of PD-L1 in tumors with *KRAS/STK11, KRAS/CDKN2A, KRAS/PIK3CA* co-mutations, and *KRAS* without co-mutations was higher than in tumors with *KRAS/STK11/KEAP1* and *KRAS/KEAP1* co-mutations. Of the 30 NSCLC tumors in the Stanford dataset with available PD-L1 immunohistochemistry results, including 19 with *KRAS/TP53* and 11 with *KRAS/KEAP1* or *KRAS/STK11/KEAP1*, CBM accurately predicted PD-L1 expression in these two groups at rates of 79% and 72%, respectively. In regards to prediction of response to PD-1/PD-L1 immunotherapy, CBM predicted the majority of patients with *KRAS/KEAP1* and *KRAS/STK11/KEAP1* to be non-responders, whereas CBM predicted the majority of patients with *KRAS/TP53, KRAS/PI3KCA*, and *KRAS* without co-mutations to be responders. The proposed mechanism for *KRAS* co-mutations' impact on PD-L1 expression from the CBM model integrates differential activation of (i) downstream pathways of *KRAS* (PI3K/AKT, RAF/ERK, and RAL) and (ii) transcription factors involved in PD-L1 expression (i.e., MYC, HIF1α, NFKβ, AP1, and STAT1/3). **Conclusion:** *KRAS* mutated NSCLC is emerging as a diverse disease based on co-mutations. The CBM approach demonstrates that PD-L1 expression varies among *KRAS* co-mutation subtypes along with likelihood of response to PD-1/PD-L1 immunotherapy. CBM provides proposed mechanisms underlying these differences and therefore, provides further rationale to examine more precise delivery of immunotherapy.

Keywords: KRAS, co-mutation, Immunotherapy

P1.04-21 THE UTILITY OF PD-L1/CD8 DUAL IMMUNOHISTOCHEMISTRY FOR PREDICTION OF RESPONSE TO IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: PD-L1 immunohistochemistry (IHC) is an important predictive biomarker for PD-(L)1 blockade in advanced non-small cell lung cancer (NSCLC); however, this assay is imperfect. The presence of CD8+ tumor infiltrating lymphocytes (TILs) may be a complimentary biomarker for response to immunotherapy. Thus, we examined the performance of PD-L1/CD8 dual IHC (dIHC) in two cohorts of NSCLC patients receiving immunotherapy. **Method:** Patients were identified through retrospective review of medical oncology and pathology databases. The first cohort predominantly received nivolumab as a 2nd or later line treatment; tissue samples were mainly obtained at initial diagnosis. The second cohort received pembrolizumab as a first line therapy, and tissue samples were procured immediately before the initiation of immunotherapy. PD-L1/CD8 dIHC was performed on those tissue samples. Percentage of tumor cells with membranous PD-L1 expression and CD8+ stromal cells were measured, and CD8+ TILs were semi-quantitatively evaluated. The quantities of CD8+ T cells were dichotomized with appropriate cut-offs. **Result:** Eighty-four patients were identified, including 60 in the Nivolumab cohort (NC) and 24 in the Pembrolizumab cohort (PC). In the NC, PD-L1 expression ≥1% was marginally associated with improved progression-free survival (PFS, p=0.09), and an increased rate of response (p=0.08). CD8+ TILs and stromal cells did not correlate with outcome. However, a subset of PD-L1-positive patients who showed abundant CD8+ TILs and stromal cells had significantly reduced PFS (p=0.04). In the PC cohort, all cases chosen exhibited PD-L1 expression in ≥50% of tumor cells. Increased CD8+ TILs were correlated with improved PFS, (p=0.0194), and an increase in both CD8+ TILs and stromal cells was also associated with improved PFS (p= 0.0238). **Conclusion:** Although limited by small sample size, this study suggests that PD-L1/CD8 dIHC improves the prediction of response to the PD-1/PD-L1 blockade in advanced NSCLC patients when it is performed on tissue samples obtained immediately before the initiation of the blockade as first-line therapy . However, for the 2nd or later line of treatment, dIHC on archival tissue samples obtained before initial therapy provides a useful but less clear picture of the tumor immune microenvironment. Reduced PFS seen in patients with PD-L1 expression and abundant CD8+ TILs and stromal cells may be due to T-cell exhaustion after the chemotherapy before the PD-1/PD-L1 blockade. These findings suggest that PD-L1/CD8 dIHC may be useful for treatment response stratification in advanced lung cancer patients.

Keywords: Immunotherapy, Programmed cell death ligand 1, Tumor infiltrating lymphocytes

P1.04-22 CD73 IMMUNOHISTOCHEMICAL EXPRESSION IN MALIGNANT CELLS AND CORRELATION WITH IMMUNE INFILTRATE IN NON-SMALL CELL LUNG CARCINOMA (NSCLC).

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Background: CD73 is potential novel target for lung cancer immunotherapy involved in the adenosine pathway that induces tumor microenvironment immunosuppression. We investigated the immunohistochemical (IHC) expression of CD73 in a large cohort of NSCLC and correlated with tumor's clinical, pathological, molecular and immune cells infiltration data. **Method:** We examined 175 surgically resected stages I-III formalin-fixed and paraffin-embedded NSCLC tumors tissue microarrays, including 107 adenocarcinomas (ADC) and 68 squamous cell carcinomas (SqCC). For IHC, we used the anti-CD73 antibody (clone D7F9A, Cell Signaling Technology) and evaluated membrane (basolateral and luminal) expression in malignant cells. In a subset of cases, CD73 IHC expression was correlated with data available on: a) *CD73* gene mRNA expression (Illumina arrays; n=91); b) *EGFR* and *KRAS* mutation status and mutational load (whole exome sequencing; n=104); and, c) density of tumor associated immune cells infiltration (CD3, CD4, CD8, CD68, CD45RO, CD57, FOXP3, and granzyme B) and immune checkpoints expression (PD-L1, PD-1, ICOS, TIM-3, IDO-1, B7-H3, B7-H4, VISTA and OX40) assessed by IHC and image analysis (n=172). **Result:** ADC showed higher CD73 IHC expression than SqCC (P<0.0001). Pathological stage I ADCs showed higher CD73 expression than higher tumor stages (P=0.0419). Using any level of CD73 expression (>1%) CD73 was expressed in 73% and 40% of ADCs and SqCs, respectively. High expression (>50% of malignant cells) was detected in 35% of ADCs and 20% of SqCC. No other significant correlations with clinical-pathological variables, including patients' outcome were found. Interestingly, ADCs with *EGFR* (P=0.04) and *KRAS* (P=0.02) mutation expressed higher CD73 levels than wild-type tumors. In ADC, CD73 IHC expression correlated significantly with the density of immune T CD3+, CD4+, CD8+, CD45RO+ and FOXP3+ cells, as well as macrophages CD68+ cells in tumors (r values range: 0.22-0.45; P values range: 0.001-0.02). Overall, we did not find significant correlations between CD73 immunostaining and the IHC expression of the immune checkpoints examined. CD73 IHC expression correlated positively with mRNA *CD73* gene expression levels in all NSCLCs (r=0.6; P<0.0001), ADCs (r=0.6; P<0.0001), and SqCCs (r=0.49, P<0.0001) histology **Conclusion:** We identified that CD73 protein expresses in a subset of resected NSCLCs, being significantly higher in adenocarcinoma histology. In this histology type, CD73 correlates with immune T cells and macrophages infiltration, and notably, with tumor's *EGFR* and *KRAS* mutation. Our data suggest that CD73 is a potential target for NSCLC, particularly for adenocarcinoma histology (Supported by grants CPRIT RP160668 and UT Lung SPORE).

Keywords: CD73, EGFR and KRAS mutation status, Non-small cell lung carcinoma

P1.04-23 EXPRESSION OF EMERGING IMMUNOTHERAPY TARGETS IN EARLY-STAGE SQUAMOUS LUNG CARCINOMA

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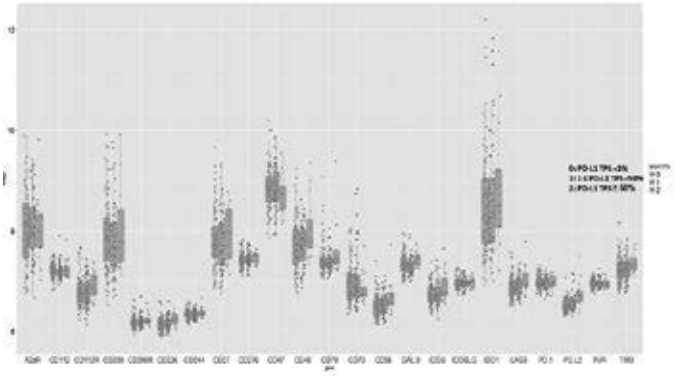
Background: Anti-PD1/PD-L1 immunotherapy has demonstrated response in approximately 20% of unselected advanced non-small cell lung cancer (NSCLC) patients. Strategies involving combination immunotherapies are under investigation to improve the overall response to immunotherapy. The objective of this study was to identify the expression of emerging immune targets in a cohort of early-stage squamous lung carcinoma (SqLC), which may be used to design combinatorial immunotherapy approaches. **Method:** 202 early stage (I-II) SqLC resected patient tumors and corresponding clinical data were collected from 6 cancer centers as part of the SPECS II program. Fourteen emerging immune targets or targeted axis were selected based on their advanced stage of development in preclinical/clinical studies. The mRNA expression level of these targets and PD-1/PD-L1 were determined by Affymetrix U133A gene expression profiling. The correlations among these targets and the overall survival were evaluated. **Result:** The mRNA levels of the immune molecules which were grouped on PD-L1 protein expression in early stage SqLC are shown in Figure 1. No correlation was

found between the mRNA level of PD-L1 and the other immune targets expressed on APC/tumor cells, except PD-L2 (r2= 0.41, p<0.00001). We found that the immune cell receptor, CD226, correlated with CD96 and CD112R respectively (r2= 0.514, p<0.00001; r2= 0.476, p<0.00001), and CD96 correlated with CD112R (r2= 0.644, p<0.00001) as well. In addition, higher expression of GAL-9, CD48 and ICOS were associated with better prognosis [p= 0.0358, HR=0.249 (0.068, 0.912); p= 0.0309, HR=1.61 (1.04, 2.49); p= 0.0429, HR=2.47 (1.03, 5.93)].



Conclusion: Several emerging immune targets were expressed at higher levels than PD-L1 in this early stage SqLC cohort. The mRNA levels of all immune targets evaluated were independent of PD-L1 expression, except PD-L2. The expression of GAL-9, CD48 and ICOS were identified as prognostic. These results may provide important information in the design of future combination immunotherapies for early-stage SqLC.

Keywords: emerging immunotherapy targets, early stage squamous lung carcinoma

P1.04 IMMUNOONCOLOGY
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P1.04-24 DIGITAL CORE NEEDLE-BIOPSY TO ASSESS PD-L1 EXPRESSION IN NON-SMALL CELL LUNG CANCER: OPTIMAL SAMPLING AND NEED FOR RE-BIOPSY

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Background: Assessing expression of PD-L1 on tumour cell membranes by immunochemistry is an important complementary or crucial companion diagnostic test to guide the use of immune modulating checkpoint inhibitors in the treatment of non-small cell lung cancer (NSCLC). Unfortunately, the known temporal and spatial heterogeneity of PD-L1 expression raises the important question of how to ensure that the small biopsy specimens with which this assessment is usually made are adequately representative of PD-L1 expression by the whole tumour. **Method:** Expression of PD-L1 was assessed in sections of 94 tissue blocks from 50 primary pulmonary adenocarcinomas using the Ventana SP263 antibody and a validated protocol. Scoring was performed by two appropriately-trained pathologists with extensive experience in its interpretation. After conventional assessment, slides were digitally scanned and divided into squares of 1mm^2 area to form a digital database (mean of 150 data-points per tumour), which were assigned co-ordinates and re-scored. By these means, multiple, "digital core biopsies" (DCBx) approximating a 17 gauge needle were simulated in sequential fashion, and expression in these was compared to that in the whole tumour and categorised by current UK prescribing guidelines* **Result:**

PD-L1 score (%)	Total number of cases	Cases where PD-L1% from single DCBx changed scoring category vs whole tumour*	Cases where PD-L1% from two DCBx changed scoring category vs whole tumour*	Cases where PD-L1% from three DCBx changed scoring category vs whole tumour*	Cases where PD-L1% from four DCBx changed scoring category vs whole tumour*	Cases where PD-L1% from five DCBx changed scoring category vs whole tumour*	Focal expression primary pattern in non-correlative cases
<1	14	2	2	2	2	2	Y
1-10	13	6	3	1	1	0	Y
11-49	10	1	1	0	0	0	Y
50-100	13	0	0	0	0	0	n/a
All	50	9 (18%)	6 (12%)	3 (6%)	3 (6%)	2 (4%)	

PD-L1, programmed death ligand 1; DCBx, Digital Core Biopsy *Based on pembrolizumab categories as: 1st line ≥50%, 2nd line 1-49%; nivolumab categories as: ≥1% (for adenocarcinoma)

Conclusion: In the majority of cases, three digital core biopsies achieved closest correlation with the whole tumour, with little greater accuracy achieved by assessing four cores or more. Correlation was weakest when expression was low and very focal, an important consideration in view of the importance of the '1% cut-off' used commonly to guide immune checkpoint therapy. Using this model as a guide, a single good quality biopsy (2x10mm^2 area) is sufficient for most tumours scoring 11% or greater PD-L1 expression. However, in the lower range of expression, re-biopsy might be routinely considered if there is doubt about specimen adequacy.

Keywords: Digital Pathology, PD-L1, Core-Biopsy

P1.04-25 THE IMPLICATION OF FRAMESHIFT MUTATION BURDEN IN NEOANTIGEN AND IMMUNE CELL LANDSCAPE IN NON-SMALL CELL LUNG CANCER (NSCLC)

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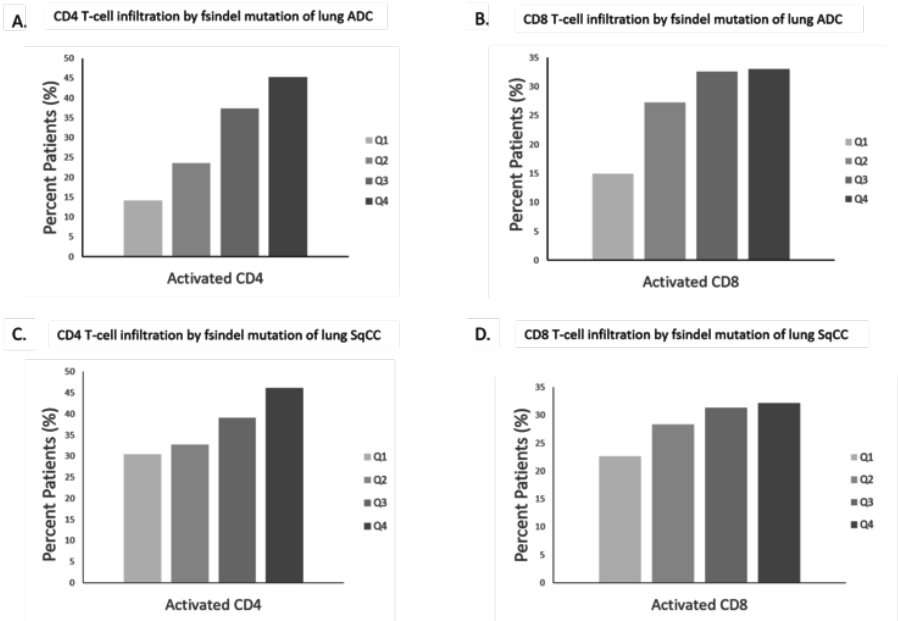
Background: Recent research has shown an association between enrichment of insertion and deletion (indel) mutations and tumor-specific neoantigens, which in turn correlated with T-cell activation in renal cell carcinomas. Furthermore, frameshift indel (fsindel) mutation counts were significantly associated with clinical response to immune checkpoint inhibitors (ICIs) in melanoma patients. However, little is currently known about such associations in NSCLC. **Method:** Neoantigen counts were based on CloudNeo, a cloud pipeline used for identifying patient-specific neoantigens. The immune cell signatures of 31 distinct immune cell types of samples were derived from RNA-sequencing of 812 immune metagenes obtained from The Cancer Genome Atlas. 511 lung adenocarcinoma (ADC) and 471 squamous cell carcinoma (SqCC) patient samples were divided into 4 quartiles (Q1-Q4) according to number of fsindel mutations in order to compare neoantigen counts and immune cell infiltration. Fsindel mutations were identified from mutation annotations generated by the Genomic Data Commons' MuTect2 somatic variation calling workflow. **Result:** The range of fsindel count of ADC and SqCC were 0-139 and 0-150, respectively, while the median fsindel count was 7 and 8, respectively. Neoantigen count showed a significant positive association with fsindel in both ADC and SqCC ($p<0.0001$, $p<0.01$ respectively). Furthermore, a higher number of fsindels was associated with significantly increased activated CD4 and CD8 T-cell infiltration in ADC (Figure 1. $p<0.001$, $p<0.01$, respectively), while a similar trend was observed in SqCC for CD4 and CD8 T-cells, although not significant (Figure 1. $p=0.056$, $p=0.341$, respectively).

Figure 1. Activated CD4 and CD8 T-cell infiltration of lung adenocarcinoma and squamous cell carcinoma according to fisindel mutation count



Conclusion: We report for the first time the association between fsindels and higher neoantigen burden and infiltration of activated CD4 and CD8 T-cells in human NSCLC. As the presence of immune cells has been shown to be an important factor in determining response to ICIs, our findings suggest that fsindels could potentially be used as a predictive marker for immunotherapy.

Keywords: predictive marker, non-small cell lung cancer, Immunotherapy

P1.04-26 PROSPECTIVE IMMUNO-BIOBANK IN NSCLC

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Background: Immune system could recognize tumor cells and eliminate them. T lymphocytes play an essential role in recognizing and lysing tumor cells. However, the humoral response (antibodies) seems also important. Recently, therapeutically progresses have been obtained with monoclonal antibodies that target inhibitory molecules expressed by T lymphocytes (anti-CTLA4, anti-PD1). Those antibodies induce reactivation or improvement of T lymphocytes' lysing capacities. This clinical benefit can last for years and has been observed in several types of tumors. This is the beginning of a therapeutic revolution and hundreds of clinical trials are on-going with the objective of better exploitation of this strategy. Several steps are needed in order to increase the proportion of patients who benefit from immunotherapies.We currently do not understand completly the reason why an immune response could be efficient or not (spontaneously or after treatment), the respective role and interactions between humoral and cellular responses and mechanisms involved in the development of side effects observed in patients **Method:** All NSCLC patients who are candidate for Immunotherapy treatment regardless of staging and line of treatment cancer will be identified within our oncology department Blood sampling will be performed (50 to 100 ml) at severals time points: before any immunotherapy and repeated every 3 months or, in case of side effects or in case of extra-ordinary evolution. We will investigate cellular (T lymphocytes) and humoral (B lymphocytes) immune responses. We will also do a sequencing of the tumor in order to investigate genetic alterations. We will question the correlations between immune response and tumor pathological and molecular characteristic's, as well as the impact of therapies administered to the patients on their immune response. **Result:** We have recruited 12 patients so far, on treatment with immune check point inhibitor. We are going to perform another sampling 3 months after the beginning of the treatment (9 patients at the present time) Currently, we are continuing to reclute patients. The first analysis will be performed once we have 50 patients within the study and presented and the incoming meeting in November 2018

Conclusion: This is, as far as we know, the first prospectiveand ongoing immune- bio-bank in NSCLC patients that is going to provide valuable information to better understand the immunological changing at serological, tissue and genomic level induced by the immunotherapy in NSCLC and the possible mechanism of resistance or progression.

Keywords: biobank, immunotherapies, Immunomodulation

P1.04 IMMUNOONCOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.04-27 SAFETY OF IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC) IN THE REAL-LIFE SETTING: A SINGLE-INSTITUTION EXPERIENCE FROM ARGENTINA.

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Background: Immunotherapy (IO) targeting programmed death-1 receptor (PD-1) has become standard of care in NSCLC treatment. Therefore, many patients will be at risk of developing toxicities from these treatments, representing a new challenge in daily clinical practice. We assessed its safety and activity in advanced NSCLC patients in the real-life setting. **Method:** We conducted a retrospective analysis of patients with NSCLC treated with immunotherapy at a single institution between January 2016 and January 2018. Safety and efficacy analyses were made by treating physician according to CTCEAE 4.0 and RECIST 1.1 respectively and retrospectively collected from medical records. Kaplan-Meier method was used to estimate progression-free survival (PFS) and overall survival (OS). **Result:** Twenty-seven patients were included. Median age was 66 years [range 45 - 79], 67% were male, 89% (n=24) had ECOG performance status (PS) of 0-1; all patients had advanced disease, with up to 2 metastatic sites in 52% (n=14) of the cases; 45% (n=12) had been tested and were positive for PDL-1 (≥ 1%). Almost all patients received immunotherapy as first or second-line treatment (n= 23, 85%). A median of 6 cycles [range 1 – 34] had been administered, with 60% exposed to nivolumab (n=16) and 40% (n=11) to pembrolizumab. Median follow-up since IO was 18 months [range 0.5 - 25.2]. Seven patients achieved partial response and eight had stable disease, giving an overall response rate of 26% and a 56% disease control rate; 44% presented progressive disease. Median PFS was 5.1 months [95%CI 2 – 8.1] and median OS was 19.3 months [95%CI 2.3 – 36.3]. A total of 10 patients (37%) developed high grade toxicity. The most common grade 3-4 related events were asthenia (n=5), adrenal insufficiency (n=2), infection (n=2), hypothyroidism (n=1), hepatitis (n=1), renal insufficiency (n=1) and thrombocytopenia (n=1) among others. Seven patients should discontinue treatment, 5 of them received glucocorticoids and almost all of them had full recovered after corticoid treatment (n=5). **Conclusion:** Activity of immunotherapy was comparable to that reported in previous studies. However, high grade toxicity rates in our practice were much higher than those reported in clinical trials, despite the highly similar proportion of patients with good performance status in both settings. Although studies populations are highly selected, this finding must lead us to question our ability in early recognition and prompt management of adverse events in daily practice.

Keywords: NSCLC, immunotherapy, toxicity

P1.04 IMMUNOONCOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.04-28 BASELINE MARKERS OF INFLAMMATION AND OUTCOME WITH NIVOLUMAB IN PRETREATED NON SMALL CELL LUNG CANCERS: A RETROSPECTIVE STUDY.

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Background: Nivolumab is a novel therapeutic option in pre-treated Non Small Cell Lung Cancer(NSCLC), independently of tumor histology and PD-L1 status. However, predictive biomarkers are lacking. We aimed to evaluate whether there is a correlation between some baseline markers of inflammation and the outcome of patients (pts) treated with Nivolumab. **Method:** All consecutive NSCLC pts treated with Nivolumab between Aug. 2015-Dec. 2017 at our Institution were analyzed. Baseline characteristics were collected and correlated with the outcome. Derived neutrophil-to-lymphocyte (dNLR) ratio was calculated as: neutrophil count/white blood count – neutrophil count. Platelet-to-lymphocyte (PLR) ratio was defined as platelet count/lymphocyte count. Overall survival (OS) was defined as time from Nivolumab start to death and Progression Free Survival (PFS) as time from Nivolumab start to progression disease or death for any cause. OS and PFS survival were estimated using the Kaplan–Meier method. Survival curves were compared using the log-rank test. **Result:** We included 45 consecutive NSCLC pts treated with Nivolumab. Baseline characteristics were as follows: median age 69 years (range 46-78), sex male 78%, female 12%, squamous histology in 51% and non-squamous in 49%. After a median follow-up of 16 months (mos), median PFS was 4.0 mos (CI 95%, 2-8) and median OS was 9.0 mos (CI 95%, 4-15). High neutrophil count (≥7500/mmc) and high lymphocyte count (≥1000/mmc) were associated with a shorter PFS (p=0.05 and p=0.01, respectively) and OS (p=0.373 and p<0.001, respectively), as well as low albumin levels (<3 g/dl) (p=0.05 for both PFS and OS). Moreover, a high dNLR (≥3), high PLR (≥160) and high LDH levels (> Upper Limit Normal) correlated with a numerically longer PFS and OS, although these differences were not statistically significant. **Conclusion:** Baseline markers of inflammation correlate with inferior outcome with Nivolumab in unselected, pretreated, NSCLCs. The relative easy estimation of these parameters may be used with other predictive biomarkers in the treatment selection of pts candidate for immunotherapy.

Keywords: PLR, dNLR, Nivolumab

P1.04 IMMUNOONCOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.04-29 SECOND OR THIRD LINE NIVOLUMAB VERSUS FIRST LINE NIVOLUMAB IN PATIENTS WITH PREVIOUSLY TREATED ADVANCED NON SMALL CELL LUNG CANCER (NSCLC)

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Background: The aim of the study was to report outcomes in advanced NSCLS patients treated with Nivolumab after progression to one versus two or three lines of chemotherapy from our everyday clinical practice. Exploratory assessments include the progression-free survival (PFS) and overall survival (OS) , the rates of chemotherapy retreatment after Nivolumab progression and toxicity profile. **Method:** Elegibility criteria included, histologically or citologically confirmed stage IV NSCLC without EGFR mutated or ALK traslocated genes treated with Nivolumab when relapsed after 1 versus 2 or 3 prior lines of chemotherapy from January of 2016 to current date. **Result:** From January of 2016 to January of 2018 , a total of 61 patients were enrolled in the study from our Hospital. The patients demographics were: median age 63 years, 4,9% (n=3) female and 95% (n=58) male. There were 59% (n=36) non squamous-cell and 41% (n=25) squamous-cell carcinoma. 96% (n=59) have received platinum-based therapy previously to Nivolumab : 57% (n=34) combined with Premetrexed and 41% (n=25) with other drugs. 60.7% % (n=37) received Nivolumab at second line and 39.3% (n=24) at 3 or more line . 45,9 % (n=28) received chemotherapy after Nivolumab. .These chemotherapy schemes icludes Bevacizumab in 40% of cases Grade 1-2 treatment related adverse events (AEs) occurred in 32% patients and the most common ones were endocrine 16% (n=7) and neumonitis 4% (n=2) but there were one case isolated of grade 3-4 encephalitis, nephritis and hypophysitis The 4% (n=29 patients need to be admitted to the hospital due Nivolumab toxicity versus 16% due to chemotherapy toxicity. The median of PFS with Nivolumab was 3 months for both groups IC 95% (2,09-3.9) and median OS for second line Nivolumab was 6 months IC 95% (2,7-9,2) and for Nivolumab at 3rd and sucesive lines of 9 months IC 95% (3,7-14,2) Median PFS for chemotherapy after Nivolumab was 5,3 months (2-12 months) Median OS was 18 months for second line Nivolumab and 26 months for the other patients and OS for all populaion was 21 months IC 95% (15.2 y 26.7) **Conclusion:** Data suggests that Nivolumab is effective and well tolerated in no selected metastatic NSCLC enabling survival of 21 months for these patients with an aceptable toxicity profile .Chemotherapy and antiangiogenic based treatments after Nivolumab are effective and well tolerated. This support benefit in heavily chemotherapy pretrated patients: a crucial question that we can not ignore.

Keywords: chemotherapy, NSCLC,immunotherapy

P1.04 IMMUNOONCOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.04-30 A POTENTIAL EFFECT OF DIABETES MELLITUS AND METFORMIN USE ON EFFICACY OF IMMUNE CHECKPOINT INHIBITORS (ICI)

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Background: Numerous studies have demonstrated metformin use is associated with decreased cancer risk in the general population, as well as improved overall response rate (ORR), progression free survival (PFS) and overall survival (OS) in cancer patients undergoing chemotherapy.

Recent in-vitro studies found several new mechanisms which granted metformin the potential to increase cancer patients' response to immune checkpoint inhibitors (ICI).

In this study we aim to explore the correlation between the daily use of metformin and benefit from ICI in patients with lung cancer and other solid malignancies. **Method:** We retrospectively evaluated all consecutive patients with metastatic solid malignancies treated with ICI therapy in a single institution between February 2015 and June 2017. Patients' clinical data was obtained from electronic medical records. Cox proportional hazards model and chi squared test were used to determine the associations between metformin use and ORR, median PFS (mPFS) and median OS. **Result:** Of 218 patients included in the analysis (202 NSCLC, 16 non lung cancers), 49 (22.5%) suffered from type 2 diabetes mellitus (T2DM). Of them 33 (15.1%) were treated with metformin and 16 (7.3%) received other, non-metformin therapy for T2DM. Comparison between non-diabetic and diabetic cancer patient groups demonstrated that mPFS was found to be significantly higher in the non-diabetic patients – 6.0 vs. 4.0 months (HR=1.47 [1.03-2.09], p=0.036). ORR was comparable (35.5% vs. 30.6%, p=0.52).

In the T2DM subgroup - mPFS and HR suggested increased efficacy in the metformin group compared to non-metformin, but the numbers were too small to reach significance 8.0 vs. 3.2 months (HR=0.63 [0.32-1.23], p=0.17). ORR was also numerically higher (36.4% vs. 18.8%, p=0.21).

In both comparisons, no significant differences were found in OS. **Conclusion:** This data suggests T2DM might be associated with decreased efficacy of ICI. While several studies demonstrated that diabetic cancer patients receiving chemotherapy gained much benefit with metformin use, the trend we observed regarding metformin use with ICI therapy was milder and should be further explored in larger prospective cohorts.

Keywords: metformin, Immunotherapy, Diabetes

P1.04 IMMUNOONCOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.04-31 EFFICACY AND TOLERANCE OF IMMUNE-CHECKPOINT INHIBITORS IN EGFR, ALK/ROS 1 NON-SMALL-CELL-LUNG-CANCER (NSCLC): GFPC 03-2016 IMAD STUDY

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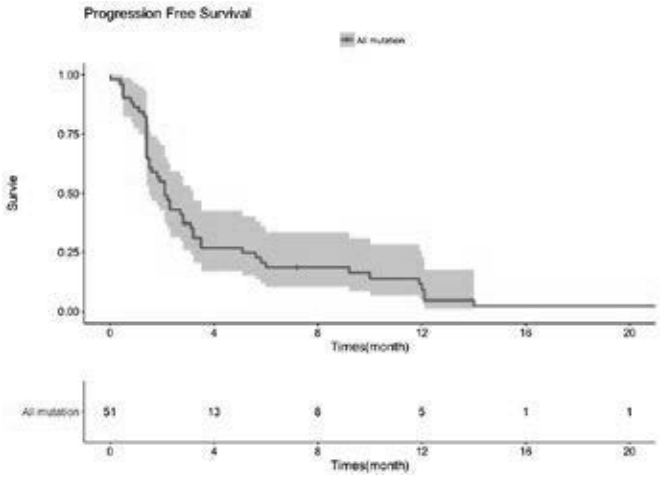
Background: Patients with molecular alterations are considered to be poor candidates for immune- checkpoint inhibitors (ICI) on the second-line phase III trials. Here, we analyze the efficacy of ICI in EGFR /ALK/ROS1 NSCLC patients in real world setting **Method:** This retrospective, multicentric study in EGFR, ALK and ROS1 NSCLC treated by ICI, analyzed clinical characteristics and outcomes (progression free survival (PFS), duration of ICI treatment and overall survival (OS), since initiation of ICI . **Result:** 51 patients were included from 20 centers in France: 100% adenocarcinoma, 60.7% never smokers, 58.8% female, 58 ± 8.8 years age at diagnosis (36-83), 82.3% EGFR mutated, 15.7 % and 2% ALK and ROS 1 translocated respectively. ICI was a third line treatment in 35,3% of cases, a fourth and more lines treatment in 64,7% of cases. Median PFS was 2.1. [95% CI: 1.5-3.2] months for the whole population, 2.15 [95% CI: 1.4-3;2], for EGFR patients and 2.4 [95% CI: 2.1; NR] for ALK tranlocated patients; 3 months-PFS were 37,3% [95% CI: 26.1; 53.2]; 8 weeks ORR were 19.6% (10 pts with partial response). The median OS for the whole population was 14.7.[95%CI: 12.1-19.2] months, 13.9 [95% CI: 8.8-20] for EGFR patients, 19.2. [95% CI: 13.1-NR] for ALK translocated; 7 (13.7%) patients were treated more than 9 months by ICI; 21.6% (11/51) of patients reported toxicities, all < grade3.



Conclusion: In this real-world setting analysis, efficacy of ICI in EGFR, ALK, ROS1 NSCLC patients appears close to the efficacy observed in pretreated unselected NSCLC patients. Large prospective studies are needed in these populations

Keywords: immune-checkpoint inhibitors, Non-Small-Cell-Lung-Cancer, molecular alterations

P1.04 IMMUNOONCOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.04-32 PHASE I/II STUDY OF THE A2AR ANTAGONIST NIR178 (PBF-509), AN ORAL IMMUNOTHERAPY, IN PATIENTS (PTS) WITH ADVANCED NSCLC

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Background: ATP is catabolized to adenosine in the tumor microenvironment, leading to excess adenosine and immunosuppressive effects via immune checkpoint protein adenosine 2A receptor (A2AR). NIR178 is an oral A2AR antagonist that selectively binds and inhibits A2AR, reactivating T cell-mediated antitumor immune response. This Phase I/II study evaluated NIR178 in previously treated pts with advanced NSCLC (NCT02403193). **Method:** Pts (ECOG PS 0—1) had received ≥1 prior line of therapy; EGFR/ALK pts had failed prior TKI therapy. Objectives: primary – determine MTD of single-agent NIR178; secondary – efficacy endpoints, PK, and evaluation of PD-L1 expression. **Result:** At 13 Dec 2017 data cut-off, 24 pts had been treated: median age 68 yrs, 46% male; 79% received prior immunotherapy; 22/24 (92%) pts had discontinued (due to progression [n=13], death [n=2], AEs [n=2] or other reasons [n=5]) and 2/24 (8%) pts remained on treatment. Dose levels evaluated: 80 (n=3), 160 (n=3), 320 (n=7), 480 (n=6), 640 mg BID (n=5). There was 1 DLT: Gr 3 nausea (640 mg). The most frequent (≥20%) any-Gr AEs regardless of causality were nausea (67%), fatigue (63%), dyspnea (46%), vomiting (33%), chest pain and other (29%), gastroesophageal reflux disease, anemia, diarrhea (all 25%), anorexia, back pain, generalized muscle weakness and cough (all 21%). Drug-related Gr 3 AEs were pneumonitis (8%) and nausea (4%); no Gr 4 AEs were reported. Potential immune-related any-Gr AEs were rash (8%), pneumonitis (8%), hypothyroidism, increased ALT/AST (all 4%). NIR178 systemic exposure (Cmax, AUC) increased more than proportionally with dose. Efficacy data for 17/24 treated pts demonstrated responses and SD across the dose range, including 1 confirmed CR (480 mg) and 1 PR (80 mg), both in immunotherapy-naïve pts. Durable SD >44 wks with tumor shrinkage was observed in 2 ongoing immunotherapy-exposed pts. Disease control was seen in pts with both high and low baseline PD-L1 expression. **Conclusion:** NIR178 was well tolerated; AEs were manageable and there were no Gr 4 drug-related AEs. Immune-related AEs may indicate immune stimulation. Clinical benefit was observed in immunotherapy-exposed and -naïve pts irrespective of PD-L1 status.

Keywords: Immunotherapy, adenosine 2A receptor, NIR178/PBF509

P1.04-33 RETROSPECTIVE DESCRIPTIVE ANALYSIS OF METFORMIN WITH ATEZOLIZUMAB IN ADVANCED NON-SMALL CELL LUNG CANCER IN THE OAK TRIAL

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Background: The randomized Phase III OAK trial investigated atezolizumab (anti–PD-L1) for treatment of advanced or metastatic previously-treated NSCLC. Atezolizumab significantly improved OS compared with docetaxel. Given that emerging studies have identified an association between metformin use and antitumor activity/immune interactions, we retrospectively explored metformin use in patients in the OAK study. **Method:** Patients received atezolizumab (1200 mg IV every 3 weeks [q3w]) until PD or loss of clinical benefit or docetaxel (75 mg/m^2 IV q3w) until PD/unacceptable toxicity. Patients who received atezolizumab or docetaxel and did or did not receive metformin as concomitant therapy were retrospectively evaluated for ORR, PFS and OS (data cutoff, July 7, 2016). Unadjusted and adjusted comparisons between metformin users and non-metformin users were done. **Result:** Of the 425 patients randomized to atezolizumab, 36 received metformin; of the 425 patients randomized to docetaxel, 35 received metformin. Key baseline characteristics are shown in the table. Most metformin users started metformin before or within 30 days of study start (92% and 7% respectively). There was a numerical improvement in ORR in Atezo-Met patients compared with Atezo-NoMet patients (25% vs 13%; unadjusted P = 0.038 [adjusted = 0.093]), whereas there was no statistically significant improvement in ORR in Doc-Met patients compared with Doc-NoMet patients (17% vs 13%; unadjusted P = 0.499 [adjusted = 0.295]). There were no observable differences in PFS or OS in either the Atezo-Met vs Atezo-NoMet or Doc-Met vs Doc-NoMet groups (median PFS, 2.8 vs 2.8 mo and 4.2 vs 4.0 mo, respectively; median OS, 12.6 vs 14.1 mo and 9.1 vs 9.7 mo, respectively). **Conclusion:** Encouraging response rates suggest patients may benefit from receiving concomitant metformin treatment with atezolizumab. Lack of difference in PFS and OS may be due to lack of treatment effect or lack of statistical power and requires further prospective investigation.

Table. Characteristics of Patients Who Received Atezolizumab (Atezo) or Docetaxel (Doc) Combined With Metformin (Met) or No-Metformin (NoMet)

	Atezo-Met, n (%) (n = 36)	Atezo-NoMet, n (%) (n = 389)	Doc-Met, n (%) (n = 35)	Doc-NoMet, n (%) (n = 390)
Diabetes mellitus type 2	33 (91.6)	28 (7.2)	33 (94.3)	26 (6.7)
Sex				
Male	28 (77.8)	233 (59.9)	28 (80.0)	231 (59.2)
Female	8 (22.2)	156 (40.1)	7 (20.0)	159 (40.8)
Tobacco use history				
Never smoker	2 (5.6)	82 (21.1)	2 (5.7)	70 (17.9)
Current/ previous smoker	34 (94.4)	307 (78.9)	33 (94.3)	320 (82.1)
Histology				
Nonsquamous	22 (61.1)	291 (74.8)	21 (60.0)	294 (75.4)
Squamous	14 (38.9)	98 (25.2)	14 (40.0)	96 (24.6)
No. of prior therapies				
1	30 (83.3)	290 (74.6)	24 (68.6)	296 (75.9)
ECOG performance status at baseline				
0	15 (41.7)	140 (36.0)	12 (34.3)	148 (37.9)
1	21 (58.3)	249 (64.0)	23 (65.7)	242 (62.1)
EGFR mutation status				
Positive	1 (2.8)	41 (10.5)	1 (2.9)	42 (10.8)
PD-L1 IHC subgroup				
TC3 or IC3 (PD-L1 ≥ 50% TC or 10% IC)	11 (30.6)	61 (15.7)	5 (14.3)	60 (15.4)
TC1/2/3 or IC1/2/3 (PD-L1 ≥ 1% on TC or IC)	27 (75.0)	214 (55.0)	19 (54.3)	203 (52.1)
TC0 and IC0 (PD-L1 < 1% on TC and IC)	9 (25.0)	171 (44.0)	16 (45.7)	183 (46.9)

TC, tumor cell; IC, tumor-infiltrating immune cell.

Keywords: metformin, atezolizumab, NSCLC

P1.04-34 STUDY ON TREATMENT OF STAGE IV SOLID TUMORS WITH MUTANT NEOANTIGEN SPECIFIC T CELLS

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Background: As an important tumor immunotherapy, the specificity and efficiency of PD1 inhibitor is not yet satisfactory. The treatment of solid tumor with mutant neoantigen specific T (Nas-T) cells developed in this study is an adoptive cell therapy which is specific for each patient. The aim is to explore the difference in safety and efficacy between Nas-T cells and PD1 inhibitors, and to evaluate the charateristic of immune repertoire (IR) as predictive biomarker. **Method:** A total number of 11 patients with advanced solid tumors who failed after multiline treatments were recruited. They were treated with Nas-T cells, PD1 inhibitors and BSC; other 11 patients were treated with PD1 inhibitors and BSC as control. Peripheral blood was collected at baseline and per cycle (21-28d) respectively. Multiple PCR and NGS on TCR beta chain was used to detect IR. **Result:** PFS of two groups had a statistical significance (P<0.05), suggesting Nas-T cells prolong patients' PFS. The safety was analyzed from routine blood urine stool test, coagulation function, liver and kidney function. There was no significant difference at baseline (P>0.05). Compared with C group, total protein and albumin in T group had a transient decrease in 3rd, 4th and 5th follow-up respectively (P<0.05), however, It can be recovered autonomously before 6th cycle. Three indexes were examined to illuminate the diversity and clonality of IR. Compared to baseline, T cell repertoir of non-responders and responders after 1st cycle showed significant changes: Shannon 1.14 vs 0.97, P=0.048; Evenness 3.90 vs 0.85, P=0.004; Clonality 1.20 vs 0.70, P=0.017. Elevated Clonality may indicate amplification of tumor specific T cells which could recognize mutant neoantigen specifically.

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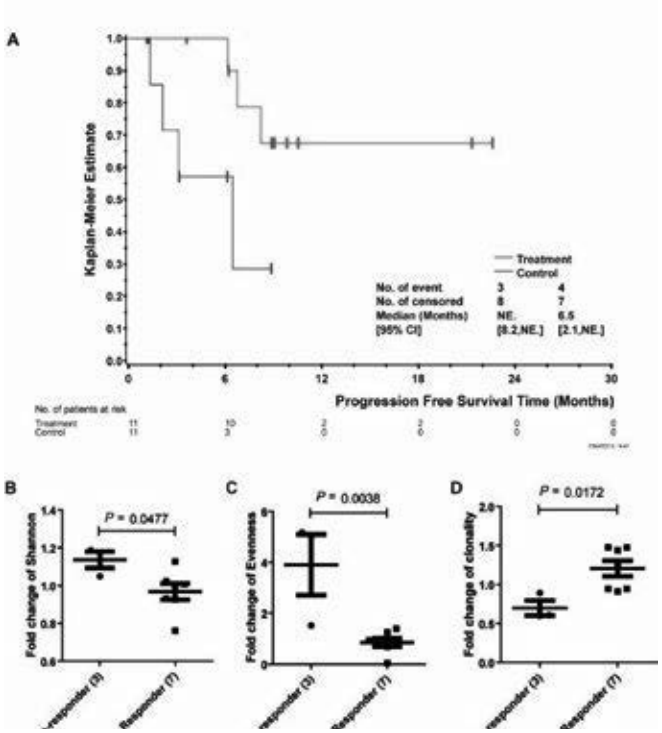

Conclusion: The combined immunotherapy of Nas-T cells and PD1 inhibitors is more effective than PD1 inhibitor alone in prolonging the PFS, and has a good safety. IR Clonality change shows its potential as a predictive biomarker.

Keywords: Immune Repertoire, Immunotherapy, NSCLC

P1.04 IMMUNOONCOLOGY
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P1.04-35 QUICK PROGRESSION (QP) IN PATIENTS TREATED BY NIVOLUMAB (IO) IN 2ND LINE OR MORE FOR NON-SMALL CELL LUNG CANCER: EORECI STUDY (GFPC 2016-04)

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Background: Nivolumab has been approved in 2nd line for advanced non-small cell lung cancer (NSCLC). However, more than half of the patients had progressive disease at 16 weeks, without any response and sometimes with deleterious progressions. This descriptive prospective study aimed to assess the characteristics of non responders with QP after IO and the following treatments. **Method:** From September 1st, 2016 to August 31th, 2017, patients (pts) treated by IO (second line or more) with QP<16 weeks were included by 20 GFPC centers. NSCLC characteristics at the diagnosis, at the IO initiation, treatments (before IO, IO and after IO) and outcomes responses, progression free survival (PFS) according to lines of treatments were recorded. **Result:** The sample included 319 pts: 64,3y± 9,6, smokers/ex-smokers: 48.0%-42.9%, male: 70.8%, PS01/2: 92.8%-7.2%, stage IV at diagnosis: 71.8%; adenocarcinoma: 63.9%. K-Ras mutated: 25.7%. Only 29% of patients had a PDL1 determination. 93% of pts received first line therapy, 32% second line, 10.3% third line before IO. First line PFS (PFS1) was 6.9m [6.43-7.8], PFS2: 9.33m [1.2-19], PFS3: 4.1m [1.56-12.43]. PFS for IO was 1.7m [0.76-4.16]. 229 (71,8%) patients had a IO PFS<2m; 14.7% of these patients stopped the treatment for toxicity. Among the 146 pts evaluable for response, PR was found in 23% of cases, SD in 30%, and PD in 47%.The table describe a comparison between two groups of QP during IO.

	QP during IO = 2months	QP during IO > 2 months	P
PFS1	6.7m	8.4m	**0.03**
PFS2	4.5m	6.0m	0.22
PFS3	5.0m	5.5m	0.9
OR 1st Line	52%	56.6%	0.86
OR 2nd line	15.4%	32.4%	**0.03**
OR 3rd line	20.3%	25.4%	0.89

Conclusion: In real life, QP during IO remains a challenge in NSCLC. Multivariate analyses will be presented to characterize these patients.

In collaboration with the GFPC team and supported by an academic grant from Pierre-Fabre pharmaceuticals. *GFPC: French Lung Cancer Group*

Keywords: Real life study, Immunotherapy, progression

P1.04 IMMUNOONCOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.04-36 TISLELIZUMAB COMBINED WITH CHEMOTHERAPY AS FIRST-LINE TREATMENT IN CHINESE PATIENTS WITH ADVANCED LUNG CANCER

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Background: Immune checkpoint inhibitors have shown efficacy in patients with NSCLC as monotherapy and in combination with chemotherapy. Tislelizumab is a humanized IgG4 monoclonal antibody to PD1 specifically engineered to minimize $F_cγR$ binding on macrophages, possibly minimizing negative interactions with other immune cells. In a phase 1 study, tislelizumab was generally well tolerated and showed antitumor activity; 200mg IV Q3W was established as the recommended dose. **Method:** This multi-arm phase 2 study, consisting of safety run-in and dose-extension phases, assessed tislelizumab in combination with platinum-based chemotherapy (by tumor histology) as a potential first-line treatment for Chinese patients with lung cancer. All patients received tislelizumab at 200mg Q3W in combination with 4–6 cycles of platinum-doublet until disease progression. Nonsquamous (nsq) NSCLC patients received pemetrexed + platinum Q3W for 4 cycles followed by pemetrexed maintenance, while squamous (sq) NSCLC patients received paclitaxel + platinum (A) or gemcitabine + platinum (B) Q3W, and small-cell lung cancer (SCLC) patients received etoposide + platinum Q3W. Tumor response (RECIST v1.1) and safety/tolerability were evaluated. **Result:** As of 21 Feb 2018, 48 patients (median age, 62 years [range: 36–75], 71% male, 71% current/former smokers) received tislelizumab treatment (median, 3 cycles [range: 1–7]); 44 patients remain on the study. Across the four cohorts, confirmed and unconfirmed partial responses were observed in 13 and 9 patients, respectively (**Table**). The most frequent AEs were chemotherapy-related hematologic toxicities. The most commonly reported grade ≥3 treatment-related AEs were neutropenia (20.8%) and anemia (12.5%); the most common grade 3 immune-related AEs were pyrexia (6.3%) and rash (6.3%). One sqNSCLC patient experienced a fatal myocarditis/myositis following one cycle of paclitaxel/cisplatin; all other treatment-related AEs were managed/resolved by study-drug interruption (n=15) or discontinuation (n=4) and appropriate treatment.

(See next page)

Best Overall Response
(Patients With ≥1 Post-Baseline Tumor Assessment)

	nsq-NSCLC (n=9)	sq-NSCLC [A] (n=12)	sq-NSCLC [B] (n=5)	SCLC (n=8)	Total (N=34)
PR	4 (44.4)	9 (75)	4 (80)	5 (62.5)	22 (64.7)
Confirmed PR	1 (11.1)	4 (33.3)	4 (80)	4 (50)	13 (38.2)
Unconfirmed PR	3 (33.3)	5 (41.7)	0 (0)	1 (12.5)	9 (26.5)
SD	3 (33.3)	2 (16.7)	1 (20)	2 (25)	8 (23.5)
PD	1 (11.1)	0 (0)	0 (0)	1 (12.5)	2 (5.9)
NE	1 (11.1)	1 (8.3)	0 (0)	0 (0)	2 (5.9)

Data presented as n (%). Abbreviations: nsq-NSCLC, non-squamous non-small cell lung cancer; NE, not evaluable; PD, progressive disease; PR, partial response; SCLC, small cell lung cancer; SD, stable disease; sq-NSCLC, squamous non-small cell lung cancer.

Conclusion: Tislelizumab, in combination with platinum doublets, demonstrated preliminary antitumor activity and was generally well tolerated in patients with advanced lung cancer.

Keywords: lung cancer, tislelizumab (BGB-A317), Chemotherapy combination

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-01 INCIDENCE AND CLINICAL RELEVANCE OF NSCLC LYMPH NODE MICRO-METASTASIS DETECTED BY STAGING EBUS-TBNA

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Background: Appropriate staging of non-small cell lung cancer (NSCLC) patients is crucial to provide accurate prognostic information and select appropriate treatment. Several publications have reported an approximate 20% incidence of occult micro-metastasis (MM) in surgically resected lymph nodes (LN) pathologically interpreted as negative by hematoxylin and eosin staining (H&E). Detection of MM was associated with worsened survival. The majority of NSCLC lymph node staging is now conducted using endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). The purpose of this study is to determine the frequency of detection of occult MM in EBUS-TBNA specimens and to evaluate the impact of the presence of MM on progression-free and overall survival. **Method:** All patients undergoing EBUS-TBNA for NSCLC lymph node staging at our institution between September 2013 and October 2017 were eligible for inclusion. Patients were identified using provider-maintained case lists, operating or procedure room electronic schedules, and tumor board patient presentations. Patients were excluded if a definitive diagnosis of NSCLC was not obtained within 3 months of the EBUS-TBNA examination or if distant metastatic disease was present at the time of diagnosis. Patient cell blocks from the EBUS-TBNA procedure were evaluated by a cytopathologist using H&E staining according to standard guidelines. Patients with N2 or N3 disease on routine cytopathology examination were excluded. Cell blocks from the included patients were sectioned into five 5 mm sections spaced at least 10 mm apart and immunohistochemistry for pan-cytokeratin was performed. The resulting slides were then reviewed for evidence of MM by a blinded cytopathologist. **Result:** Of 887 patients screened, 44 patients were identified fitting inclusion criteria with sufficient additional tissue for testing. The mean age and smoking history were 68 ± 10 years and 45 pack-year history, respectively. The patients were majority male (61%) and Caucasian (75%). Fifty-two percent of patients were stage 1 at the time of diagnosis, 34% were stage 2, and 14% were stage 3a. Three patients (6.8%) were found to have pan-cytokeratin positive MMs. All 3 MMs detected were at N2 LN stations. The presence of MMs was associated with significantly decreased progression-free (median 210 vs. 1293 days, p=0.0099) and overall survival (median 238 vs. 1120 days, p=0.0357). **Conclusion:** LN micro-metastases can be detected during EBUS-TBNA staging examinations and are associated with poor clinical outcomes. If prospectively confirmed in a larger study, these results have significant implications for EBUS-TBNA specimen analyses and the current NSCLC staging paradigm.

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-02 ENDOBRONCHIAL ULTRASOUND-TRANSBRONCHIAL NEEDLE ASPIRATION FOR LYMPHOMA IN PATIENTS WITH MEDIASTINAL LYMPHADENOPATHY

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Background: Surgical excision and core biopsy are the current preferred sampling techniques for diagnosing lymphoma. However, In patients who present with intrathoracic adenopathy that is suspicious for lymphoma, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is an attractive option. **Method:** The cases of patients who had undergone EBUS-TBNA for 31 cases of suspected lymphoma were retrospectively reviewed. **Result:** EBUS-TBNA diagnosis was that : 6 cases was diagnostic lymphoma, but not subtyping, 6 cases was specific lymphoma using cell block (2 cases of diffuse large B-cell lymphoma, NOS, 1 case of mantle cell lymphoma, 1 case of NK-T cell lymphoma, 1 case of anaplastic large cell lymphoma, and 1 case Hodgkin lymphoma) , 5 cases was granuloma, 4 cases carcinoma, 6 cases diagnostic lymphoid tissue without specific diagnosis, and 4 cases non-diagnostic. Of 31 cases, 14 (45.2%) were finally diagnosed with lymphoma. In EBUS-TBNA, these cases were diagnosed as lymphoma (12 cases) and non-diagnostic (2cases). Other diagnosis in EBUS-TBNA was not finally diagnosed as lymphoma. **Conclusion:** EBUS-TBNA is effective at diagnosing suspected lymphoma in patients with mediastinal lymphadenopathy. A specific EBUS-TBNA features, such as granulomas and carcinoma, are associated without a probability of lymphoma.

Keywords: mediastinum, lymphoma, EBUS-TBNA

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-03 SIGNIFICANCE OF LYMPH NODE SUVMAX IN PREDICTING NODAL METASTASIS BY EBUS IN LUNG CANCER PATIENTS

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Background: Nodal staging of non-small-cell lung cancer (NSCLC) patients begins with imaging such as Positron emission tomography–computed tomography (PET-CT). It provides information about lymph node (LN) location, enlargement, and metabolic activity as measured by the maximum standardized uptake value (SUVmax). However, more definitive information can only be obtained by direct sampling through cervical mediastinoscopy (Med) and/or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS). There remains discrepancy when comparing the diagnostic accuracy of these two methods for detecting nodal metastasis. Further, there is inadequate data on the value of SUVmax magnitude in predicting nodal metastasis by EBUS. **Method:** This was a retrospective analysis of 148 biopsy-confirmed NSCLC patients who underwent Med and/or EBUS for staging purposes from 2010-2015 (2013 excluded). Two groups matched by age, sex, and year of procedure were analyzed to determine if the diagnostic accuracy was comparable between the two methods. Primary tumour and LN SUVmax was correlated with the likelihood of finding LN metastasis by either method. Chi-squared tests and Student's t-tests were used to assess for significance where appropriate. **Result:** The mean SUVmax of true positive LNs was significantly higher than true negative LNs sampled by EBUS (7.77 vs. 4.06, p=0.0047, t-test). Among PET-positive LNs, there was a significant correlation between likelihood of positive findings by EBUS and increased SUVmax>4 (p=0.018, Chi-squared test). There were no significant differences between Med and EBUS in sensitivity, specificity, PPV, or NPV. However, Med had significantly higher diagnostic yield (p<0.0001, Chi-squared test). **Conclusion:** Our results suggest that among PET-positive LNs, there is a significant correlation between SUVmax magnitude and likelihood of detecting true LN metastasis by EBUS. Additional studies should aim to further characterize this relationship.

Keywords: non-small cell lung cancer, maximum standardized uptake value, endobronchial ultrasound

P1.05-04 CONE-BEAM CT CONFIRMS THE STATUS OF TRANSBRONCHIAL BIOPSY UNDER VIRTUAL BRONCHOSCOPIC NAVIGATION FOR PERIPHERAL LUNG LESIONS

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Background: CT guided transbronchial biopsy has been reported to have a high accuracy for the diagnosis of peripheral lung lesion. Recently, C-arm cone-beam CT (CBCT) with a flatpanel detector system has been developed and offers greater flexibility in orientating the detector around the patient than closed CT gantry systems. We have introduced CBCT to the transbronchial lung biopsy and report the usefulness of the method. **Method:** Patients with undiagnosed peripheral lung lesions 3 cm or less in size between June 2016 and August 2017 were enrolled. An ultrathin bronchoscope was inserted as far as possible to the target bronchus by comparing the direct vision and virtual bronchoscopic navigation images displayed simultaneously at same monitor. After reaching the target bronchus, the biopsy forceps was introduced to the target bronchus under conventional fluoroscopy. After the biopsy forceps reach the target bronchus, a CBCT scan data was taken. We categorized the CBCT findings into three types according to positions of the target lesion and the forceps as follows: (Type A: The forceps clearly reached within the lesion. Type B: It could not be categorized into neither type A nor C. Type C: The forceps could not reach the lesion.). The diagnosis yields of biopsy or cytology results was examined. **Result:** Twenty-two patients (12 males and 10 females) were included in the study and age ranged from 50 to 87 with average age of 72.8 years. Thirteen lesions were located at the upper lobe, seven lesions at lower lobe and one lesion at middle lobe. Size of the lesions ranged from 9 to 29 mm with average of 20 mm. They included 13 solid lesions and 8 mixed GGO lesions. Regarding CBCT type, A was 16 cases, B was 4 cases, and C was 1 case. Bronchoscopic diagnosis was malignant in 11 cases, benign in 10 cases (4 mycobacterium infections and 6 non-specific inflammations) and undiagnostic in 1 case. There was one false negative case whose bronchoscopic diagnosis as non-specific inflammation was finally proved as adenocarcinoma. Overall the diagnostic accuracy was 91%(20/22). Based on the CBCT category, the accuracy was 100% (17/17), 75% (3/4), 0% (0/1) in Type A, B and C respectively. **Conclusion:** CBCT guided bronchoscopy is valuable in the diagnosis of peripheral lung lesions and useful for confirming the position of the forceps.

Keywords: diagnosis, bronchoscopy

P1.05-05 ENDOBRONCHIAL ULTRASOUND-GUIDED TRANSBRONCHIAL NEEDLE ASPIRATION FOR SUSPECTED MALIGNANCY; CURRENT STATUS AND ISSUES

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Background: The number of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is now increasing, since it is less invasive and useful for the pathological diagnosis of lung cancer or thoracic and hilar lymph node enlargement. However, there are some problems to be solved, such as diagnostic accuracy and complications. Here, we retrospectively reviewed our experiences of EBUS-TBNA performed for diagnosis of malignant diseases. **Method:** Between July 2009 and December 2017, 489 patients underwent EBUS-TBNA. Among them, the subject of this study was 424 cases underwent EBUS-TBNA for diagnosis of malignancy. We retrospectively analyzed the completion rate, the complication rate, the adequate sample collection rate and the diagnostic accuracy of EBUS-TBNA among these 424 patients. **Result:** Among all 424 cases, the target lesions of EBUS-TBNA consisted of mediastinal lesions (n=303), hilar lesions (n=69) and both mediastinal and hilar lesions (n=52). Almost all EBUS-TBNAs were performed under conscious anesthesia, while 9 EBUS-TBNAs were performed under general anesthesia. Among 424 cases, EBUS-TBNA was completed in 408 cases (96.2%) and the collection of adequate sample was performed in 382 cases (90.1%). There were four complications (0.94%); they consisted of mediastinal infection (n=2), obstructive pneumonia (n=1) and airway obstruction (n=1). All 4 cases were treated medically and fully recovered. Among 16 incomplete cases, 10 cases were histologically diagnosed with having malignancy; 5 cases were surgically diagnosed, and other 5 cases were diagnosed by EBUS-TBNA under general anesthesia. Other 3 cases were clinically diagnosed with having malignant diseases. Among 26 patients in whom adequate samples were not collected, 14 patients were finally diagnosed with having malignancy. On the other hand, among 382 patients in whom adequate samples were collected, the sensitivity, specificity, positive predictive value and negative predictive value were 90.0%, 100.0%, 100.0% and 76.0%, respectively. Furthermore, the diagnostic accuracy of EBUS-TBNA for hilar lesions was the least among the three lesions (mediastinal: 94.2%, hilar: 83.9%, both mediastinal and hilar: 91.8%, p=0.029). **Conclusion:** Among the patients in whom adequate samples were collected, the outcome of EBUS-TBNA was favorable. Since complications are rare but can happen, early recognition and treatment for complication are important. When EBUS-TBNA under conscious sedation is not completed, EBUS-TBNA under general anesthesia or other diagnostic approaches such as mediastinoscopy and video-assisted thoracoscopic surgery are to be considered.

Keywords: incomplete cases, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), complications

P1.05-06 BRONCHOSCOPIC IMAGE-GUIDED MICROWAVE ABLATION OF PERIPHERAL LUNG TUMOURS – EARLY RESULTS

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Background: Thermal ablation is indicated for the treatment of early lung cancer in medically inoperable patients, and for oligometastatic disease. However, percutaneous ablation is associated with 30-50% pneumothorax, haemothorax, pleural effusion and pain. Peripheral lung tumours can be reached by electromagnetic navigation bronchoscopy (ENB) without breaching the pleura. Intraprocedural cone-beam CT (CBCT) and transbronchial access instruments allow lesions in the lung periphery to be reached with accuracy. Another advantage of the bronchoscopic approach is the ability to concurrently obtain tissue for diagnosis and molecular characterization, and to perform full nodal staging. Bronchoscopic radiofrequency ablation (RFA) has been described for tumours with positive bronchus sign, but the effectiveness of RFA is limited by impedence of air and heat-sink effects of vessels. Microwave avoids these limitations. We present our early experience of bronchoscopic microwave ablation of tumours with CBCT guidance and transbronchial access. **Method:** ENB (Superdimension, Medtronic, Minneapolis) was carried out under general anaesthesia. A CBCT (Philips, Eindhoven) confirms probe position and its relationship to the lesion. Transbronchial access with CrossCountry device (Medtronic, Minneapolis) was used as required to reach extrabronchial lesions. A flexible microwave ablation catheter (Emprint, Medtronic) was advanced to the lesion. Ablation was planned with OncoSuite (Philips, Eindhoven) to ensure the ablation zone encompassed the lesion with a 5mm margin. Ablation was carried out and a fiducial was placed at the ablation site to facilitate follow-up. A control CBCT was carried out post procedure. **Result:** Between February and April 2018, three patients (2F:1M, mean age 70.3) with oligometastatic disease (2 colorectal, 1 endometrial) underwent bronchoscopic microwave ablation to 4 lung lesions (two RLL nodules (in one patient), LUL and LLL, median size 10.5mm (range 7-13mm), 3 without bronchus sign). All lesions were reached, with the LUL nodule requiring transbronchial access. All lesions were treated at 100W for 10 minutes. CBCT confirmed ground-glass opacification of the ablation zones encompassing the lesions. There were no procedural complications, pneumothorax or bleeding. Two patients with lesions close to the pleura experienced mild, localised chest discomfort which resolved by 24 hours. All patients were discharged the following day. A CT at 30 days for the first patient showed a 25x32mm area of dense ovoid consolidation representing the ablation zone, with no complications. **Conclusion:** Our early experience shows bronchoscopic microwave ablation is safe and feasible with low morbidity. The accuracy of the procedure is enhanced by CBCT control. Lesions remote from the bronchial tree could be accessed and safely treated.

Keywords: Bronchoscopic ablation, Cone beam CT, navigation bronchoscopy

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-07 CLINICAL SIGNIFICANCE OF PLEURAL INDENTATION OF LUNG ADENOCARCINOMA PRESENTED AS GROUND GLASS OPACITIES

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Background: After the emphasis on lung cancer screening, incidental detection of ground glass opacities (GGOs) has increased. Such GGOs commonly have peripheral location and pleural indentation, which may increase the risk of visceral pleural invasion (VPI). Although the impact of pleural indentation among solid lung cancers is well established, such impact among GGO lung cancers is not well known. **Method:** Patients who underwent lung resection with curative intention of GGO lung cancer from April 2007 to January 2016 were retrospectively evaluated. Demographics, radiographic findings, pathological findings, and clinical outcomes including recurrence were analyzed. **Result:** A total 404 of patients were analyzed, and pleural indentation was observed in 258 patients (63.9%). All cancers turned out to be adenocarcinoma. Older age, worse lung function, longer diameter, and tumor shadow disappearance rate were associated with indentation. VPI was observed in 36 (8.9%) patients, and indentation was independently associated with VPI (odds ratio 9.34, p=0.032) after adjustment of pleural attachment, diameter, and tumor shadow disappearance rate. During a median follow-up duration of 48.3 months, 34 (8.4%) patients recurred. Although indentation was not associated with earlier recurrence (adjusted hazard ratio 2.16, p=0.168), concurrent pleural attachment with indentation was associated with recurrence among those with solid portion≥8mm (adjusted hazard ratio 3.05, p=0.019). **Conclusion:** Pleural indentation was associated with increased risk of VPI in GGO lung adenocarcinoma. Although indentation itself did not increase the risk of recurrence, concurrent pleural attachment with indentation may increase the risk of recurrence among selected patients.

Keywords: Indentation, Ground glass opacity, visceral pleural invasion

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-08 SPREAD THROUGH AIR SPACES (STAS) IN INVASIVE MUCINOUS ADENOCARCINOMA OF THE LUNG: INCIDENCE, PROGNOSTIC IMPACT, AND PREDICTIVE FACTORS

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Background: Spread through air spaces (STAS) is a recently recognized as a novel negative impact on prognosis in lung adenocarcinoma, however was almost investigated non-mucinous adenocarcinoma. We investigated the incidence of STAS in invasive mucinous adenocarcinoma (IMA) of the lung and whether tumor STAS was a risk factor of disease recurrence even in IMA, and determined clinico-radiologic factors in patients with IMA harboring STAS. **Method:** We reviewed pathologic specimens and imaging characteristics of primary tumors from 132 consecutive patients who underwent surgical resection for IMA. On pathology, the presence of aerogenous spread (AS), mucin, and STAS were evaluated. Two groups determined by STAS were compared with respect to clinical characteristics as well as CT imaging using the Pearson $\chi 2$ test or the Fisher exact test. Multivariate logistic regression was used to explore the clinico-radiologic features that facilitate the detection of STAS in IMA, for which receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance. The relationships between all variables including STAS and survival (overall survival [OS] and disease-free survival [DFS]) were analyzed by using Kaplan–Meier curves and Cox regression analyses. **Result:** Of 119 patients with full pathologic specimens, STAS was observed in 86 patients (72.3%). On multivariate analysis, IMA patients with STAS were significantly tended to be lobectomy (odds ratio [OR] = 7.120, 95% confidence interval [CI] = 1.184 to 42.825, P value = 0.032), older (OR = 2.979, 95% CI = 1.109 to 8.001, P value = 0.030) and the absence of peripheral GGO on CT (OR =0.376, CI=0.141 to 0.999 , P value = 0.049), where the predictive model for presence of STAS showed discrimination performance with an area under the receiver operating characteristic curve (AUC) of 0.798 (95% CI = 0.711 to 0.884, P value < 0.005). The DFS was lower in patients with STAS compared with in those without STAS, whereas there was no statistically significant difference (P value =0.091). On multivariate analysis for DFS, STAS failed to be an independent predictor, but lymph node metastasis (hazard ratio [HR], 2.505; 95% CI 1.288–11.089, absence of mucin on pathologic specimen (HR, 0.46; 95% CI 0.194–0.985) and CT angiogram sign (HR, 2.872; 95% CI 1.036–7.963) remained independent predictors for disease recurrence. **Conclusion:** IMA with STAS represented older age, absence of peripheral GGO on CT, more frequent lobectomy than limited resection. STAS was associated with reduced DFS, but failed to be a significant prognostic factor.

Keywords: Invasive mucinous adenocarcinoma; Spread through air spaces; Recurrence, Computed tomography, Ground-glass opacity.

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-09 DIELECTRIC PROPERTY TEST FOR THE RAPID DIFFERENTIAL DIAGNOSIS OF LUNG NODULES/MASS

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Background: Developing new methods for rapid diagnosis for lung nodules/mass has always been one of the most attractive topics. And it has been found that the dielectric property, including permittivity and conductivity, varies from benign tissues to malignancies. However, no studies comparing the dielectric property between lung benign tumors to malignancies has been reported and whether dielectric property test could be used for differential diagnosis remains uncertain. **Method:** Patients with lung nodules/mass who received surgical resection were included for permittivity and conductivity test right after the occupying lesions were removed and before sent for pathological examination. The informed consents were obtained before surgery. Independent-samples T Test and multiple variables for ROC curve analysis were used. **Result:** More than 250 lesions were expected to be tested for calculating the differential diagnosing cutoff value. For each lesion, 4000 datasets of permittivity and conductivity at different frequencies from 1MHz to 4000MHz were collected. By far, 73 patients with 74 lung occupying lesions were enrolled for dielectric property test, including 19 lung benign tumors and 55 malignancies. Though the differences of mean permittivity and conductivity between the 2 groups were not statistically significant (p>0.05), there might be a tendency to distinguish the 2 groups. And the mean values of permittivity and conductivity and their independent values at frequency 1MHz, 500MHz, 1000MHz, 1500MHz, 2000MHz, 2500MHz, 3000MHz, 3500MHz, 4000MHz were chosen as multiple variables for ROC curve analysis. With the false positive rate of 10%, the cutoff value P_{cutoff} was 0.8588 and the logistic regression formula for differential diagnosis were shown as followed, of which the area under the ROC curve was 0.905. Funding The study was supported by the Presidential Foundation of Nanfang Hospital, Southern Medical University (2016B018).

$$P_{cutoff}=1/(1+e^{-(-20.571-40.244p_M-0.129c_M-0.511c_{1MHz}-39.65c_{500MHz}+13.21c_{1000MHz}+47.714c_{1500MHz}+13.273c_{2000MHz})}\times e^{-(-7.072c_{2500MHz}-1.622c_{3000MHz}-29.830c_{3500MHz}+21.6c_{4000MHz}-0.00032p_{1MHz}+0.424p_{500MHz}+0.475p_{1000MHz})}\times e^{-(-0.192p_{1500MHz}+0.523p_{2000MHz}+0.266p_{2500MHz}+0.554p_{3000MHz}+1.052p_{3500MHz}-1.935p_{4000MHz})}).$$

Conclusion: With more data collected, dielectric property test might become another rapid way of distinguishing lung malignancies from benign tumors.

Keywords: dielectric property test, rapid diagnosis

P1.05-10 USEFULNESS OF RESPIRATORY DILATATION BALLOON IN TRACHEOBRONCHIAL STENOSIS REQUIRING SILICONE Y-STENT TREATMENT

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Background: The Dumon silicone Y-stent (Novatech SA, La Ciotat, France) is useful for releasing tracheobronchial stenosis but requires sufficient predilation because of the weak expansion force of silicone Y-stents. We have performed mechanical expansion (debulking or coreout) by rigid bronchoscopy, microwave coagulation, and balloon expansion (Fogarty catheter). In recent years, however, we have used a respiratory dilatation balloon (CRE Pulmonary Balloon Dilator; Boston Scientific, Marlborough, MA). We investigated the feasibility, efficacy, and safety of stenting using a silicone Y-stent or additional self-expanding metallic stent (SEMS), focusing especially on the usefulness of a pulmonary balloon dilator, in patients with malignant tracheobronchial stenosis. **Method:** From May 2012 to November 2017, 75 patients (54 male, 21 female; mean age, 64 years; range, 30–91 years) who underwent Dumon silicone Y-stent placement for malignant tracheobronchial stenosis in our department were retrospectively examined. Forty-six patients had lung cancer, 20 had esophageal cancer, 5 had tracheal carcinoma, and 4 had other carcinomas. All procedures were performed in the operating room under general anesthesia, and the stents were implanted via rigid bronchoscopy. The patients were divided into three groups according to the method of predilatation before stenting: no use of balloon expansion (Group N, n=36), use of a Fogarty catheter (Group F, n=22), and use of a respiratory dilatation balloon (Group B, n=17). **Result:** Stents were implanted and symptoms were resolved in all patients. No operative death occurred. The types of indwelling stents were only a Y-stent in 46 patients and a Y-stent with additional SEMS in 29. Although the mean number of additional SEMS was significantly higher in Group B (0.7 stents/patient) than in Groups N and F (0.3 stents/patient, respectively), there was no difference in the median (range) operation time among Groups N, F, and B: 55 (32–115), 59 (29–110), and 49 (17–102) minutes, respectively. In the 46 patients who underwent placement of only a Y-stent without a SEMS, the operation time was significantly shorter in Group B [n=6, 39 (17–64) minutes] than in Groups N [n=25, 53 (32–115) minutes] and F [n=15, 59 (29–106) minutes] (p=0.028). There were no differences in the amount of bleeding, postoperative performance status, or hospitalization days. **Conclusion:** A respiratory dilatation balloon is useful for predilatation in patients with tracheobronchial stenosis requiring a silicone Y-stent. Such balloons also contribute to a shorter operation time and more efficient procedure for severe stenosis requiring additional stenting.

Keywords: tracheobronchial stenosis, silicone Y-stent, respiratory dilatation ball

P1.05-11 ROLE OF EBUS-TBNA IN EVALUATION OF MEDIASTINAL LYMPHADENOPATHY AND MASSES IN PATIENTS WITH KNOWN OR SUSPECTED EXTRA-PULMONARY MALIGNANCIES

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Background: Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) has recently emerged as a minimally invasive and safe modality for the evaluation of mediastinal lymphadenopathy, particularly in staging of lung carcinoma patients. Our aim was to evaluate its utility in patients with non-pulmonary malignancies presenting with mediastinal lymphadenopathy. **Method:** A computerized database search was performed for all EBUS-TBNA aspirations performed from 2015 to 2017 on patients with known or suspected extra-pulmonary malignancy and presence of mediastinal lymphadenopathy and/or masses on imaging. All archived cytology material was reviewed and categorized as positive, negative and unsatisfactory. Follow-up histology samples served as comparison standard. **Result:** One-hundred-twenty-one patients were included. In 99 patients with known malignancy, primary sites were in the head and neck (25%), breast (22%), female genital tract (9%), lower gastrointestinal (GI)-tract (8%), genitourinary tract (7%), and upper GI-tract (5%). Six patients had history of hematolymphoid malignancy while primary site or type of malignancy was unknown in the remaining (18%). EBUS-TBNA diagnosed metastases or lymphoma relapse in 48 (40%), identified new malignancy in 18 (15%), granulomatous inflammation in 15 (12%), tuberculosis in 2 (1%), reactive lymphadenitis in 21 (17%) patients and was inadequate in 17 (14%) patients. Cell block was adequate in 43% (23/53) cases and was indispensible for diagnosis in 13% (7/53) cases. Subcarinal and right paratracheal lymphnodes were most commonly aspirated (77%) while hilar and paratracheal masses of non-lymphnode origin were assessed in 10% cases. Follow-up histology samples (available only in 13 cases) showed 100% concordance with EBUS-TBNA results (no false positive or false negative cases). Two cases unsatisfactory on EBUS-TBNA were positive for malignancy on histology. **Conclusion:** EBUS-TBNA is a highly efficient modality for the evaluation of mediastinal lymphnodes and masses in patients with extra-pulmonary malignancies with an overall diagnostic yield of 86%.

Keywords: mediastinal lymphadenopathy, extra-pulmonary malignancy, EBUS-TBNA

P1.05-12 ^{18}F-FDG PET/CT FINDINGS MAY PREDICT POSTOPERATIVE ACUTE EXACERBATION OF INTERSTITIAL PNEUMONIA IN LUNG CANCER PATIENTS

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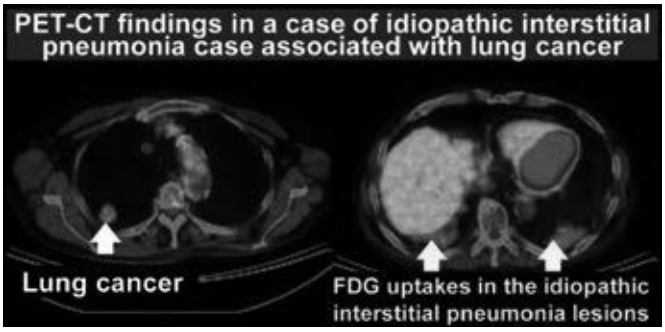
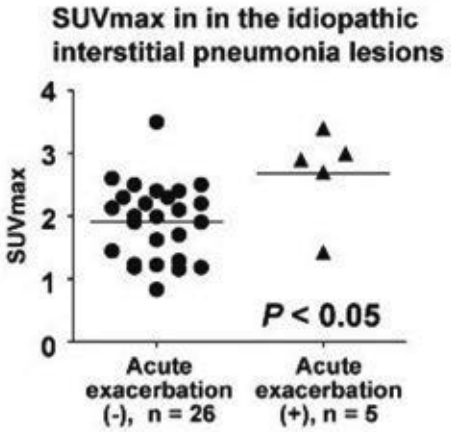
Background: Acute exacerbation could be life-threatening for idiopathic interstitial pneumonia (IIP) patients. It is often challenging to choose a surgical treatment for a patient with IIP associated with lung cancer because lung resection is one of the risk factors of acute exacerbation. The objective of this present study was to investigate the correlation between preoperative findings of ^{18}F-FDG PET/CT and postoperative acute exacerbation in patients with IIP associated with lung cancer. **Method:** We retrospectively reviewed the data of 450 patients who underwent lung resection for non-small cell lung cancer between November 2012 and October 2017. We excluded patients who had preoperative radiotherapy (25 patients) from the analysis. All these patients preoperatively underwent ^{18}F-FDG PET/CT for staging lung cancer. The maximum standardized uptake value (was obtained.



Result: CT findings of IIPs were found in 31 out of 425 patients (7.1%). Five out of 31 patients (16.1%) developed acute exacerbation after lung resection. These 5 patients had significantly higher SUVmax in the lesions of IIPs compared 26 patients without postoperative acute exacerbation.



Conclusion: This study demonstrated that ^{18}F-FDG PET/CT findings may predict postoperative acute exacerbation of IIP in lung cancer patients.

Keywords: acute exacerbation, Interstitial pneumonia, FDG PET/CT

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-13 THE DEMONSTRATION OF THE POSSIBILITY OF THE PLEURA CRYO BIOPSY – A PRELIMINARY REPORT

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Background: The demonstration of the possibility of diagnosing changes located in the parietal pleura by means of cryo probe guided by videopleuroscopy. **Method:** The study consisted of five patients with lesions of the parietal pleura and accumulation of fluid in the pleural space suspected of neoplastic disease. The previous diagnostic procedures did not confirm the etiology of the hydrothorax, therefore, the patients were qualified for the videopleuroscopy under local anesthesia and sedation. The ultrasound examination confirmed the presence of the pleural fluid and videotrocar was introduced into the pleural cavity. The videopleuroscope was inserted into the pleural cavity, the fluid was removed and the parietal lesions were visualised. The 1,9 mm cryo probe was introduced through the 2 mm working channel of the videopleuroscope and samples of the parietal pleura were taken. The sampling procedure was repeated with standard forceps. Talc slurry administration and drainage of the pleural cavity were performed eventually. All the patient were discharged a few days after the procedure. **Result:** Mesothelioma was confirmed in one case, primary lung adenocarcinoma in one case, metastatic adenocarcinoma in one case, Ewing sarcoma in one case and chronic pleuritis in one case. Histology samples taken with the cryo probe were much bigger and of better quality than the samples taken by the forceps. **Conclusion:** The cryo probe guided by the videopleuroscopy is an effective and safe procedure regarding diagnosing pleural lesions suspected of the neoplastic disease. The cryo probe provides very good samples of the parietal pleura for the pathologic and immunohistochemistry evaluation

Keywords: pleura, Videopleuroscopy, cryo biopsy

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-14 AUTOFLUORESCENCE MODE OF THORACOSCOPE IMPROVES VISCERAL PLEURAL INVASION DIAGNOSIS IN NON-SMALL CELL LUNG CANCER

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Background: Visceral pleural invasion of non-small cell lung cancer is an important prognostic factor, and tumors with visceral pleural invasion are classified as T2a, even if they are 3 cm or less. However, visceral pleural invasion is usually diagnosed by postoperative pathologic examination and it is difficult to diagnose it by preoperative imaging or intraoperative macroscopic findings. This study was conducted to evaluate the accuracy of autofluorescence mode diagnosis for visceral pleural invasion of non-small cell lung cancer compared with white light mode diagnosis. **Method:** Two thoracic surgeons blind to pathological diagnosis reviewed operation videos of 56 cases and evaluated visceral pleural invasion under white light mode and autofluorescence mode. These cases were selected according to the following criteria. 1) Primary non-small cell lung cancer patients who underwent video-assisted thoracic surgery from October 2011 to March 2018. 2) Tumor attached to visceral pleura on the lung window of CT images. 3) Thoracic cavity was explored using both white light and autofluorescence modes using a D-Light AutoFluorescence system (Karl Storz, Tuttlingen, Germany). 4) Lung tumors were resected and evaluated histopathologically using elastic stains. The mean age was 67 years and 31 patients (55%) were male. They included 43 adenocarcinomas, 11 squamous cell carcinoma and 2 others. The mean tumor size was 22 mm (7–30 mm). There were 9 pathological visceral pleural invasion positive cases. For white light mode, if either one of the following pleural change; 1) whitish, 2) granular, 3) hypervascular was observed at the tumor site, the tumor was diagnosed as visceral pleural invasion positive. For autofluorescence mode, we defined attenuation or a defect in autofluorescence of the pleura at the tumor site as a positive finding of visceral pleural invasion. **Result:** *The sensitivity, specificity, and accuracy of visceral pleural invasion diagnosis by white light vs autofluorescence mode were 77.8% vs 77.8%, 66.0%% vs 83.0%, and 67.9% vs 82.1%, respectively.* **Conclusion:** The specificity, and accuracy of visceral pleural invasion diagnosis was improved through the additional use of autofluorescence mode compared with white light mode alone.

Keywords: visceral pleural invasion, non-small cell lung cancer, autofluorescence

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P1.05-15 BENIGN LUNG NODULE RESECTIONS IN THE ERA OF ADVANCED IMAGING AND CLINICAL GUIDELINES:IMAGING FEATURES AND HOW WE CAN REDUCE THE RESECTION RATE

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Background: Evaluation of lung nodules is a long standing clinical problem. Despite advances in diagnostics, many nodules are still resected that are benign. Although certain imaging characteristic can distinguish benign from malignant lung nodules on CT and PET/CT, overlap exists. Our purpose is to understand the benign resection rate with use of PET and PET/CT, and to review the patient and imaging characteristics of benign resected nodules in the PET-PET/CT era. **Method:** We reviewed all 557 surgically resected lung nodules from 2001-2012. Patient demographics, smoking and cancer history, diagnostic tests prior to surgery, and pathology results were collected. All preoperative CT examinations were reviewed for nodule location, size, shape, border and attenuation, and PET/CTs for FDG-avidity. **Result:** Of 557 resected nodules in 541 patients, 39 nodules in 38 patients were benign (15 females, 23 male) for a benign resection rate of 7% (39/557). There was no significant difference between benign and malignant groups across sex, race, nodule size or attenuation. Patients with benign nodules were younger (mean age 59 vs. 65 years in the malignant group; p=0.005). 75% of patients with benign nodules were smokers versus 80% in the malignant group (p=0.04). In the benign nodule group, 14 patients (36%) had a cancer history. Benign pathology results were: 15 granuloma, 6 chronic inflammation, 5 hamartoma, 5 abscesses, 2 inflammatory pseudotumor, 2 organizing pneumonia and 1 case each of bronchogenic cyst, fibrous tumor, lipoid pneumonia and lymphoepithelioma. 62% of were in the right lung, and 46% were in an upper lobe. Nodule size was 10-95 mm (mean 29). CT nodule morphology was round/ovoid in 16, and triangular/angular in 3. Nodule border was lobulated in 4, smooth in 7 and spiculated in 8. Cavitation was present in 4 nodules, 14 were exclusively soft tissue attenuation and one contained fat. By attenuation, 18 were solid, and 1 was non solid (ground glass). Of the 18/38 (47%) patients who underwent preoperative PET/CT scan, nodule FDG uptake was: 5 intense, 10 mild, 3 none. **Conclusion:** Our benign resection rate for lung nodules is 7%. While in many cases the imaging characteristics of surgically proven benign lung nodules and their clinical management are appropriate, following clinical guidelines for nodule management may further reduce the benign resection rate. The use of PET/CT and follow up low dose chest CT for PET/CT negative or mild uptake lesions to confirm nodule stability over time is a pathway for management that requires reinforcement.

Keywords: nodules, imaging, benign

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-16 CLINICAL UTILITY OF ELECTROMAGNETIC NAVIGATION BRONCHOSCOPY IN THE DIAGNOSIS OF LUNG CANCER

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Background: Lung cancer remains the leading cause of mortality from malignancy in the United States despite significant advances. With the recent validation of low dose helix computed tomography (LD-CT) as a screening modality, there have been an increased number of diagnosed peripheral lung nodules that require evaluation. Electromagnetic navigation bronchoscopy (ENB) has emerged in recent years as a novel diagnostic modality that is purported to be equivalent to CT transthoracic needle aspiration (CT-TTNA) in diagnostic yield with a superior safety profile. We set out to evaluate the diagnostic yield and the number of adverse events of ENBs performed at the Brooklyn Veterans Affairs

Hospital. **Method:** A retrospective chart review was done of ENB cases performed from 2012 until present. 45 cases were identified and chart review done to identify nodule size. location, distance to the pleura, PET-CT standardized uptake value (SUV), pathological yield, and clinical course following procedure. Two cases were excluded due to patients having been diagnosed with malignancy prior to ENB, thus 43 cases were included for final analysis. **Result:** 12 patients were identified with false negative biopsies (negative biopsy from ENB with subsequent positive pathologic diagnosis from either repeat ENB or surgical biopsy). 14 patients were found with disease, thus sensitivity of this test was calculated at 58.3%. 19 patients were found to have positive initial biopsies, thus negative predictive value (NPV) was calculated at 68.5%. There was an incidence of .04% of pneumothoraxes in our patient population whereas the incidence of pneumothorax following CT-TTA is reported to be approximately 20%.

Table 1: Sensitivity and negative predictive value (NPV) of ENB at our institution

	Malignancy	No Malignancy		
Positive Biopsy	14	0		
Negative Biopsy	10	19	65.5%	NPV
	58.3%			
	Sensitivity			

Conclusion: We demonstrated that ENB in our institution is not as sensitive a modality in ruling out malignancy as previously described. While this raises the question of the clinical utility of ENB as a diagnostic tool, it still remains significantly safer than CT-TTNA in the evaluation of peripheral lung nodules.

Keywords: Electromagnetic Navigation Bronchoscopy, lung cancer, Veterans

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-17 CLINICOPATHOLOGICAL CHARACTERISTICS OF PRIMARY LUNG CANCERS ASSOCIATED WITH EMPHYSEMATOUS BULLAE

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Background: Lung cancers associated with emphysematous bullae (EB) comprise approximately 5% of all primary lung cancers, but the clinicopathological characteristics remain unclear. This study aims to investigate the clinicopathological characteristics and postoperative prognosis of lung cancers associated with EB. **Method:** From 2008 through 2012, consecutive 517 patients who underwent complete surgical resection for primary lung cancer at our institution, were retrospectively reviewed. Lung cancer associated with EB was defined as lung cancer adjoining emphysematous airspace >1cm, without lung parenchyma, on preoperative thin-slice computed tomography scans. Among the 517 patients, 35 (6.8%) had lung cancers associated with EB (EB group). Their clinicopathological features and prognosis were retrospectively compared with those in the patients having lung cancer not associated with EB (non-EB group). **Result:** The median follow-up duration was 42 months (range, 2-85 months). The median age of EB group was 70 (39-79) years, while that for non-EB group was younger 59 (33-91) years (p = 0.07). The EB group included more men (94% vs. 6%, p < 0.01), smokers (97% vs 63%, p < 0.01), and the patients with low FEV1.0% (< 70%) (91% vs 27%, p < 0.01). In the EB group, frequency of cancer in the right upper lobe was significantly higher than in the non-EB group (60% vs 25%, p < 0.01). Histologically, non-adenocarcinomas, including squamous cell carcinoma, neuroendocrine tumor and large cell carcinoma, were common in the EB group compared with in the non-EB group (57% vs 24%, p < 0.01). Among the EB group, 16 patients (45%) were p-stage I, 16 (45%) were p-stage II, three (9%) were p-stage III, and none (0%) were p-stage IV (WHO 8th classification). The 5-year overall survival (OS) rate for EB and non-EB groups was 75% and 88%, respectively, without significant difference (p = 0.20). The 5-year recurrence-free survival (RFS) rate was also not different between EB and non-EB groups (75% vs. 79%, p = 0.85). The multivariate analysis did not demonstrate that the association with EB to be a significant prognostic factor (p = 0.39). **Conclusion:** Lung cancers associated with EB have clinicopathological features including the predominance of men, heavy-smoking history, and non-adenocarcinoma histology compared with lung cancer not associated with EB. However, in the current analysis, the survival was not different between patients with lung cancers with and without EB.

Keywords: emphysematous bullae, lung cancer

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-18 PREDICTIVE PERFORMANCE OF SEMI-QUANTITATIVE METABOLIC METRICS ON FDG-PET/CT FOR THE IDENTIFICATION OF EGFR MUTATIONS

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Background: FDG-PET/CT is highly useful in evaluating biological malingancy of lung cancer cases. The maximum standardized uptake values (SUVmax) of the primary lesion is widely reported to be associated with prognosis in lung cancer while other metabolic metrics, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have also been explored as a measure of metabolic tumor burden in recent years. Several recent reports have shown that measurement of these metabolic metrics on PET/CT could be beneficial for the identification of driver gene mutational status such as EGFR and KRAS. The purpose of this study is to investigate the role of quantitative metabolic metrics (SUVmax, MTV, TLG) in identifying adenocarcinoma harboring EGFR mutations. **Method:** We enrolled 247 patients with clinical stage I adenocarcinoma with pre- or postoperative EGFR genotyping. All the patients underwent surgical resection after preoperative FDG-PET/CT scanning during the period from January 2012 to January 2018. SUVmax, MTV, and TLG of each lung tumor were determined with Synapse Vincent System (Fujifilm Medical, Tokyo, Japan) as the volume viewer software. MTV is defined as the volume of the area of SUV 2.5 or higher while TLG was calculated as meanSUV x MTV. Correlation between age, gender, smoking history, clinical stage, SUVmax, MTV, TLG, and EGFR gene mutation status was analyzed. **Result:** A total of 114patients (46%) were identified as having EGFR mutations. Univariate analysis showed that sex (p = 0.001), smoking status (p = 0.019), SUVmax (p = 0.001), MTV (p = 0.007), and TLG (p = 0.014) were significantly associated with EGFR mutations. Multivariate analysis demonstrated that sex (p = 0.004) and SUVmax (P = 0.004) were independent predictors of EGFR mutations. The receiver operating characteristic curve yielded area under the curve values of 0.622, 0.604, and 0.609 for SUVmax, MTV, and TLG, respectively (SUVmax of 2.95, MTV of 0.10mm3, and TLG of 0.26, respectively). The frequency of EGFR mutations of patients with SUVmax < 2.95, MTV < 0.10mm3, TLG < 0.26, female, and never-smokers were 64.2%, 64.2%, 64.2%, 63.5%, and 61.2%, respectively. **Conclusion:** In clinical stage I lung adenocarcinoma, SUVmax, MTV, and TLG measured by FDG-PET/CT were associated with EGFR mutation status.

Keywords: MTV, EGFR, TLG

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-19 CT AND PET/CT PARAMETERS OF LEPIDIC PREDOMINANT PATTERN LUNG ADENOCARCINOMA AND INVASIVENESS ON PATHOLOGY

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Background: The 8th edition of TNM classification of lung cancer introduced new categories of Tis and T1mi for adenocarcinoma. Patients classified into these categories are estimated to present 100% or near-100% disease-free survival after complete resection. It is expected we are able to identify them on preoperative imaging because they might fit for limited resection. A retrospective study was conducted evaluating preoperative radiologic parameters of lepidic predominant pattern lung adenocarcinoma to predict invasiveness on pathology. **Method:** Pathologically classified 20 adenocarcinoma in situ (AIS), 27 minimally invasive adenocarcinoma (MIA) and 8 lepidic predominant

invasive adenocarcinoma (LPA) from 50 patients operated from January 2017 to March 2018 were evaluated. Preoperative CT parameters including maximum diameter, maximum area and mean CT value of the both whole lesions and solid components were evaluated. SUVmax of the lesions were measured at FDG-PET/CT images. Three experienced pathologist determined invasive size based on hematoxylin-eosin and Elastica van Gieson staining slides. Radiologic - pathologic associations were examined using Kruskal-Wallis test and the Spearman correlation coefficient. **Result:** *Increasing maximum diameter, maximum area and mean CT value of the whole lesions on CT were significantly associated with invasiveness (p = 0.04, p = 0.03 and p =0 .002, respectively). Increasing maximum diameter and maximum area of the solid components were also significantly associated with invasiveness (p < 0.001 and p < 0.001, respectively). Higher SUVmax value of the lesions was significantly associated with invasiveness (p < 0.015). However, we were not able to find any correlation between the radiologic parameters including maximum diameter of solid components and pathologic invasive size when we analyzed MIA and LPA cases. And, when we evaluated clinical T according to the 8th edition of TNM classification, the sensitivity to diagnose AIS, MIA and IPA were 57.1%, 14.8% and 87.5%, respectively, and the specificity to diagnose AIS, MIA and IPA were 97.5%, 82.1% and 48.9%, respectively,* **Conclusion:** *Both whole tumor size and solid component size increase in association with tumor invasiveness. And SUVmax value also increases with tumor invasiveness. However, it is difficult to predict pathologic invasive size based on radiologic parameters. It is expected that novel preoperative or intraoperative diagnostic tools for tumor invasiveness of lepidic predominant pattern lung adenocarcinoma will be developed.*

Keywords: lung adenocarcinoma, minimally invasive adenocarcinoma, CT

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
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P1.05-20 THERAPEUTIC CONDITION OF PHOTODYNAMIC THERAPY USING TARAPORFIN SODIUM FOR CENTRAL AIRWAY STENOSIS

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Background: Central airway stenosis is life threatening, and some kinds of debulking procedures are recommended especially for endobronchial lesions. Previous reports have shown the efficacy and safety of PDT using porphimer sodium as a photosensitizer in debulking. However, the detail of taraporfin sodium, the second generation photosensitizer in this setting has not been known well yet. Therefore, we reviewed the cases that underwent PDT using taraporfin sodium for central airway stenosis. **Method:** Consecutive patients who underwent PDT using taraporfin sodium for central airway stenosis in our institute from 2012 to 2017 were collected. The dose of the photosensitizer, the time to laser irradiation, the laser dose, the therapeutic effect and the adverse events were assessed. **Result:** Seventeen lesions were performed PDT in 9 patients (the average number of lesions was 1.9 per parson). The dose of taraporfin sodium was 40 mg/m^2, and the time from administration of the photosensitizer to laser irradiation was 5 hours in all cases. The laser dose was 150 J/cm^2 in 5 lesions, while 100 J/cm2 in 11 lesions, and 50 J/cm^2 in 1 lesion. This treatment condition was selected in accordance with PDT for central type early stage lung cancer: the dose of the photosensitizer was 40 mg/m^2, the time to laser irradiation was 4-6 hours, and the laser dose was 100 J/cm^2. Meanwhile, 2 patients were treated after electrocautery, and 1 patient was after argon plasma coagulation. Almost all patients showed improvement of airway stenosis except for 1 lesion with the laser dose of 50 J/cm^2. There was no significant difference in the effect between the laser dose of 150 J/cm^2 and 100 J/cm^2. There was no serious adverse event. **Conclusion:** PDT using taraporfin sodium is a feasible procedure with sufficient efficacy and safety for central airway stenosis.

Keywords: lung cancer, Airway stenosis, photodynamic therapy

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.05-21 CT-GUIDED BIOPSY OF LUNG LESIONS WITH OUTER CANNULA WASHING CYTOLOGY

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Background: Although several studies have reported the use of CT lung biopsy for histological diagnosis or aspiration cytology, only a few have reported on the simultaneous use of biopsy and cytodiagnosis. Our hospital has used an outer cannula washing solution cytology in conjunction with a biopsy. We examined the usefulness of outer cannula washing cytodiagnosis. **Method:** At our hospital, 37 patients (mean age, 68 [range, 33-84] years; 23 males and 14 females; 15 adenocarcinomas, 4 small cells, 3 SCC, 10 other cases, and 5 metastases) were diagnosed with pulmonary lesions between June 2016 and March 2018. While the inner needle was washed with formalin and submitted for tissue examination, the washing solution inside the outer cannula was submitted for cytodiagnosis.

Result: In all 37 patients, we successfully performed the procedure without any serious complications. In 33 patients, we observed malignant findings in histopathology or cytodiagnosis. However, we obtained only cytological malignant findings in the three patients. Although one case was negative for histological diagnosis and cytological examination, it was malignant after that. Of note, remaining three other cases were benign. The sensitivity, specificity, and accuracy of the cutting-needle histological biopsy were 88.2%, 100%, and 89.2%, respectively; of washing cytology were 82.6%, 81.3%, and 81.8%, respectively; and of histology and cytology were 97.1%, 100%, and 97.3%, respectively. Although the accuracy was 89.2% only by the conventional tissue method, it was 97.3% when combined with cytodiagnosis (P=0.072). **Conclusion:** Washing cytology of the outer cannula could be beneficial in the biopsy.

Keywords: Computed Tomography-guided Biopsy, cytology, Lung Lesion

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.05-22 NEW METHODS OF BRACHYRADIOTHERAPY CATHETER STABILIZATION IN THE AIRWAYS

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Background: Endobronchial brachytherapy(EBBT) is mainly used for palliation of obstructive symptoms, most commonly for malignancies located in the central airways (ei. trachea and main bronchi). However, the EBBT has a curative potential in those tumors, which are small to moderate in size, are not metastasized to the lymph nodes and are other wisely untreatable. Typically, EBBT is indicated in patients diagnosed with locally advanced non-small cell lung carcinoma (NSCLC) in the central airways. Endobronchial brachytherapy, as other methods of interventional bronchoscopic procedures such as use of laser, cryo or electrotherapy, and variations of mechanical airways passage maintenance, should not be understood as a marginal option from the modalities list. All of these mentioned methods are complementary and by a combination, one can achieve satisfactory clinical results **Method:** Two new methods of brachyradiotherapy catether fixation are described

. First one utilises unique star-shaped fixation device manually made from Microtech stent holding 5Fr probe in the center of airways. In the second case the brachytherapy catheter was fixed in the designated position in the trachea using a Novatech-Dumon stent (20x40 mm) and consecutively, single-dose brachytherapy of 8 Gy was applied. . **Result:** In both our referred cases, the patients undergone procedure of HDR-EBBT without any complication with the use of a fixation devices which kept an afterloading probe in selected area of the airways and allowed a symmetrical radiation distribution **Conclusion:** In our presented case studies local control of intraluminal tumor growth has been achieved with the HDR-EBBT. In the case of our first patient along with surgery and cryotherapy and in the other case along with the third-line chemotherapy based on docetaxel.

Keywords: bronchoscopy, silicone stent, brachytherapy

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.05-23 EVALUATION OF THE 8TH EDITION OF THE TNM CLASSIFICATION FOR LUNG CANCER AT A SINGLE INSTITUTION

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Background: The 7th edition has been used more than10 y ears and has proven reliable, but various problems had been indicated.The latest (8th) edition of the lung cancer staging classification was published in 2017. The purpose of this retrospective study is to make a external validation to the 8th edition of the lung cancer staging system. **Method:** Subjects included 3,229 patients who underwent pulmonary resection for primary non-small cell lung cancer.Survival characteristics were compared using the 7th and 8th editions of the staging system. **Result:**

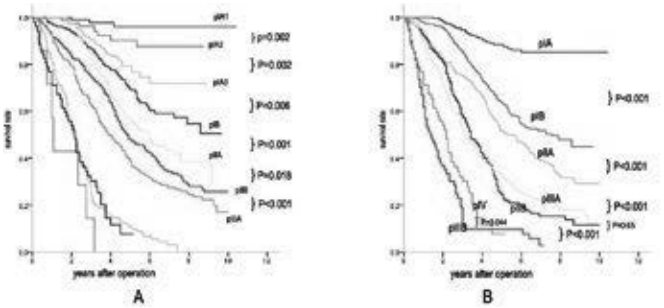

Fig. 1 Survival curves for patient subgroups stratified according to stage groupings.(The P value between each adjacent subgroup are indicated.) A. With respect to the 8th edition. B. With respect to the 7th edition.

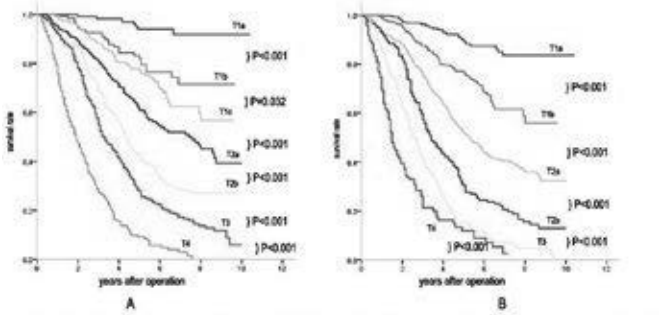

Fig. 2 Survival curves for patient subgroups stratified according to tumor size.(The P value between each adjacent subgroup are indicated.) A. With respect to the 8th edition. B. With respect to the 7th edition.

According to the 7th edition, there was no significant difference between pStages IIB and IIIA(P = 0.650), however, according to the 8th edition, there were significant differences between each adjacent stage group. Moreover, to the T descriptor(tumor size), which got most emphasis in the 8th edition, there were significant differences between each adjacent pT classification, either according to the 7th edition or the 8th edition.

Conclusion: The UICC 8th edition staging system is considered valid for non-small cell lung cancer patients and appears to be superior in defining different prognostic groups than the 7th edition.

Keywords: lung cancer, stage, 8th

P1.05 INTERVENTIONAL DIAGNOSTICS/PULMONOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.05-24 CLINICAL CHARACTERISTICS AND PROGNOSTIC ANALYSIS OF MULTIPLE PRIMARY MALIGNANT

Neoplasms in Patients with Lung Cancer

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Background: To investigate the clinical characteristics, survival status and prognostic factors of multiple primary malignant neoplasm (MPMN) patients with lung cancer. **Method:** The clinical and pathological data of 14,528 lung cancer patients who were diagnosed and treated in the affiliated cancer hospital of Zhengzhou University from January 2008 to August 2015 were retrospectively analyzed. **Result:** Of the total lung cancer patients, 2.5% (364/14,528) were MPMN cases and 3.6% (13/364) were diagnosed with 3 primary malignancies, 0.3% (1/364) with 4 primary malignancies and 96.2% (350/364) with 2 primary malignancies. Among the 350 lung cancer patients diagnosed with 2 primary malignancies, 26.6% (93/350) had lung cancer diagnosed first (LCF) and 73.4% (257/350) had other cancers diagnosed initially (OCF), whereas synchronous MPMN (SMPMN) accounted for 21.1% (74/350) and metachronous MPMN (MMPMN) accounted for 78.9% (276/350) of cases.Detection of first primary neoplasms were at an early stage for LCF patients and the age of the first lung cancer diagnosis was 59.3 years vs 55.4 years in the OCF group (P = 0.008), whereas the onset age of second primary neoplasm diagnosis was similar in both groups (62.5 and 61.6 years, P = 0.544). The median survival times of the OCF and LCF groups were 86 months vs 58 months (P < 0.001). The median survival times of MMPMN and SMPMN patients were 94 months vs 27 months (P < 0.001).Multivariate analysis showed that SMPMN, LCF and the age of the primary cancer diagnosed first (≥ 60 years) were independent factors for inferior prognosis of patients. **Conclusion:** Though LCF was diagnosed in earlier stages than OCF, the survival rate was inferior and the time until the development of the second primary malignancy was shorter than in the OCF group. SMPMN patients had a worse prognosis than MMPMN patients in both the LCF and OCF groups. Also ≥ 60 years of age at the time of the primary cancer diagnosis was an independent factor for inferior prognosis in all patients.

Keywords: metachronous, multiple primary malignant neoplasms, synchronous

P1.09 PATHOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.09-01 PD-L1 TESTING ON NSCLC CYTOLOGY SAMPLESIN A UK TEACHING HOSPITAL

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Background: Immunotherapy, specifically pembrolizumab, is now approved in the UK as first-line therapy in patients with advanced non-small cell lung cancer (NSCLC) and no activating EGFR mutation or ALK translocation if high PD-L1 expression (≥50%) can be demonstrated on tumour samples. Furthermore, second line treatment is approved with PD-L1 expression ≥1%. Initial studies were performed exclusively on histological samples. We present our experience of PD-L1 testing purely on cytology samples. **Method:** Prospectively maintained cytology databases were analysed to identify all lung cancer cytology samples from our institute tested for PD-L1 expression between January 2017 and March 2018. Cell blocks from endo-bronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) performed using rapid on-site evaluation (ROSE), FNA of other sites, pleural fluid and bronchial brush samples were prepared and immunohistochemistry performed on sections using the Dako 22c3 antibody to determine PD-L1 expression. **Result:** A total of 99 samples were tested for PD-L1. There was sufficient material for PD-L1 testing in 95% (n=94). Male 62%, female 38%, age range 26-84. EBUS-TBNA accounted for 79% of samples, percutaneous Fine Needle Aspirate (FNA) 11%, pleural fluid samples 7%, bronchial brush 2% and endoscopic ultrasound FNA 1%. Table-1 provides a breakdown of the methods of sample acquisition with adequacy rates and PD-L1 expression.

(See next page)

Table 1						
	PD-L1 samples	Adequate	Inadequate	Negative	Positive	Positivity
EBUS	78	76	2	19	57	1-50% 31
						≥50% 26
FNA	11	9	2	2	7	1-50% 2
						≥50% 5
Pleural fluid	7	6	1	0	6	1-50% 5
						≥50% 1
Bronchial brush	2	2	0	0	2	1-50% 0
						≥50% 2
EUS FNA	1	1	0	1	0	1-50% 0
						≥50% 0
Total	99	94	5	22	72	1-50% 38
						≥50% 34

Overall PD-L1 expression was highly (≥50%) positive in 34/94 (36%), low (≥1-50%) positive in 38/94 (40%), and negative in 22/94 (23%). The proportion of patients expressing high (≥50%) PD-L1 positivity in the different pathological subtypes were: adenocarcinoma 23/62 (37%), squamous cell carcinoma 8/21 (38%), NSCLC-NOS 3/9 (33%). The proportion of patients with low (≥1-50%) PD-L1 positivity were: adenocarcinoma 27/62 (44%), squamous cell carcinoma 9/21 (43%), NSCLC-NOS 2/9 (22%). Neither of 2 neuroendocrine NSCLC tested expressed PD-L1 **Conclusion:** Our experience demonstrates that cytological samples obtained at our institute are suitable for PD-L1 testing with an adequacy rate of 95%.

Keywords: Immunotherapy, EBUS, cytology

P1.09 PATHOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.09-02 PD-L1 EXPRESSION PATTERN IN LARGE CELL NEUROENDOCRINE CARCINOMA OF THE LUNG: THE GFPC 03-2017 "EPNEC" STUDY.

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Background: Large cell neuroendocrine carcinomas of the lung (LCNECs) are rare neoplasms with few therapeutics options especially for stage IV diseases. Pathological diagnostic of LCNECs may be difficult with low interobserver reproducibility and need immunohistochemical (IHC) staining. Immune checkpoint inhibitors targeting tumoral and immune cells interaction have revolutionized the treatment of NSCLC, but few data's are available on LCNECs immune environment and particulary the expression of PD-L1 on both tumors (TC) and immune infiltrating (IC) cells. The objective of the present study is to determine the pattern of PD-L1 staining in a cohort of LCNECs patients. **Method:** Clinical files and tumors biopsies of patients (pts) with a LCNEC diagnosed between 01.01.2014 and 31.12.2016 were retrospectively collected (GFPC 03-2017). All histological samples were centrally reviewed by a panel of six independent pathologists, according to the WHO 2015 classification. LCNEC was confirmed and PD-L1 expression was determined both in TC and IC, using the anti-PD-L1 antibody 22C3 (kit and automat Dako). PD-L1 expression was scored on TC as the percentage of PD-L1 positive cells (0 to 100%). PD-L1 expression on IC was determined as follows: IC0: positive IC representing<1% of the tumor surface; IC1: positive IC representing>=1% but<5% of the tumor surface; IC2: positive IC representing>=5% but<10% of the tumor surface; and IC3: positive IC representing>10% of the tumor surface. **Result:** Eighty-six pts were initially included in the study.Twenty-eight (32%) of them were excluded for non-LCNEC diagnosis after review. Among the 58 remaining pts with confirmed LCNEC, five (8%) had a mixed histology with a NSCLC component.The mean age of the population was 65 years, mainly mens (86%) and former or current heavy smokers (93%). Fifty-five and 51 tumors samples were respectively available for TC and IC PD-L1 IHC expression. PD-L1 expression on TC was found in only 12% of the samples (7/55), while 76% (39/51) of the samples shows IC PD-L1 positive, with respectively 18 (35%) IC3, 8 (14%) IC 2, and 13 (25%) IC1. **Conclusion:** Histological diagnosis of LCNEC remains difficult, and prospective studies concerning patients with LCNEC should include a centrally pathological review of tumors.The PD-L1 expression pattern looks different for LCNEC in comparison to other lung carcinomas, as few TC were found positive although IC were frequently positive, half of the tumors having high PD-L1 IC infiltration (IC3/2). This PD-L1 pattern may suggest a potential effectiveness of therapeutic anti PD-L1 antibodies and this hypothesis have to be adressed in clinical trials.

Keywords: large cell neuroendocrine carcinoma, PD-L1 expression, Immune infiltrating cells

P1.09 PATHOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.09-03 CHALLENGES IN PD-L1 IMMUNOEXPRESSION IN LIQUID BASED CYTOLOGY SAMPLES OF ADVANCED STAGE NON-SMALL CELL LUNG CARCINOMAS

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Background: Study of programmed death-ligand 1 (PD-L1) expression is essential in patients of advanced lung cancer to determine their eligibility and predict responsiveness for immune-checkpoint inhibitors. Lung cancer is frequently diagnosed on cytology specimens. Although PD-L1 IHC assays are validated on formalin fixed paraffin embedded (FFPE) tissue, evidences are present in literature which showed high concordance of cytology samples with paired biopsies. However liquid based cytology (LBC) processed specimens have not been tested for PD-L1 expression. **Method:** Immunohistochemistry using the anti-PD-L1 clone SP263 was performed on BD SurePath LBC processed bronchial washing and brushing smears and paired FFPE endobronchial biopsy specimens. The presence of 100 viable tumor cells was considered adequate for PD-L1 testing. Staining was interpreted positive if membranous and/or cytoplasmic protein expression at any intensity greater than background staining was detected in at least 25% of tumor cells. **Result:** There were 26 patients with 13 adenocarcinomas and 13 squamous cell carcinomas which were diagnosed by bronchial brushings, washings and concurrently obtained endobronchial biopsy. Twelve out of total 26 biopsies showed cytoplasmic and membranous PD-L1 positivity in >25% tumor cells (46%). Corresponding LBC smear showed PD-L1 positivity in 9 cases establishing concordance of 88.4%. No negative case was positive on cytology. However, there were following challenges while interpreting PDL1 IHC on LBC processed smears: 1. Thick clusters of cells: LBC can cause rounding up of epithelial cells and create thick clusters of tumor cells. Therefore, it was necessary to see under higher magnification (40x) for proper interpretation of membrane staining. 2. Identification of tumor cells: Although identification of tumor cells was done before PD-L1 staining, after staining they were interpreted only on higher magnification to better differentiate them from alveolar macrophages. 3. PD-L1 staining in macrophages: Five cases showed very strong cytoplasmic positivity in macrophages. Since tumor cells showed cytoplasmic and membranous positivity it was easy to differentiate tumor cell positivity from macrophage positivity. Necrotic background in one case stained strongly with PD-L1 immunocytochemistry. 4. Nuclear positivity of PD-L1 positivity: One case, where corresponding biopsy was positive for PD-L1 IHC, showed aberrant nuclear positivity. **Conclusion:** PD-L1 IHC can be performed on LBC processed smears. Though there are challenges in interpretation of immunoexpression inherent to the LBC smears, they can be used in situations when histology material is not available. Future studies are needed to determine their ability to predict response to immunotherapy.

Keywords: PD-L1, lung cancer, immunocytochemistry

P1.09 PATHOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.09-04 OPTIMIZATION OF PD-L1 TESTING SPECIMEN FLOW IN THE GREATER HAMILTON, ONTARIO REGION

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Background: Immunotherapy targeted at the programmed cell death 1 (PD-1) receptor and its ligand (PD-L1) is a new treatment option for non-small-cell lung cancer (NSCLC). Immunohistochemistry (IHC) for the PD-L1 protein has been shown to predict response. The 22C3 IHC assay is the only clinically validated PD-L1 test. We present the Hamilton, Ontario, Canada experience of local PD-L1 analysis using the 22C3 assay including both histology and cytology specimens. **Method:** All data for requests for PD-L1 testing from within Hamilton were collected for one year. Unstained slides were cut for IHC analysis. Both histology and formalin fixed cytology specimens were accepted. Slides were sent for PD-L1 staining centrally at Dynacare in Bowmanville, Ontario, Canada. IHC interpretation was done in Hamilton. The assay was positive if ≥50% of tumour cells (TCs) had any intensity staining. The assay was negative if no TCs had staining. The assay was interpreted as low positive if 1-49% TCs had any intensity staining. Samples with less than 100 cells were considered inadequate. Turn around-time was defined as the accession date to PD-L1 sign out date. **Result:** 401 samples were evaluated; 108 cytology(C) and 293 histology(H). 36% of samples tested positive (43%:C;33%:H); 20% of samples tested low positive (14%:C;23%:H); 39% of samples tested negative (29%:C;42%:H); 5% were insufficient for evaluation (15%:C;1%:H). Chi-squared analysis identified a statistically significant ($\chi^2 < 0.02$) difference in the distribution of test results comparing histology and cytology. The mean turn-around-time (TAT) was 28.9 days (range 12-144). TAT varied by hospital of origin. TAT for PD-L1 results from the hospital with dedicated thoracic pathologists was on average 10 days shorter than from other Hamilton hospitals. TAT in our hospital with dedicated thoracic pathologists improved with time from a mean of 49 days to a mean of 22 days while TAT from other hospitals did not improve over the course of the year. **Conclusion:** Our cohort mirrors findings in the literature and demonstrates that the 22C3 assay for PD-L1 can be done on both histology and cytopathology specimens; however, the insufficient rates are higher for cytopathology. Cytopathology specimens have a higher PD-L1 positivity rate, a finding that may reflect differences in tumour biology and/or stage in this subgroup. Turnaround times were different based on the hospital of origin, and suggest centralized specimen collection or use of dedicated thoracic pathologists may be advantageous. Correlation with clinical outcomes on our cytology cases will be presented in a separate abstract.

Keywords: quality improvement, PD-L1, biomarker testing

P1.09 PATHOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.09-05 WHY DOES PD-L1 (22C3) EXPRESSION RATE SHOW DIFFERENCE AMONG REGIONAL HOSPITALS?

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Background: The immune checkpoints inhibitors, such as anti-programmed cell death 1 (PD-1) receptor antibodies and anti-PD-L1 (its major ligand against PD-1) were applied for several advanced cancer. On 2017, Pembrolizumab was approved for non-small cell lung cancer (NSCLC) as 2nd immune checkpoint inhibitor in Japan. At same time, immuneohistochemical examination by anti-PD-L1 antibody (22c3) was approved as companion diagnostic staining for Pembrorizumab treatment. However, PD-L1 expression rate shows quite difference among hospitals in routine clinical examination. The purpose of this study is probed the reason of the difference in each hospital. **Method:** The questionnaire about PD-L1 staining was sent via e-mail to 14 Hospitals in Ibaraki prefecture, Japan. The questionnaire included PD-L1 expression in each histology (adenocarcinoma (AD), squamous cell carcinoma (SQ), and other NSCLC, and fixation condition. **Result:** Eleven hospitals (A to K) answered with the questionnaire. Total staining cases were 651: ADs were 384, SQs were 185 and the other NSCLCs were 79. The rates of PD-L1 No expression showed 18% to 71% among each hospitals. (figure 1 and 2)

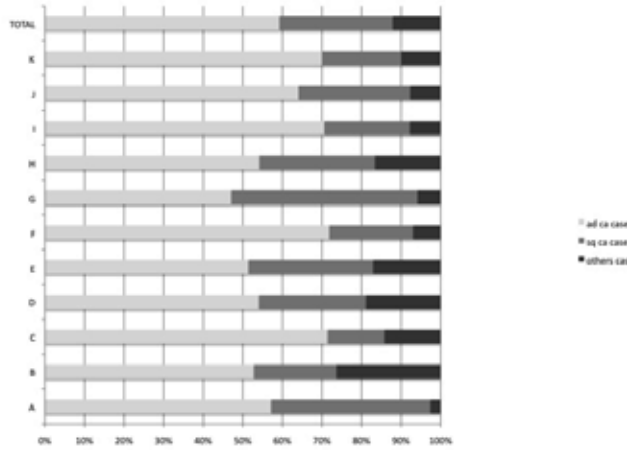
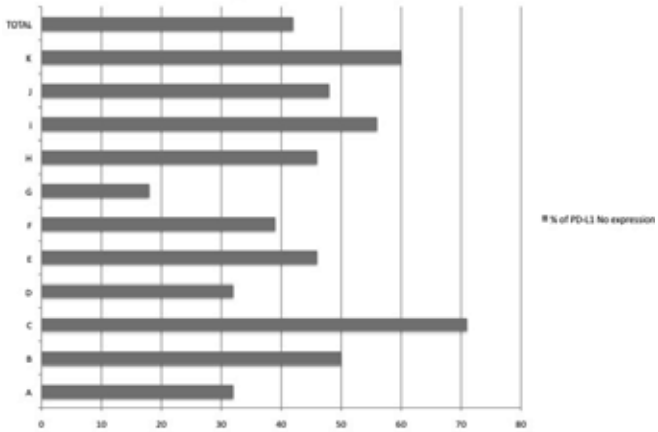


Figure 2: The rate of PD-L1 No expression



Conclusion: The result of TPS is quite different from clinical study. The reason is thought to be caused of the histological configuration was appreciably difference among regional hospitals.

Keywords: PD-L1(22c3), Expression rate, histological configuration

P1.09 PATHOLOGY
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P1.09-06 THE INCIDENCE OF PD-L1 IN NSCLC AND ITS CORRELATION WITH DRIVER MUTATIONS IN TURKISH PATIENTS; A SINGLE CENTER EXPERIENCE.

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Background: PD-L1 testing have become the new standard of care for patient diagnosis in advance Non-Small Cell Lung Carcinoma (NSCLC). NSCLC also is characterized by driver mutations in epidermal growth factor receptor (EGFR), alterations anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1). This study aimed to evaluate and to compare with immunotherapy related biomarker PD-L1 and driver mutations biomarkers (EGFR, ALK, and ROS1) in Turkish patients with NSCLC retrospectively. PD-L1 positivity also was examined whether related to some clinico-pathological parameters in NSCLC patients. **Method:** A retrospective cohort composed of 650 consecutive patients diagnosis with NSCLC were tested for PD-L1 between November of 2016 and February of 2018. PD-L1 immunostaining was performed using and 22c3 (DAKO platform) or SP263 (Ventana platform). Pathology report were reviewed to collect patient demographic data, smoking status, tumor sup-types, and specimen types. For EGFR mutational analysis were examined using a real time assay (The **cobas v2** ® EGFR Mutation Test). ALK and ROS1 translocations were evaluated by IHC + FISH method. For statistical analysis Pearson chi -square test was used. **Result: TABLE I**

(See next page)

Parameter	PD-L1 status				Statistic
	total	<1%	1-49%	≥50%	P-value (Pearson Chi-Square)
Age					
≤60	282 (44.4%)	80 (28.4%)	110 (39.0%)	92 (32.6%)	0.070
>60	353 (55.6%)	113 (32.0%)	154 (43.6%)	86 (24.4%)	
Gender					
female	140 (22.0%)	46 (32.9%)	65 (46.4%)	29 (20.7%)	0.090
male	495 (78.0%)	147 (29.7%)	199 (40.2%)	149 (30.0%)	
Smoking					
no	77 (14.4%)	27 (35.1%)	37 (48.1%)	13 (16.9%)	0.072
yes	456 (85.6%)	143 (31.4%)	179 (39.3%)	134 (29.4%)	
Pathology					
adenoca	404 (63.8%)	134 (33.2%)	171 (42.3%)	99 (24.5%)	0.018
non-adenoca	229 (36.2%)	59 (25.8%)	91 (39.7%)	79 (34.5%)	
EGFR status					
wild type	429 (90.7%)	120 (28.0%)	179 (41.0%)	130 (30.3%)	0.002
exon 19	26 (5.5%)	17 (65.4%)	7 (26.9%)	2 (7.7%)	
exon 21	13 (2.7%)	6 (46.2%)	6 (46.2%)	1 (7.7%)	
others	5 (1.1%)	2 (40.0%)	1 (20.0%)	2 (40.0%)	
ALK status					
negative	414 (94.7%)	116 (28.0%)	177 (42.8%)	121 (29.2%)	0.890
positive	23 (5.3%)	6 (26.1%)	11 (47.8%)	6 (26.1%)	
ROS1 status					
negative	412 (97.6%)	116 (28.2%)	179 (43.4%)	117 (28.4%)	0.251
positive	10 (2.4%)	1 (10.0%)	4 (40.0%)	5 (50.0%)	

Clinico-pathological characteristics of NSCLC patients (n=650) and their relationships with PD-L1 expression were presented on Table I. **Conclusion:** This is the first study to compare PD-L1 expression with clinico-pathological parameters in Turkish NSCLC patients (n=650). The majority of Turkish patients were smokers (85.6%). Although there was no statistical significance between PD-L1 positivity and smoking status, smoker patients showed more PD-L1 high tumor proportion score (H-TPS = ≥50%) than non-smoker patients; 29.4% to 16.9% respectively. The majority of patients were Adenocarcinoma patients (63.8%). PD-L1 positivity was higher in Non-adenocarcinoma patients than Adenocarcinomas **(p=0.018).** This study demonstrated that PD-L1 positivity in lung adenocarcinoma, was strongly associated with EGFR wild-type status **(p=0.002)** which was parallel to literature. There was no correlation between ALK and ROS1 translocation with PD-L1 status.

Keywords: PD-L1 status, NSCLC, Driver mutation

P1.09-07 PD-L1 PROTEIN EXPRESSION IS A PREDICTOR OF BENEFIT FROM ADJUVANT CHEMOTHERAPY IN RESECTED NON-SMALL CELL LUNG CARCINOMA

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Background: Programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) are important targets of immunotherapy and its expression has been closely correlated with response and survival benefit from anti-PD-1/PD-L1 immune checkpoint inhibitor therapies in advanced non-small cell lung carcinoma (NSCLC). But it is still unclear whether PD-L1 is a prognostic or a predictive marker of adjuvant chemotherapy. The aim of this study is to examine the prognostic value of PD-L1 protein expression and its predictive role for adjuvant chemotherapy in surgically resected NSCLC. **Method:** A total of 407 NSCLC were examined. The male:female ratio was 288:119; the age range was between 38 and 85 years of age and the mean age was 68.5 years. Pathological stage's ratio (I:II:III) was 147:154:106. Adenocarcinoma:Squamous cell carcinoma:Others' ratio was 251:135:21 in histology. Adjuvant chemotherapy was performed in 173 patients. The follow up duration was from 0.4 months to 168.7 months and the mean duration was 61.9 months. Tissue microarray was constructed and PD-L1 protein expression was analyzed using immunohistochemistry (clone SP263, Ventana Medical Systems. Inc., Tucson, AZ). The PD-L1 staining percentage in tumor cells were classified as follows: Negative, 0%; Weak positive, 1-49%; Strong positive, 50-100%. The score of PD-L1 staining was correlated with clinicopathological backgrounds, molecular features, patient outcome and potential benefit of adjuvant chemotherapy. **Result:** The score of PD-L1 staining was as follows: Negative, 265 (65%); Weak positive, 82 (20%); Strong positive, 60 (15%). PD-L1 expression status was associated with sex, smoking history, pathological stage, histology, p53 protein expression, MIB-1 labeling index. 5-year overall survival (OS) was as follows: Negative, 63.5%; Weak positive, 62.1%; Strong positive, 54.8% and 5-year recurrence-free survival (RFS) was as follows: Negative, 51.6%; Weak positive, 55%; Strong positive, 42.5%, respectively. These results were not statistically significant. Untreated patients with a strong positive PD-L1 expression had significantly worse OS than patients with a negative PD-L1 expression {hazard ratio (HR)=1.98; 95% CI, 1.21-3.24; p=0.006}. However, patients with a strong positive PD-L1 expression had a significantly better survival benefit from adjuvant chemotherapy (HR=0.43; p=0.03) compared with patients with a negative PD-L1 expression (HR=1.04; p=0.82). **Conclusion:** PD-L1 protein expression is not a prognostic marker, however it is a significant predictive marker of benefit from adjuvant chemotherapy in resected NSCLC.

Keywords: PD-L1, Predictive, chemotherapy

P1.09-08 INTEGRATING NGS INFORMATION FOR STAGING MULTIPLE LUNG ADENOCARCINOMA: A MCGILL UNIVERSITY HEALTH CENTRE RETROSPECTIVE STUDY.

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Background: The incidence of patients with multiple primary lung adenocarcinoma (MPLC) is increasing and the optimal management of these patients remains unclear. Distinguishing between MPLC and intrapulmonary metastases is at the heart of the diagnostic dilemma. The Comprehensive Histologic Assessment (CHA) relies on microscopic examination including histological subtypes, cytological and stromal features. CHA has shown a good reproducibility but with a non-negligible rate of disagreement, even between expert pathologists. Moreover, predictive biomarker testing has become standard of care for lung cancer patients and the use of Next-Generation Sequencing (NGS) is now widely available. The goal of this study was to evaluate how the NGS information may be integrated in the diagnostic strategy for distinguishing between MPLC and patients with stage III/IV disease. **Method:** We conducted a retrospective study of all surgical patients with > 1 synchronous lung carcinoma over two years. We identified 59 cases and reviewed initial clinical, pathological and molecular reports. Patients having multifocal lung adenocarcinoma with prominent lepidic component or an adenocarcinoma associated with another histological type were considered as synchronous primaries and not tested for molecular aberrations. The NGS panel analysis using an Illumina miSeq platform included the following genes: *AKT1, BRAF, EGFR, ERBB2, FOXL2, GNA11, GNAQ, KIT, KRAS, MET, NRAS, PDGFRA, PIK3A, RET*, and *TP53*. **Result:** Histologically, the majority were considered as MPLC with only four suspected metastases. Twenty-five patients had adenocarcinoma with prominent lepidic component and one case had two different histological differentiations (adenocarcinoma and squamous cell carcinoma). Most of the suspected synchronous primary tumours had different mutations in the separate tumours. Relevant mutations were found in *KRAS* and *P53* genes, with fewer mutations in *EGFR*, *PIK3CA* and *BRAF* genes, in accordance with known frequencies. In 12% of the cases, the NGS was not informative with no molecular mutation in either tumours. One case was reclassified from MPLC to intra-pulmonary metastases and restaged after NGS. For one patient, a *TP53* mutation allowed us to reclassify two nodules as metastases from a previous adenocarcinoma originally diagnosed in 2012. In one patient having three separate nodules, different *KRAS* and *TP53* mutations allowed the diagnosis of two nodules as intrapulmonary metastases and one contralateral nodule as synchronous primary adenocarcinoma. **Conclusion:** Although CHA is an efficient method for diagnosing MPLC from intra-pulmonary metastases there are still difficult cases with a risk of misdiagnosis. Integrating NGS analysis in the diagnostic strategy may lead to improved quality and accuracy in the staging of MPLC.

Keywords: Synchronous primary tumours, Comprehensive histologic assessment, next-generation sequencing

P1.09-09 EVALUATION OF A NOVEL ROS1 IMMUNOHISTOCHEMISTRY CLONE (SP384) FOR THE IDENTIFICATION OF ROS1 REARRANGEMENTS IN NSCLC PATIENTS

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Background: After the approval of crizotinib in *ROS1* rearranged NSCLCs, the importance of accurately identifying those patients has never been greater. Although the recently updated guideline for molecular testing supports the use of ROS1 IHC as a screening test, to the best of our knowledge, only one ROS1 clone is commercially available and most published comparison studies involve a relatively small numer of positive cases. This situation prompted us to investigate a novel ROS1 IHC antibody in a large series of *ROS1* positive NSCLCs samples. **Method:** Thirty-nine *ROS1* FISH-positive (i.e., gold standard) samples from patients with NSCLCs procured at 22 hospitals were used for this

study. In addition, 20 consecutive *ROS1* FISH-negative samples from NSCLCs diagnosed at the referral institution were included as negative controls. The material available for all tumors had been formalin-fixed and paraffin-embedded. The specifics of formalin fixation were unknown. All specimens were independently screened for ROS1 expression by two IHC antibodies (clone D4D6 from Cell Signaling Technology and clone SP384 provided by Ventana Medical Systems, Inc.) according to previously published methodology or the manufacturer´s instructions. FISH-validated *ROS1*-positive external controls were included in all the slides. The slides were reviewed by two pathologists blinded to FISH results. The results of both ROS1 IHC assays were evaluated using a modified H-score: strong cytoplasmic staining (3+), clearly visible using a ×2 or ×4 objective; moderate staining (2+), requiring a ×10 or ×20 objective to be clearly seen; and weak staining (1+), cannot be seen until a ×40 objective is used. Both anti-ROS1 IHC staining results were finally interpreted using a binary scoring system: positive (3+ or 2+) or negative (1+ or 0). **Result:** In *ROS1* FISH-negative cases, positive immunoreactivity (3+ or 2+) was observed in 25% and 5% of samples by SP384 and D4D6, respectively. In *ROS1* FISH-positive cases, positive expression above the threshold was always present with both antibodies except for one sample that was only stained with SP384. In 4 positive cases (10.3%) by SP384 and 22 positive tumors (56.4%) by D4D6, we noted significant intratumoral heterogeneity, ranging from weak to strong protein expression. **Conclusion:** We have studied a very large series of *ROS1* FISH-positive NSCLCs with a novel IHC clone, which showed excellent sensitivity. The predominantly homogeneous and intense staining may support the use of a dichotomous scoring approach, before confirmation with FISH or a molecular method. Funding: I+D+I 2013-2016/Feder. ISCIII: PI14/01176

Keywords: FISH, ros1, Immunohistochemistry

P1.09 PATHOLOGY
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P1.09-10 TARGETED SEQUENCING OF PULMONARY ENTERIC ADENOCARCINOMA REVEALS DISTINCTIVE MUTATION PROFILE FROM CONVENTIONAL TYPE OF LUNG ADENOCARCINOMA

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Background: Pulmonary primary enteric adenocarcinoma (PEAD) is a rare subtype of lung cancer, which is defined in the new edition of 2015 WHO classification. However, genetic profiling and information about targeted therapy of PEAD remain unclear. **Method:** Resected 56 cases of PEAD were retrospectively reviewed. The pathological diagnosis of PEAD was confirmed by immunohistochemistry based on morphology and over 1 year's follow-up. We use targeted ultra-deep sequencing to test 56 therapeutically relevant genes alterations of PEAD. **Result:** The majority of PEAD patients were male (41/56, 73.2%). Molecular analysis revealed that KRAS was the most frequently mutated gene (18/56, 32.1%) with no targetable mutation co-existence, and then EGFR (9/56, 16.1%), ERBB2 exon 20 insertion mutations (4/56, 7.1%) and ERBB2 amplification (8/56, 14.3%). 3 cases harboring rare fusion genes were identified, TACC3-FGFR3 (2/56, 3.6%) in 2 cases and CD74-NRG1 in one case, respectively. APC gene mutation was negative in all cases. One postoperative patient with EGFR exon 21 L858R mutation was treated with 4 cycles' NP chemotherapy regimen. PET-CT found the progression lesion of right rib. Treatment was switched to gefitinib for 8 monthly cycles. Response was poor with brain metastasis. Patient received gamma knife treatment. And then, the results of molecular testing showed no EGFR T790M mutation by using the pleural effusion specimen. Pemetrexed regimen was employed to patient. Follow-up of the patient remains ongoing. **Conclusion:** Pulmonary primary enteric adenocarcinoma exhibited distinctive features of genetic profile. Despite KRAS appearing as the most important mutated gene in PEAD tumors, PEAD patients with sensitive mutations were eligible for targeted therapy.

Keywords: genetic profile, Targeted therapy, pulmonary enteric adenocarcinoma

P1.09 PATHOLOGY
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P1.09-11 IMMUNOHISTOCHEMICAL ASSESSMENT OF BRCA1 ASSOCIATED PROTEIN-1 (BAP1) IN PULMONARY MUCOEPIDERMOID CARCINOMAS

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Background: Primary pulmonary mucoepidermoid carcinomas (PMEC) are rare tumors that account for <1% of all lung carcinomas. They are presumed to originate from the minor salivary glands lining the tracheobronchial tree. PMEC are the most common malignant salivary gland tumors of tracheobronchial tree. Despite recent advances in diagnosis and treatment, there has not been much improvement in the outcome of patients with MECs, thus necessitating the identification of novel targeted therapeutic agents. Comprehensive genomic profiling has recently revealed genomic aberrations in *BRCA1 associated protein-1* (*BAP1)* gene in a subset of their non-pulmonary salivary gland counterparts. We conducted this study to identify loss of BAP1 by immunohistochemistry (IHC) in a cohort of PMECs. **Method:** Cases of PMECs were retrieved from the departmental archives. Hematoxylin and eosin stained sections were reviewed. Immunohistochemistry for BAP1 was performed on formalin fixed paraffin-embedded tumor sections. **Result:** Twenty-five PMEC cases were retrieved, out of which sufficient tumor tissue for IHC was available only in 15 PMECs. Thirteen (86.7%) tumors were tracheobronchial in location, while two (13.3%) were intraparenchymal. All were low grade MECs. On immunohistochemistry, BAP1 nuclear staining was retained in all cases (100%), irrespective of tumor location or grade. **Conclusion:** Identification of easily applicable techniques to detect *BAP1* loss in PMECs is needed for therapeutic decisions. Using IHC, loss of BAP1 staining was not seen in any of our cases, suggesting either the extreme rarity of BAP1 loss in PMEC or insensitivity of BAP1 IHC to detect aberrations at genomic level. Analysis of aberrations in *BAP1* gene by genomic approaches in PMECs may be done before excluding the possibility of *BAP1* gene as a predictive biomarker for targeted therapies.

Keywords: Primary pulmonary mucoepidermoid carcinomas, BRCA1 associated protein-1, Immunohistochemistry

P1.09 PATHOLOGY
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P1.09-12 SIMULTANEOUS PLATFORM OF GENOTYPING EGFR, ALK, AND ROS1 IN PATIENTS WITH NSCLC HIGHLIGHTS CORRELATION OF ROS1 AND PD-L1 EXPRESSION

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Background: *ROS1*oncogene rearrangement is targetable oncogene of non-small-cell cancer (NSCLC) and recently approved for crizotinib. Prior to drug approval, we integrated *ROS1*fluorescent in situ hybridization (FISH) screening test in our routine simultaneous genotyping platform. Furthermore, the frequency of overlap of above oncogenic aberration with programmed death ligand 1 (PD-L1) in routine clinical practice is not well known in Asian cohort. **Method:** Reflex simultaneous genomic screening panel of *EGFR*by PNA clamping, *ALK*and *ROS1*by FISH was performed on all NSCLCs at the time of pathologic diagnosis in our institution. PD-L1 22C3 assay kit was then integrated in our routine biomarker test panel. We retrospectively evaluated genetic aberration, clinicopathologic characteristics and PD-L1 status. **Result:** Of 407 consecutive NSCLC patients, simultaneous genotyping identified 14 (3.4%) *ROS1*and 19 (4.7%) *ALK* rearrangements,106 (26%) *EGFR*(26%) mutations in tumors. All three genetic aberrations shared similar clinical features including younger age, female, adenocarcinoma, and advanced stage. PD-L1 assay was performed on 130 consecutive NSCLC samples. High PD-L1 expression (50%) was seen in 22.3% of tumors. PD-L1 expression (≥ 1%) was significantly associated with *EGFR Wild type*status, while *ROS1*rearrangement was associated with High PD-L1 TPS (≥ 50%). Of 14 cases with *ROS1*rearrangement, 5 (35.7%) showed High PD-L1 expression. **Conclusion:** In our routine simultaneous biomarker screening of NSCLCs, 22C3 PD-L1 high expression was frequently overlapped with *ROS1*rearrangement in comparison to its negative correlation with *EGFR*mutation. PD-L1 expression status may not be characterized according to status of oncogenic driver mutation.

Keywords: ros1, non small cell lung cancer, PD-L1

P1.09 PATHOLOGY
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P1.09-13 DETECTION OF ACTIONABLE MUTATIONS IN PLASMA CFDNA SAMPLES FROM NSCLC PATIENTS USING A NOVEL AMPLICON-BASED FIREFLY NGS ASSAY

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Background: Detection of EGFR, KRAS and BRAF mutations can help guide cancer treatment for non-small cell lung cancer (NSCLC) patients. To identify an easy to use, accurate, multiplex molecular diagnostic assay, we evaluated the performance of a novel next-generation sequencing (NGS)-based cell-free DNA (cfDNA) assay, Firefly assay, which employs a concatemer-based noise suppression mechanism with an amplicon workflow. **Method:** Performance of amplicon based Firefly assay, with a panel covering EGFR, BRAF, and KRAS mutations designed for targeted therapy selection of NSCLC was first evaluated using a cfDNA reference standard and blank control samples. This panel was then used to analyze plasma cfDNA samples from 134 NSCLC cancer patients and 50 non-cancerous controls, and results were compared with tumor tissue ARMS and cfDNA ddPCR results. **Result:** Firefly assay demonstrated superior sensitivity and specificity with median detection of 100% at allele frequency of 0.1% for 20ng of cfDNA and zero false positive in all blank control samples. In cfDNA from plasma collected before treatment, EGFR mutation detection by Firefly assay was 94% concordant with tumor tissue ARMS. Firefly assay demonstrated strong per-variant detection-rate concordance (98%) and allele frequency concordance (R2 = 0.95) when compared with cfDNA ddPCR result. **Conclusion:** The amplicon-based Firefly assay offers multiplex capacity, *de novo* variant detection, high sensitivity and specificity. Thus, Firefly assay is a kitable NGS solution for cfDNA analysis, which can help guide targeted therapy selection, drug resistance detection, and disease monitoring in NSCLC and other cancer patients.

Keywords: non-small cell lung cancer (NSCLC), liquid biopsy, amplicon-based next-generation sequencing (NGS)

P1.09 PATHOLOGY
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P1.09-14 ANALYSIS OF REAL-WORD MUTATIONS OF LUNG CANCER DRIVER GENES IN 3081 PATIENTS FROM CHINA

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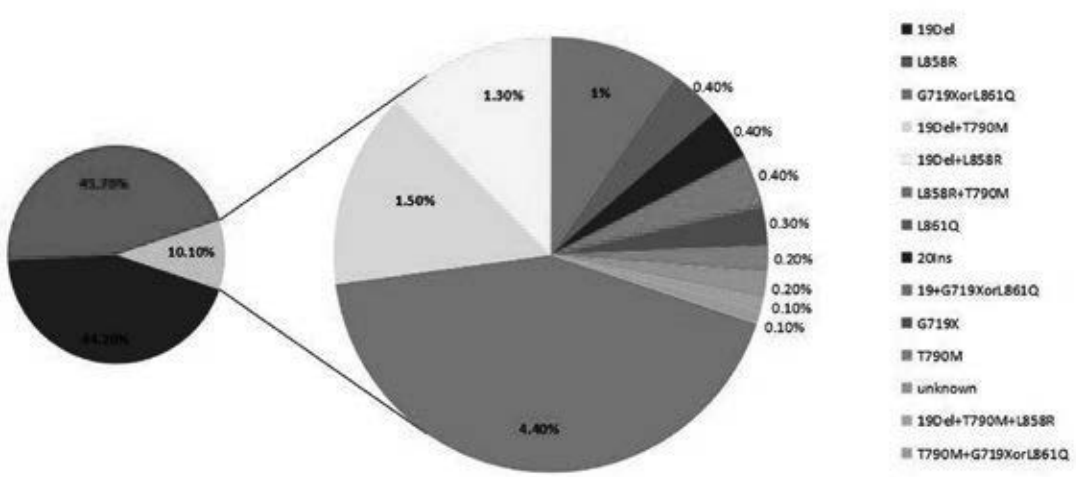
Background: Patients with different races and regions have different mutation characteristics in driver genes. This study included 3081 lung cancer patients that were detected for three major driver genes from five regions of China. **Method:** EGFR, EML4-ALK and ROS1 gene mutations were detected by fluorescence quantitative PCR (all use the same kit from AmoyDx). Chi-square test and logistic regressive analysis were used to analyze the clinicopathological features. **Result:** From January 1 to December 31, 2017, a total of 1,449 driver genes were detected mutations (47.03%). The EGFR gene mutation rate was 40.1% (1259/3081), the EML4-ALK was 5.5% (169/3081), and the ROS1 was 1.3% (39/3081). EGFR and EML4-ALK coexistence in 17 cases (0.5%), 1 case of EGFR and ROS1 coexistence (0.03%). The EGFR gene mutation sites were mainly 19Del (557/3081) and 21 exon L858R (575/3081). The proportions of EGFR mutation sites are shown in the figure. EGFR gene mutation was negatively correlated with EML4-ALK and ROS1. Patients with EGFR, EML4-ALK, and ROS1 mutations have different population characteristics, which were listed in the table.



Logistic analysis of EGFR, ALK, ROS1 gene mutation

Clinical feature	EGFR Number of positive	EGFR P value	EGFR Exp(B)	EGFR 95% Confidence Interval for Exp(B) Lower Bound	EGFR Upper Bound	ALK Number of positive	ALK P value	ALK Exp(B)	ALK 95% Confidence Interval for Exp(B) Lower Bound	ALK Upper Bound	ROS1 Number of positive	ROS1 P value	ROS1 Exp(B)	ROS1 95% Confidence Interval for Exp(B) Lower Bound	ROS1 Upper Bound
Gender															
Male	770					80					12				
Female	481	0.000*	2.377	1.657	3.043	88	0.392	0.938	0.580	1.477	20	0.636	1.453	0.575	3.021
Age(year)							0.008*					0.018*			
<50	384	0.703	1.084	0.790	1.379	69	0.008*	0.986	3.129	7.835	12	0.005*	3.435	1.683	8.906
50~60	373	0.806	0.966	0.802	1.212	72	0.008*	3.461	2.267	5.223	15	0.060	2.181	0.868	4.904
>60	781					47					12				
Smoke status															
No	881	0.005*	1.450	1.114	1.838	115	0.068*	1.882	1.691	2.027	30	0.373	1.411	0.584	4.504
Yes	372					54					2				
Histology							0.998					1.000			
Adeno	1150	0.000*	7.530	5.645	16.000	148	0.263	3.074	0.395	24.002	38	1.000	1.231	0.600	
Squamous	32	0.515	0.757	0.328	1.744	14	0.132	4.038	0.836	36.888	0	0.987	2.24257	0.000	
Adenosquamous	39	0.000*	8.960	3.723	21.995	2	0.586	2.085	0.181	23.945	0	1.000	0.797	0.000	
Others	9					1					0				
Stage							0.067*					3.34			
I	395					25					4				
II	394	0.392	0.862	0.497	1.148	23	0.491	1.252	0.889	2.279	5	0.258	2.149	0.549	8.120
III	211	0.002*	0.457	0.502	0.863	37	0.057	1.088	0.986	2.889	12	0.024*	3.822	1.188	13.222
IV	274	0.432	0.904	0.798	1.150	83	0.008*	1.942	1.172	3.128	15	0.058	2.833	0.840	8.867
ALK															
-	1258	0.000*	12.428	7.189	21.454	—					38				
+	17					—					0				
ROS1															
-	1258	0.000*	98.376	7.583	456.407	169					—				
+	1					0					—				

Conclusion: The real-word driver gene mutations in large population of China are far higher than in the US and Europe, slightly less than in other reports of specially screened Asian populations.

Keywords: driver gene, clinicopathological feature, large population of China

P1.09-15 PRELIMINARY EXPERIENCE WITH LIQUID BIOPSIES IN A RESOURCE CONSTRAINED SETTING AND ITS IMPACT ON TREATMENT DECISION MAKING

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Background: Liquid biopsies are potentially useful for molecular testing in the presence of inadequate tissue and for detection of resistance mechanisms in EGFR mutated NSCLC patients. Initial experience with liquid biopsies for advanced/metastatic NSCLC patients in a resource constrained setting is described herein. **Method:** Retrospective audit of liquid biopsies performed over a 21-month period for NSCLC patients at a tertiary referral centre in North India. Testing methods included digital-droplet-PCR (ddPCR), Next-Generation-Sequencing (NGS) and Real-Time-PCR (RT-PCR). ddPCR was used to detect specific EGFR mutations (L858R exon21, E746_A750 exon19 deletions and T790M exon20) in ctDNA (detection limit based upon amplifiable DNA ranging from 0.5%-<0.01% of mutant allele). For NGS, cfDNA extracted from plasma was subjected to target enrichment by high multiplex PCR amplification and analyzed for mutations using gene panel (BRAF, EGFR, ERBB2/HER2, KRAS, MET) on the Ion Proton semiconductor sequencer (Life Technology, USA). RT-PCR assay using EGFR-RT52 kit (EntroGen USA) detects known somatic mutations in exons 18-21 of EGFR by amplifying mutant-specific sequences and relies on fluorescent probes for detection (detection limit of 1%). **Result:** 42 patients [61.9% (n=26) males] underwent liquid biopsies. ddPCR, NGS and RT-PCR were performed in 31(73.8%), 7(16.7%) and 4(9.5%) patients respectively. Timing was prior to/during first-line treatment in 23(54.8%) and at progression on first-line treatment in 19(45.2%) patients. In the former, indication was inadequate tissue for molecular analysis (n=15), detection of other targetable mutation (after EGFR wild type status on tissue; n=3) and checking ctDNA status of T790M exon 20 detected in tissue (n=5). Among 19 patients with progression on first-line treatment, 17 were those with a sensitizing EGFR mutation at baseline who had progressed on EGFR-TKI of which 47.1% (n=8) were found to have T790M exon 20 mutation. The primary EGFR sensitizing mutation detected in tissue at baseline was also detected in ctDNA in 9 of 20 patients with a sensitivity of 45.0%. Agreement between results of tissue testing and liquid biopsy testing for EGFR mutations was 48.0% (12/25). Potential change in management with use of liquid biopsies was observed in 12 patients (28.6% overall and 52.6% if done at progression). **Conclusion:** Preliminary experience in our resource constrained setting indicates that greatest utility of liquid biopsies is for EGFR mutated patients with progression on EGFR-TKI wherein T790M detection rates are comparable to those reported in literature. However, the overall sensitivity and agreement is lower than that reported in literature and perhaps may be related to small number of patients.

Keywords: PCR, T790M, liquid biopsy, ctDNA

P1.09-16 NOVEL SOMATIC GENE MUTATION OF SLC17A9, DETECTED IN EARLY-STAGE LUNG ADENOCARCINOMA

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Background: Lung adenocarcinoma is an example of a tumor that shows a wide range of mutations, such as *EGFR*, *KRAS*, *ALK*, *ROS*, and *RET*. However, with the exception of *EGFR* and *KRAS*, most mutations in lung adenocarcinoma have been detected in advanced tumors. We have encountered one interesting case of multiple lung adenocarcinomas. The patient was a 68-year-old Japanese male in whom two tumors were detected in the left upper lobe and lobectomy was performed. One of which was diagnosed as lepidic adenocarcinoma and the other as minimally invasive adenocarcinoma (MIA). We considered that these two adenocarcinomas were synchronous and independent. Two years later, eight ground glass nodules were newly found in the left lower lobe. After chemotherapy, these tumors were also resected surgically, and all eight were found to show a lepidic pattern histologically. Moreover, two of the tumors were diagnosed as MIA. Therefore, it was very difficult to determine which of the tumors were multicentric and which were possibly metastatic from the previous adenocarcinoma. In order to clarify the genetic background of these tumors, we examined the resected materials using next-generation sequencing. **Method:** We secured snap-frozen samples from one primary adenocarcinoma and two secondary adenocarcinomas. The DNAs were extracted and subjected to exome sequencing (Next-seq-500, Illumina). The mutations were validated by amplicon sequencing. Amplicon sequencing was also performed using DNAs extracted from FFPE blocks of the other tumors. **Result:** From the exome sequences, 26, 365 and 308 mutations were detected from one primary tumor and two secondary tumors, respectively. Among these mutations, those of two genes, *EGFR* (L858R) and *SLC17A9* (G78R), were detected as common mutations. This result was validated by amplicon sequencing of the same DNA. Amplicon analysis of the remaining 7 tumors revealed that all tumors had the same *EGFR* mutation, but that only 6 had the *SLC17A9* mutation and one primary adenocarcinoma (MIA) lacked the mutation. These results indicated that the primary tumors were multicentric whereas the secondary tumors were metastatic from the primary lepidic adenocarcinoma. **Conclusion:** Our study of multiple early-stage adenocarcinomas and their metastases has revealed a common somatic mutation of *SLC17A9* as well as *EGFR* mutation (L858R). *SLC17A9* is a lysosomal ATP transporter that regulates cell viability. Although somatic mutation of *SLC17A9* has not been reported previously in lung adenocarcinoma, *SLC17A9* has been considered to have an oncogenic function. The present findings suggest that *SLC17A9* gene alteration and its dysfunction may contribute to progression of lung adenocarcinoma.

Keywords: Multiple adenocarcinoma, EGFR, SLC17A9

P1.09-17 CTNNB1 (BETA-CATENIN) MUTATIONS IN NON-SMALL CELL LUNG CARCINOMA: A CLINICOPATHOLOGICAL STUDY OF 18 CASES

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Background: Beta-catenin, encoded by the *CTNNB1* gene, plays an important role in a signaling pathway of progenitor cell proliferation and differentiation. Mutations of *CTNNB1* are oncogenic in several tumor types and are often associated with a nuclear abnormal expression. However, such mutations have only rarely been reported in non-small cell lung carcinomas and their clinical signification is not well described. Otherwise, beta-catenin expression by immuno-histochemistry has been described as a prognostic factor in non-small cell lung carcinomas. **Method:** Our study was conducted on 18 *CTNNB1*-mutated non-small cell lung carcinomas. Tumors were routinely tested by next generation sequencing for mutations in exon 3 of *CTNNB1* gene. Fifteen cases (2.6%) were from a series of 568 consecutive and contributive analyses performed between January 2017 and March 2018, on 417 adenocarcinomas, 60 squamous cell carcinomas and 91 large cell carcinomas. The 3 other cases dated from before this series. The hospital files of the 18 patients and pathological data from surgical samples (*n*=11), small biopsies (*n*=3) and trans-bronchial fine needle aspirations (*n*=4) were reviewed. Immuno-histochemistry was performed with an anti-beta-catenin antibody. **Result:** There were 6 female and 12 male patients aged 54 to 83 (mean = 66). Six of the 18 patients were non-smokers (< 5 pack-years). There were 17 adenocarcinomas and 1 squamous cell carcinoma. Most adenocarcinomas were TTF1-positive (16/17) and had a papillary component accounting for more than 30% of their volume (*n*=11). Eight cases (44%) with *CTNNB1* mutations showed associated *EGFR* mutations including exon 19 deletion (*n*=5) and L858R (*n*=2). Oncogenic *KRAS* mutations were only found in 3 cases (17%). The frequency of *CTNNB1* mutations among *EGFR* mutated adenocarcinomas was 9% (7/79). The most frequent *CTNNB1* mutations were S37F (*n*=7) and S45P (*n*=4). Immuno-histochemistry showed normal membrane expression with no nuclear or cytoplasmic abnormal expression in all cases. **Conclusion:** Our study shows that *CTNNB1* mutations are rare in non-small cell lung carcinomas and mostly occur in TTF1-positive adenocarcinomas with a papillary pattern. These mutations are similar to those observed in other tumor types but they probably do not play the same oncogenic role. Furthermore, in lung carcinomas, *CTNNB1* mutations were often associated with *EGFR* mutations and may interfere in the mechanism of resistance to tyrosine kinase inhibitors. This should be thoroughly investigated in larges series evaluating the degree of response to EGFR tyrosine kinase inhibitors.

Keywords: Non-small cell lung carcinoma, CTNNB1 mutation, Beta-catenin

P1.09-18 15 CASES OF CLINICAL AND MOLECULAR FEATURES ANALYSIS IN PULMONARY ADENOID CYSTIC CARCINOMA

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Background: Pulmonary adenoid cystic carcinoma (PACC) of the lung is a malignant tumor arising in the tracheobronchial glands distributed in the airway submucosa. The aim of this study is to investigate the molecular characteristics of PACC. **Method:** From July 2013 to December 2016, 15 PACC patients received treatment. All the patients were diagnosed by pathology. We retrospectively reviewed the clinical data and genetic state. **Result:** EGFR mutation rate was 6.67% (1/15), and it was 19del, the relationship between EGFR gene status and gender (P=1.000), age (P=1.000), smoking status (P=1.000) and stage (P=1.000) were no significant, and ALK fusion and ROS1 fusion gene was not detected. **Conclusion:** Gene change exists PACC, and the gene detection cannot be ignored in PACC.

Keywords: molecular features, gene detection, adenoid cystic carcinoma

P1.09-19 POSITIVE CORRELATION BETWEEN WHOLE GENOMIC COPY NUMBER VARIANT SCORING AND THE GRADING SYSTEM IN LUNG NON-MUCINOUS INVASIVE ADENOCARCINOMA

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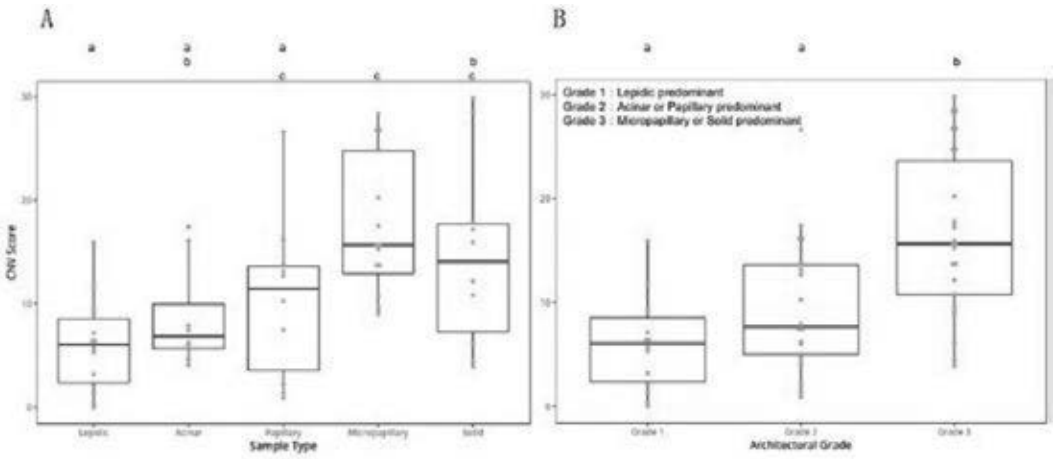
Background: Grading systems of Lung adenocarcinoma have been proposed by Sica and Kadota in stage I tumors,but the predominant architectural subtypes grading system is applicable for resection samples mostly. The correlation between the histological subtypes and grading with whole genomic copy number variation(WGCNV) is unknown, and was investigated in lung non-mucinous invasive adenocarcinoma (LNMIA) at this study. **Method:** The predominant histological subtype from 58 resection specimens of LNMIA and 20 para-cancerous lung tissues were collected by laser microdissection from HE staining FrameSlides PEN-Membrane slides.7 of 58 specimens,two predominant subtypes in one cancerous nodule were collected simultaneously. Whole genome amplification followed by high-throughput sequencing was used to deteted WGCNV with the para-cancerous lung tissues as normal reference set and WGCNV was scored by a particular formula.

Result:

Table 1 WGCNV scores of different histological subtypes and the three tiered grades

Histological Subtypes (Number)	WGCNV score-low (0-7.15) (%, Number/Sum)	WGCNV score-medium (7.16-15.31) (%, Number/Sum)	WGCNV score-high (15.32-29.89) (%, Number/Sum)	Median WGCNV scores	Chi-Squared test# *p* value < 0.05
Lepidic type(14)	71.4%(10/14)	21.4%(3/14)	7.2%(1/14)	6.06(0-15.94)	a
Acinar type(8)	50.0%(4/8)	25.0%(2/8)	25.0%(2/8)	6.83(4.07-17.39)	ab
Papillary type(10)	30.0%(3/10)	50.0%(5/10)	20.0%(2/10)	11.46(0.93-26.59)	abc
Micropapillary type(16)	0%(0/16)	43.8%(7/16)	56.2%(9/16)	15.66(4.6-28.38)	d
Solid type(10)	30.0%(3/10)	20.0%(2/10)	50.0%(5/10)	14.07(3.91-29.85)	bcd
Architectural Grading System (Subtypes, Number)					
Grade 1 (Lepidic,14)	71.4%(10/14)	21.4%(3/14)	7.2%(1/14)	6.06(0-15.94)	a
Grade 2 (Acinar or Papillary,18)	38.9%(7/18)	38.9%(7/18)	22.2%(4/18)	7.7(0.93-26.59)	a
Grade 3 (Micropapillary or Solid, 26)	11.5%(3/26)	34.6%(9/26)	53.9%(14/26)	15.66(3.91-29.85)	b
# Same letters mean no significant differences by chi-squared test					



WGCNV median scores of 5 histological subtypes of LNMIA with three tiered architectural grades are shown in Table1. The WGCNV scores have a positive correlation with either histological subtypes and architectural grading system (Figure1 A and B). The differences of WGCNV scores are detected betweem two predominant subtypes in one cancerous nodule. **Conclusion:** GWCNV scores display a positive correlation with three tiered architectural grading system and may has a potential value to predict prognosis in LNMIA.

Keywords: Whole genomic copy number variation, invasive lung adenocarcinoma, grading

P1.09-20 CORRELATION BETWEEN WHOLE GENOMIC COPY NUMBER VARIANT SCORING AND PATHOLOGICAL CLASSIFICATION, STAGING IN LUNG NON-MUCINOUS ADENOCARCINOMA

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Background: The new classification of lung adenocarcinoma composing of adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and invasive adenocarcinoma (IA) has been applicable worldwide. Both the histological classification and TNM staging of lung adenocarcinoma have important values in indicating prognosis, but their correlations with whole genomic copy number variation (WGCNV) are still unknown.
Method: Lung non-mucinous adenocarcinoma(LNMA) including AIS, MIA and IA resection specimens, malignant pleural effusion (MPE), metastatic nodules (MN) biopsy and 20 para-cancerous non-tumor lung tissue samples were selected. The cells of predominant histological subtype from each LNMA and non-tumor smaples were collected by laser microdissection from HE staining FrameSlides PEN-Membrane slides. Whole genome amplification followed by high-throughput sequencing was used to detect the somatic CNV with the para-cancerous lung tissues as normal reference set. WGCNV was scored by a particular formula.

Result:

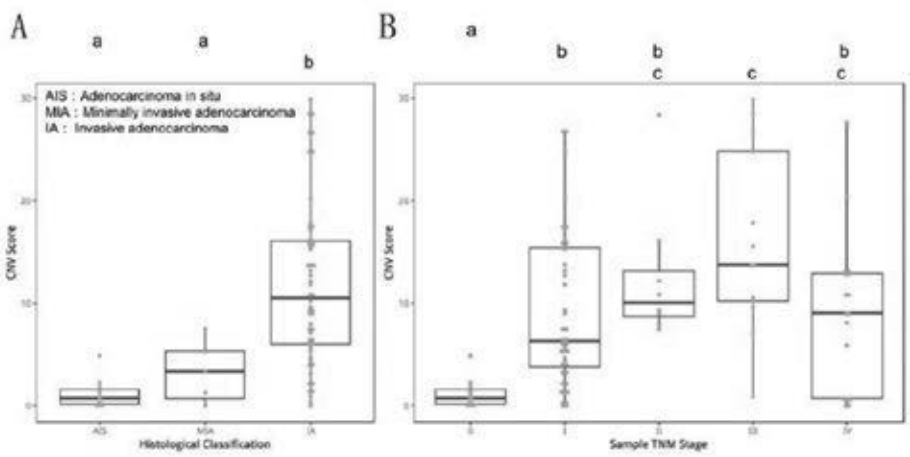

Table 1 WGCNV scores of different pathological subcategories and T&TNM stages

Pathological subcategories (Number)	WGCNV score-low (0-5.21) (%, Number/Sum)	WGCNV score-medium (5.22-12.70) (%, Number/Sum)	WGCNV score-high (12.71-29.85) (%, Number/Sum)	Median WGCNV scores	Chi-Squared test# *p* value<0.05
AIS(11)	100.0%(11/11)	0.0%(0/11)	0.0%(0/11)	0.74(0-4.88)	a
MIA(7)	71.4%(5/7)	28.6%(2/7)	0.0%(0/7)	3.36(0-7.5)	ab
IA(58)	20.7%(12/58)	37.9%(22/58)	41.4%(24/58)	10.49(0-29.85)	c
MPE & MN(15)	20.0%(3/15)	40.0%(6/15)	40.0%(6/15)	10.76(0-27.6)	bc
T&TNM Staging(Number)					
TIS(11)	100.0%(11/11)	0.0%(0/11)	0.0%(0/11)	0.74(0-4.88)	a
T1(43)	32.6%(14/43)	32.6%(14/43)	34.9%(15/43)	7.46(0-26.84)	b
T2(10)	20.0%(2/10)	50.0%(5/10)	30.0%(3/10)	9.16(2.22-28.38)	b
T3(4)	0.0%(0/4)	50.0%(2/4)	50.0%(2/4)	13.44(7.47-17.87)	b
T4(8)	12.5%(1/8)	37.5%(3/8)	50.0%(4/8)	11.93(0.93-29.85)	b
Tx(MPE & MN,15)	20.0%(3/15)	40.0%(6/15)	40.0%(6/15)	10.76(0-27.6)	b
Stage 0(11)	100.0%(11/11)	0.0%(0/11)	0.0%(0/11)	0.74(0-4.88)	a
Stage I (44)	36.4%(16/44)	31.8%(14/44)	31.8%(14/44)	6.31(0-26.84)	b
Stage II(8)	0.0%(0/8)	75.0%(6/8)	25.0%(2/8)	10.08(7.47-28.38)	c
Stage III(13)	7.7%(1/13)	30.8%(4/13)	61.5%(8/13)	13.77(0.93-29.85)	bc
Stage IV(15)	20.0%(3/15)	40.0%(6/15)	40.0%(6/15)	10.76(0-27.6)	bc

Abbreviation: AIS: Adenocarcinoma *in situ*, MIA: Minimally invasive adenocarcinoma, IA: Invasive adenocarcinoma, MPE: Malignant pleural effusion, MN: Metastatic nodules. #Same letters mean no significant differences by chi-squared test

WGCNV median scores and distributions of pathological subcategories and TNM staging were shown in Table 1 and their trends were displayed in Figure 1.WGCNV scores display the positive correlation or significant differences among diversified histological subcategories of LNMA, but not in T & TMN staging **Conclusion:** WGCNV scoring displays the positive correlation or significant differences among diversified subcategories and may has a potential value prediecting prognosis in LNMA.

Keywords: lung adenocarcinoma, TNM staging, Histological classification

P1.09 PATHOLOGY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.09-21 CIRCULATING TUMOR DNA IMPROVES GENOTYPIFICATION AND DETECTION OF TARGETABLE ALTERATIONS IN SELECTED LUNG CANCER PATIENTS

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Background: Several studies have shown that NSCLC genomic background among Hispanics differs from other populations. The finding of low frequency genomic alterations in cfDNA to increase diagnostic accuracy in NSCLC could refine the treatment. We hypothesized that cfDNA can be an alternative or complement for detection of low frequency genomic targets. We aimed to understand the landscape of cfDNA-identified genomic drivers in a cohort of patients (pts) with NSCLC of Hispanic ancestry. **Method:** We collected data from 51 Hispanic pts (Mexico and Colombia) with advanced NSCLC (Stage III/IV) who previously underwent tissue screening for *ALK*, *EGFR*, and *ROS1*. CfDNA was extracted from plasma and analyzed by a commercial NGS test (Guardant360ª) which detects genomic alterations (alts) in up to 73 genes. **Result:** Median age was 56 years (31-83). Most pts were female (64.7%) and never smokers (76.5%). 94% of cases (48/51) had cfDNA detectable alts with a mean number of 3.37 cfDNA alts per test (range, 1 -10). Of the 48 pts with cfDNA genomic alts, 23 (47.9%) had a known genomic driver (*EGFR* (27.4%), *TP53* (13.7%), *ALK* (7.8%), *KRAS* (5.8%), and *BRAF* (3.9%)). Interestingly, cfDNA was able to detect some genomic alts previously undetected by tissue biopsy (either due to false negatives or to technical limitations such as insufficient or low-quality DNA). In the case of *EGFR*, 12 pts had *EGFR* alts through cfDNA which were previously undetected by tissue biopsy. Similarly, cfDNA detected 3 alterations in *ALK* which were previously undetected by tissue sample. Of 48 pts, 35.4% were switched to a targeted therapy as a result of alts detected through cfDNA, with adequate responses: disease control rate was 82.4% (partial response 47.2% and stable disease 35.2%) and progression free survival was 7.4 months (95%CI 2.6-28.1). **Conclusion:** In a selected population of young Hispanics (especially never smokers and women) with NSCLC the use of comprehensive cfDNA analysis allowed a treatment change in 35% of the cases. Our data confirms the usefulness of Guardant360ª as non-invasive panel to identify genomic alts in cfDNA.

Keywords: liquid biopsy, Targeted therapy, Genotypification

P1.09 PATHOLOGY
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P1.09-22 DETECTION OF ALK GENE REARRANGEMENT IN FFPE TISSUES OF NON-SMALL CELL LUNG CANCER USING IN SITU RNA HYBRIDIZATION

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Background: Approximately 4-7% of non-small cell lung cancer (NSCLC) harbor anaplastic lymphoma kinase (ALK) gene rearrangements which lead to overexpression of ALK fusion protein and constitutive activation of the kinase. The tumor with ALK gene rearrangements is sensitive to its inhibitor, so identification of this molecular feature from the patients accurately is important. Fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) are conventional methods for testing ALK gene rearrangement and protein overexpression respectively; however it is challenge for distinguishing some rare variations by FISH, or determining the equivocal stain by IHC. A morphology related method under bright field about rearranged mRNA expression (RNAscope) of ALK gene fusion was developed, which is helpful to realize the biological behavior of ALK gene, together with FISH (break apart FISH probe kit, Abbott) and IHC (D5F3 clone, Ventana). **Method:** We explored 7 cases of formalin-fixed paraffin-embedded (FFPE) samples from NSCLC patients by RNAscope® 2.5 Red assay **Result:** Three of seven samples were found with ALK positive by RNAscope, which matched with FISH and IHC results. In these 3 ALK positive samples, exon 19-29 of ALK gene transcribed RNA signals were revealed by probe-Hs-ALK E1-E18 (score 1 to 2 in >50% cells), whereas exon 1-18 transcribed RNA signals were not shown by probe-Hs-ALK E19-E29, which confirmed by FISH results (with break apart signals). In 2 of 4 ALK RNAscope negative cases, ALK RNA signals were detected by both probe-Hs-ALK E1-E18 (score 2) and probe-Hs-ALK E19-E29 (score 2) in small regions (showed a small number of signals), which may indicate that ALK gene amplification and also confirmed by FISH results (with more than 2 fusion signals). And these 2 typical ALK RNAscope negative samples were considered close to be disomy by FISH. **Conclusion:** Our results demonstrate that RNAscope® 2.5 Red assay is a reliable and precise method to detect ALK mRNA expression caused by ALK gene fusion and also a one to discover the ALK gene amplification as well in FFPE samples of NSCLC, even though latter's clinical significant is not clear. RNAscope® 2.5 Red assay is a both sensitive and specific method to provide information on the spatial distribution of ALK gene status and morphologic characteristic of tumors simultaneously under the bright field microscope.

Keywords: mRNA, lung cancer, anaplastic lymphoma kinase (ALK)

P1.09 PATHOLOGY
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P1.09-23 EFFECT OF PLASMA INPUT ON THE CLINICAL SENSITIVITY OF A REAL-TIME PCR ASSAY FOR THE DETECTION OF EGFR MUTATION IN PLASMA CTDNA FROM NSCLC PATIENTS

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Background: Plasma based EGFR mutation testing is a less invasive and feasible testing option for patients with advanced non-small cell lung cancer (NSCLC) when traditional tissue biopsy testing is challenging. A fast and sensitive real-time PCR method has been developed for the detection of EGFR mutations in plasma circulating tumor DNA (ctDNA). To define the effect of plasma input on the clinical sensitivity of the assay, clinical evaluation was conducted in the present study. **Method:** A total of 203 patients with advanced NSCLC were recruited who provided plasma and matched tumor tissue samples, 109 of whom providing samples had adequate plasma for both 2 mL and 4 mL plasma testing, and the rest providing 2 mL plasma samples. ctDNA was isolated and tested for the presence of EGFR mutation by the AmoyDx Super-ARMS EGFR Mutation Detection Kit (Super-ARMS EGFR). Tumor tissue DNA was isolated and tested for EGFR mutation by AmoyDx ARMS EGFR Mutation Detection Kit (ARMS EGFR). Clinical sensitivity and specificity of ctDNA testing were analyzed by using tumor tissue testing as a reference. **Result:** In pairs of tumor biopsy and plasma samples, the sensitivity, specificity and overall concordance of EGFR mutation status determined in 4 mL of plasma by Super-ARMS EGFR test and matched tissue samples were 82.0% [50/61], 100% [48/48], and 89.9% [98/109] (N=109), respectively. These rates were much higher than those of mutation status determined in 2 mL of plasma and matched tissue samples (65.55% [78/119], 97.62% [82/84] and 78.82% [160/203], N=203). **Conclusion:** Super-ARMS EGFR assay is a highly reliable and sensitive method for the detection of EGFR mutation in lung cancer plasma ctDNA samples. Plasma samples of 4 mL volume is more appropriate for ctDNA EGFR mutation assessment than determination in 2 mL volume of plasma.

Keywords: Super-ARMS, EGFR mutation, plasma ctDNA

P1.09 PATHOLOGY
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P1.09-24 THE EFFECTS OF NLR AND PLR OF EFFECT ON PROGNOSIS IN PATIENTS WITH THE LUNG CANCER

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Background: Inflammation has an important role in the pathogenesis of cancer. Platelet/Lymphocyte (PLR) and Neutrophil/Lymphocyte ratios (NLR) are known as parameters that indicate the status of inflammation and can be used in determining the prognosis of cancer. The object of this study is to investigate the effect of the preoperative NLR and PLR on disease-free (DFS) and overall survival (OS) in patients with lung cancer. **Method:** In this study, 68 patients, who underwent surgery and received a diagnosis of lung cancer between 2004 and 2014 were evaluated retrospectively. Date of diagnosis, demographic characteristics, tumor stage and location, vascular invasion status, perineural invasion status, lymph node involvement, histological type, grade, adjuvant treatment status, preoperative neutrophils, lymphocytes and platellet number were analyzed. Preoperative PLR and NLR computed and median value of these rates were determined. The Kaplan-Meier method was used for DFS and OS analysis of patients who were above or below the median. Confidence interval and statistically significant p-value was considered

respectively %95 , <0.05. **Result:** 68 patients, 7 were female and 61 male, mean age was 57. 23 of 68 patients Stage1, 33 patients Stage 2, 12 patients and Stage 3. Histopathological analyse performed, and the end of analyse; 48,5% adenocarcinoma, 42,6% squamous cell carcinoma 8,9% other types were watched. Average PLR and average NLR was seen as respectively 120 and 2,2. DFS (47.3 months versus 50.8 months) was shorter in lung cancer patients with high NLR, but OS was longer (82.3 months versus 78.2). DFS (42.8 months versus 55.4 months) was shorter in lung cancer patients with high PLR and OS was longer (84.5 months versus 76.7 months). The difference between the two groups was not statistically significant. **Conclusion:** The effect of high NLR and PLR on DFS and OS in patients with lung cancer was not statistically significant. Prognostic value of NLR and PLR before treatment is not clearly demonstrated, and extensive prospective studies should be performed with multiple centers and more patient.

Keywords: lung cancer, Platelet/Lymphocyte Ratio (PLR), Neutrophil/Lymphocyte Ratio (NLR)

P1.09 PATHOLOGY
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P1.09-25 INVASIVE SIZE (NOT TOTAL SIZE) PREDICTS OVERALL SURVIVAL IN INVASIVE MUCINOUS ADENOCARCINOMAS

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Background: The 8th TNM pathological staging system advocates usage of the invasive size, rather than the total size, in the pT staging of pulmonary non-mucinous adenocarcinomas. However, few studies have addressed this issue regarding invasive mucinous adenocarcinomas (IMAs). Our study aimed to determine whether invasive size correlates with individual histological parameters and also whether it provides better prognostic stratification than overall tumour size. **Method:** We reviewed a series of 101 cases of IMAs resected between 2000 to 2012, comprised of stage I~IV tumours. In each IMA, the percentage of each growth pattern (lepidic, acinar, papillary, solid, micropapillary, and cribriform) was assessed in 5% increments. Due to the frequent multifocal nature of IMAs, the invasive size was calculated by multiplying the total tumour size with the total percentage of invasive (non-lepidic) components in all cases. The adjusted T (aT) stage, as determined by the cumulative size of invasive components, was correlated with disease-free (DFS) and overall survival (OS). Correlation with 7th and 8th T stage (using total tumour size) were also performed as comparison. **Result:** The 7th aT stage was positively correlated with higher host response (tumour-associated inflammation), necrosis, pleural invasion, and nodal metastasis, while the 8th aT stage was significantly correlated with necrosis, vascular invasion, pleural invasion, and nodal metastasis. Using aT stage for risk stratification, we found a significant difference in OS in both 7th and 8th aT stage between the subgroups (p = 0.002 and 0.006, respectively), whereas DFS failed to reach statistical significance. There was a significant difference in DFS when using the 8th T stage (p = 0.002), whereas no significant difference was noted in OS. A trend was noted in DFS (p = 0.054) while OS failed to reach statistical significance when applying the 7th T staging. **Conclusion:** Our study showed that invasive size may be a superior prognostic indicator compared to total size, which provides a rationale for prognostic stratification of IMAs based on the extent of invasive growth patterns (or invasive size) rather than total tumour size.

Keywords: Mucinous Adenocarcinoma, Tumour size, Prognosis

P1.09 PATHOLOGY
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P1.09-26 A CASE REPORT OF DISCORDANT MARKERS OF LUNG CANCER TUMOR CELLS: AN UNUSUAL IMMUNOPHENOTYPE OF UNCERTAIN SIGNIFICANCE

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Background: Introduction Non Small Cell Lung Cancer (NSCLC) is the most frequent type of lung tumor, with two major histological subtypes: adenocarcinomas and squamous cell carcinomas. Tissue transcription factor-1 (TTF-1) and Napsin A are expressed in up to 75%- 80% of primary lung adenocarcinomas respectively and the sensitivity of both p40 and p63 for squamous cell carcinoma is 92%. Here, we report an unusual case of NSCLC with coexisting histology within the same tumor cells. **Case** A 65-year-old male with 50 pack year smoking history underwent screening CT chest and was found to have a right upper lobe mass measuring 10 cm x 8.6 cm x 6.9 cm with narrowing of the right upper lobe bronchus in the posterior segment. Bronchoscopy and EBUS guided biopsy of the right paratracheal node revealed NSCLC, poorly differentiated, with TTF-1, Napsin A, P40 and P63 staining positive (70-80%) for both adenocarcinoma and squamous cell carcinoma within the same tumor cells. Subsequent Brain MRI and PET did not reveal any evidence of metastatic disease and the patient was classified as T4 N1 stage IIIB disease. **Discussion** The line between lung adenocarcinoma and squamous cell carcinoma has already been shaken by an uncommon adenosquamous variant, but our case represents a new histologic subtype that expands on the understanding of lung cancer. Adenosquamous carcinoma (ADSQC) of the lung is a rare classification of NSCLC with a reported incidence of 0.4-4%. Histology defined by the World Health Organization defines ADSQC as a mixed type of tumor, with each component representing greater than 10% of the entire tumor. Based on studies by Naunheim et al, the median survival of patients with stage III ADSQC was 5.0 months compared to 9.0 months with adenocarcinoma and 7.8 months with squamous cell carcinoma. However, our case is different, as immunohistochemistry was positive for TTF-1, Napsin A, p40 and p63 biomarkers within the same individual tumor cells, thus diagnosing an entirely different pathology. After review of the literature, this is the third case with such co-expression. This case is important as it promotes awareness of this rare pathology. Both clinicians and pathologists need to be aware of its existence, in order to prevent misdiagnosis and treatment delay in what may be hypothesized as an aggressive tumor. As more cases emerge, further studies can determine incidence, prognosis, presence of driver mutations, and treatment implications. **Method:** Section not applicable **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: A Case Report of Discordant Tumor Markers of Lung Cancer

P1.09 PATHOLOGY
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P1.09-27 CLEAR CELL ADENOCARCINOMA SUBTYPE IS AN INDEPENDENT PREDICTOR OF BETTER SURVIVAL IN PATIENTS WITH LUNG ADENOCARCINOMA

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Background: Clear cell adenocarcinoma (CCA) has been considered as a rare subtype of lung adenocarcinoma. However, the 2011 World Health Organization (WHO) classification of lung adenocarcinoma proposed to discontinue CCA due to lack of available data with clinical significance. The role of CCA in patient prognosis needs to be investigated by using large data sources. **Method:** Lung adenocarcinoma patients were queried from The Surveillance, Epidemiology, and End Results Program (SEER) database and were divided into CCA and 'not otherwise specified' category (NOS). Cancer-specific survival was studied according to gender (male, female), age (0-69,70+), SEER specific stage A system (localized, regional and distant), year of diagnosis (1973-2000, 2001-2013), surgery (yes, no), and radiation therapy (yes, no) using Kaplan–Meier curves. Statistical difference was estimated with log-rank test using JMP software. Multivariate analysis was used to study independent predictors of cancer-specific survival. **Result:** A total of 198,042 patients with the diagnosis of lung adenocarcinoma were found in the SEER database of which 921 patients were diagnosed with CCA. CCA histology was significantly associated with an early year of diagnosis, younger age, early stage, surgery, and lack of radiation. Kaplan–Meier curves showed that patients with CCA histology, age 0-69, year of diagnosis 2001-2013, female gender, localized disease, undergoing surgery, and lack of radiation had significantly better cancer-specific survival (p<0.0001, Log-Rank). Subset analysis demonstrated difference in cancer-specific survival between CCA and NOS histology was significant in localized and regional but not distant stage (p=0.0453, 0.0009, 0.0664, respectively). **Conclusion:** Patients with CCA histology have superior survival according to our SEER analysis, suggesting its unique role in prognosis despite its removed from 2011 WHO classification.

Keywords: Clear cell adenocarcinoma, lung adenocarcinoma, SEER

P1.09 PATHOLOGY
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P1.09-28 CLINICAL UTILITY OF RAPID IMMUNOHISTOCHEMISTRY FOR DIFFERENTIATION OF SOLITARY PULMONARY ADENOCARCINOMAS

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Background: Intraoperative differentiation between pulmonary metastasis and primary lung cancer is necessary for determining the appropriate range of excision. Although conventional immunohistochemistry is often used for such differentiation, its intraoperative use is limited by time constraints. We therefore developed a device that enables complete and rapid immunohistochemistry (R-IHC) within 20 minutes, and used it with anti-thyroid transcription factor-1 (TTF-1) for differential diagnosis of pulmonary adenocarcinoma. However, the diagnostic accuracy of the method likely can be improved by using a combination of two or more antibodies. We therefore evaluated the clinical utility of R-IHC with combinations of antibodies for discriminating the etiology of solitary pulmonary adenocarcinomas. **Method:** Twenty-two patients with pulmonary adenocarcinomas treated between February 2015 and May 2017 were enrolled in this prospective study. Tumor samples were sectioned, labeled with multiple antibodies using R-IHC, and pathologically evaluated. The standard used for comparison was conventional hematoxylin eosin (HE) staining and IHC. **Result:** All intraoperative diagnoses made using R-IHC were consistent with the final diagnosis; that is, the accuracy was 100%. Moreover, the respective staining with each antibody corresponded between intraoperative R-IHC and IHC with the permanent specimen. For rapid intraoperative diagnosis differentiating pulmonary adenocarcinoma from lung metastasis from colon cancer, R-IHC with a combination of TTF-1, cytokeratin (CK) 7, and CK20 antibodies was highly effective. **Conclusion:** Our novel R-IHC method with multiple antibodies was highly effective for diagnosis and differentiation of solitary pulmonary adenocarcinomas. This technology may prove to be an important supplement to standard intraoperative pathologic diagnosis in routine practice.

Keywords: Pulmonary tumor, Immunohistochemistry, Intraoperative diagnosis

P1.09 PATHOLOGY
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P1.09-29 IN SITU GROWTH PATTERN IN LUNG ADENOCARCINOMA IS DIVISIBLE INTO DISTINCT CATEGORIES WITH DIVERGENT BIOLOGICAL AND SURVIVAL IMPLICATIONS

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Background: The morphological stepwise progression of lung adenocarcinomas is well established, but little is known about the molecular events that underlie this. In particular, *in situ* patterns of growth are frequently seen in adenocarcinomas, and often it is not clear if this truly always represents early-stage preinvasive disease. Therefore we set out to better characterise *in situ* tumour growth, and to identify molecular and biological correlates of tumour invasion. **Method:** We constructed a retrospective cohort of 964 locally held adenocarcinomas, with patient data and tissue microarrays (TMAs). Immunohistochemistry for Ki67 and epithelial-mesenchymal transition markers was applied to TMAs and quantified. In situ and adjacent invasive areas of 23 early tumours were subjected to further *in situ* assays and laser capture microdissection. Genomic DNA was extracted and driver genes were panel sequenced. **Result:** We morphologically identified two distinct types of *in situ* tumour growth in early mixed pattern tumours: a low-grade precursor ('C1'- after the classic Noguchi classification) associated with higher-grade invasive disease, and a high-grade lepidic outgrowth ('C2') associated with invasive growth of similar cytological grade. C1 and C2-type *in situ* tumour growth are sharply separated by their proliferation rate (P=0.005) and their propensity for nodal metastasis (P=0.03), suggesting that this distinction is likely to be important in future grading/growth pattern classification. Furthermore, molecular analysis supports the classification; invasive areas of C1 tumours show driver mutations which are absent from neighbouring in situ disease (4/18 cases), indicating molecular progression, while in 5 sequenced C2 cases no evidence of molecular progression was seen. The difference between low-grade precursor and high-grade in situ patterns was further investigated in our full set of 964 tumours. We find that the prognostic power of proliferation rate (Ki67) is driven almost entirely by its effects in *in situ* areas of tumour growth. Proliferation rate in invasive tumour areas at most weakly predictive of patient outcome. **Conclusion:** We make several key findings: i) In situ disease in lung adenocaricnoma is divided into two biologically and prognostically distinct groups, with implications for our understanding of stepwise progression in lung cancer ii) These two groups can easily be separated on the basis of cellular proliferation rate ii) We identify mutations in key driver genes that are explicitly asociated with the transition from *in situ* to invasive growth iii) Proliferation rate is a potentially valuable prognostic marker, but this may be restricted to its ability to separate these two key biologically distinct growth patterns

Keywords: growth pattern, Adenocarcinoma, invasion

P1.09 PATHOLOGY
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P1.09-30 HETEROTOPIC EXPRESSION OF CERULOPLASMIN IN LUNG ADENOCARCINOMA AND ITS POSSIBLE CLINICAL USE AS A TUMOR BIOMARKER

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Background: Ceruloplasmin (CP) is a well-known copper binding protein synthesized mainly in the liver, and its expression is well known to be elevated in the serum of cancer patients and in malignant tumor cells. Lung cancer is the leading cause of cancer-related death worldwide, and adenocarcinoma is the main histological type of lung cancer. Previously, we reported that the expression of CP mRNA was significantly higher in early but invasive adenocarcinoma than in adenocarcinoma in situ (AIS) on the basis of cDNA microarray analysis (Shiba, Int. J. Cancer 2011). However, the role of CP in lung adenocarcinoma is still unclear. Here, we examined and compared the expression of CP in various histological subtypes of lung adenocarcinoma and its correlation with patient outcome. **Method:** CP expression in resected specimens of lung adenocarcinoma and lung adenocarcinoma cell lines was determined using quantitative real-time RT-PCR and western blot analysis. Immunohistochemistry for CP was carried out using 196 specimens of lung adenocarcinoma and we divided the cases into a high expression group (H-score >90: 92 cases) and a low expression group (H-score <90: 104 cases). **Result:** CP expression was significantly higher in invasive adenocarcinoma than in AIS. The high expression group had a significantly poorer outcome than the low expression group ($p < 0.01$) and high expression of CP was also correlated with pathological stage, pT, and pN ($p < 0.01$). Multivariate analysis showed that CP expression was an independent prognostic factor in lung adenocarcinoma patients (HR 1.642, 95% CI 1.050-2.568, p=0.030). CP secreted from cancer cells was also detected by western blot analysis the medium used for culture of lung adenocarcinoma cell lines. **Conclusion:** CP is produced heterotopically by lung adenocarcinoma cells and its expression is associated with tumor progression. In view of the presence of the secreted form of CP in tumor cells, CP may be a useful biomarker for lung adenocarcinoma.

Keywords: biomarker, Ceruloplasmin, lung adenocarcinoma

P1.09 PATHOLOGY
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P1.09-31 PRELIMINARY EXPERIENCE WITH LIQUID BIOPSIES IN A RESOURCE CONSTRAINED SETTING AND ITS IMPACT ON TREATMENT DECISION MAKING

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Background: Liquid biopsies are potentially useful for molecular testing in the presence of inadequate tissue and for detection of resistance mechanisms in EGFR mutated NSCLC patients. Initial experience with liquid biopsies for advanced/metastatic NSCLC patients in a resource constrained setting is described herein. **Method:** Retrospective audit of liquid biopsies performed over a 21-month period for NSCLC patients at a

tertiary referral centre in North India. Testing methods included digital-droplet-PCR (ddPCR), Next-Generation-Sequencing (NGS) and Real-Time-PCR (RT-PCR). ddPCR was used to detect specific EGFR mutations (L858R exon21, E746_A750 exon19 deletions and T790M exon20) in ctDNA (detection limit based upon amplifiable DNA ranging from 0.5%-<0.01% of mutant allele). For NGS, cfDNA extracted from plasma was subjected to target enrichment by high multiplex PCR amplification and analyzed for mutations using gene panel (BRAF, EGFR, ERBB2/HER2, KRAS, MET) on the Ion Proton semiconductor sequencer (Life Technology, USA). RT-PCR assay using EGFR-RT52 kit (EntroGen USA) detects known somatic mutations in exons 18-21 of EGFR by amplifying mutant-specific sequences and relies on fluorescent probes for detection (detection limit of 1%). **Result:** 42 patients [61.9% (n=26) males] underwent liquid biopsies. ddPCR, NGS and RT-PCR were performed in 31(73.8%), 7(16.7%) and 4(9.5%) patients respectively. Timing was prior to/during first-line treatment in 23(54.8%) and at progression on first-line treatment in 19(45.2%) patients. In the former, indication was inadequate tissue for molecular analysis (n=15), detection of other targetable mutation (after EGFR wild type status on tissue; n=3) and checking ctDNA status of T790M exon 20 detected in tissue (n=5). Among 19 patients with progression on first-line treatment, 17 were those with a sensitizing EGFR mutation at baseline who had progressed on EGFR-TKI of which 47.1% (n=8) were found to have T790M exon 20 mutation. The primary EGFR sensitizing mutation detected in tissue at baseline was also detected in ctDNA in 9 of 20 patients with a sensitivity of 45.0%. Agreement between results of tissue testing and liquid biopsy testing for EGFR mutations was 48.0% (12/25). Potential change in management with use of liquid biopsies was observed in 12 patients (28.6% overall and 52.6% if done at progression). **Conclusion:** Preliminary experience in our resource constrained setting indicates that greatest utility of liquid biopsies is for EGFR mutated patients with progression on EGFR-TKI wherein T790M detection rates are comparable to those reported in literature. However, the overall sensitivity and agreement is lower than that reported in literature and perhaps may be related to small number of patients.

Keywords: liquid biopsy, T790M, progression

P1.09 PATHOLOGY
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P1.09-32 CLASSIFICATION AND MUTATION PREDICTION FROM NON-SMALL CELL LUNG CANCER HISTOPATHOLOGY IMAGES USING DEEP LEARNING

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Background: Visual inspection of histopathology slides of lung tissues is one of the primary methods used by pathologists to assess pathological stage and classifications of lung cancer. Adenocarcinoma and squamous cell carcinoma are the two most prevalent types of non-small cell lung cancer (NSCLC), but their distinction can be challenging and time-consuming even for the expert eye. Furthermore, the increasing prevalence of new treatment modalities relies on classification of NSCLC mutational analyses of the tumor to guide targeted therapy and provide prognostic information. **Method:** In this study, we trained a deep convolutional neural network (CNN) model (inception v3) on histology images obtained from The Cancer Genome Atlas (TCGA) to accurately and automatically classify whole-slide images into adenocarcinoma, squamous cell carcinoma or normal lung tissue. Furthermore, we trained the neural network to predict the ten most commonly mutated genes in lung adenocarcinoma. Our model was then validated on independent datasets of images obtained from both frozen and formalin-fixed paraffin-embedded tissue, including resection and biopsy specimens. **Result:** We found that the performance of our method is comparable, in terms of sensitivity and specificity, to that of pathologists, with a 0.97 average Area Under the Curve (AUC) on a held-out population of whole-slide images for the sub-type classification on frozen sections. Additionally, we found that six of the ten most commonly mutated genes – STK11, EGFR, FAT1, SETBP1, KRAS and TP53 – can be predicted by the algorithm solely using information from histologic images with an accuracy ranging from 0.733 to 0.856, as measured by the AUC on the held-out population. **Conclusion:** These findings suggest that deep learning models can offer both pathologists and patients a fast, accurate, and inexpensive classification of NSCLC or gene mutations, and thus have a significant impact on cancer treatment. Our computational approach can be applied to any cancer type and the code is available as free open-source software at https://github.com/ncoudray/DeepPATH.

Keywords: deep-learning, image analysis, precision medicine

P1.09 PATHOLOGY
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P1.09-33 VALIDITY OF NON-SMALL CELL LUNG CANCER NOT OTHERWISE SPECIFIED TO USE IMMUNOHISTOCHEMISTRY ON TREATMENT OUTCOME

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Background: In non-small cell lung cancer, histologic samples have become significantly important to administrate tumor type specific cytotoxic and molecular-targeted therapies. When a biopsy sample shows lacking definite morphology, diagnosis is made into three subtypes, favour adenocarcinoma, favour squamous cell carcinoma and NOS-null, according to the immunohistochemistry (IHC) results. However, in terms of the patient outcome, validity of IHC-based these classification have been unknown yet. **Method:** A series of 152 advanced NSCLC patients whose diagnosis was made by morphology and homogeneously treated was enrolled. We performed IHC staining (TTF-1, SP-A, p40, and CK5/6) of these samples and refined diagnoses into 3 subtypes. We analyzed the pathological subgroup depends on IHC staining with clinical characteristics including molecular analysis, response of chemotherapy and prognosis. **Result:** IHC profiling displayed that 50% of cases was favour Ad, 31% was favour SqCC, and 19% was NOS-null. On the patient background, there was no difference in age, smoking history, and PS, but there were differences in gender, and the favour Ad group had more females than other groups. EGFR mutation was significantly more expressed in favour Ad group than in the other groups, and molecular targeted drugs in initial treatment were used in favour Ad group in a large proportion. Compared with favour Ad and SqCC group, NOS-null group showed significantly poorer outcome in terms of median overall survival (OS). Between favour Ad and favour SqCC group, median OS was better in favour Ad group (19.5 months vs 15.0 months, p = 0.018). Excluding patients using molecular targeted drugs, there was no difference in median OS between favour Ad and favour SqCC group (15.2 months vs 15.0 months p = 0.29). Pemetrexed containing platinum regimen showed similar response rate as other platinum regimen in the favour Ad cohort (43% vs 46%), whereas poorer response in the favour SqCC (0% vs 50%) and NOS-null (0% vs 24%) cohort. Although patients to be received pemetrexed containing platinum regimen compared to those to be received other platinum regimen demonstrated a trend toward good PFS in favour Ad group, there were no statistically differences. **Conclusion:** This study made clear chemo-responsiveness, the expression frequency of driver mutation and prognosis in NSCLC favour Ad, SqCC and NOS-null. These findings support that histological subtyping in biopsy specimen by IHC would be mandatory to archive appropriate therapy.

Keywords: Subtyping, Immnunohistochemistry, Non small cell lung cancer

P1.09 PATHOLOGY
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P1.09-34 PROGNOSTIC IMPACT OF INVASIVE SIZE, ACTUAL TUMOR SIZE, AND MUCINOUS TUMOR SIZE IN INVASIVE MUCINOUS ADENOCARCINOMA OF THE LUNG.

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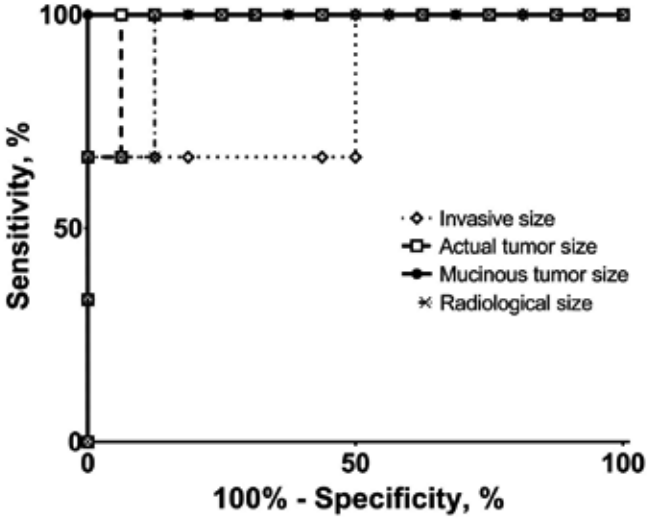
Background: Currently, tumor size of invasive mucinous adenocarcinoma such as invasive mucinous adenocarcinoma (IMA) is defined by the spread of mucinous component regardless of the existence of tumor cells. The aim of this study is to investigate the prognostic impact of the size of invasive lesion, actual tumor spread, mucinous component in IMA. **Method:** Consecutive 19 patients with pN0M0 IMAs which were completely resected between Jan. 2009 and Dec 2015 were retrospectively analyzed. Invasive size (IS), actual tumor size (aTS), and mucinous tumor size (mTS, current T factor) were measured on the identical pathological section, and radiological tumor size (rTS) was also recorded by thorax computed tomography. The prognostic value for postoperative recurrence was evaluated by area under the receiver-operating characteristic (ROC) curves and compared by DeLong's test. **Result:** Based on mTS, study population included 2 patients T1a, 3 with

T1b, 7 with T1c, 4 with T2a, and 3 with T2b. Median age, follow-up, IS, aTS, mTS, and rTS were 75 years, 39 monts, 11mm, 25mm, 26mm and 30mm, respectively. During follow-up, 1 mortality and 3 recurrences were observed. The area under the ROC curves for IS, aTS, mTS, and rTS were 0.833 (p=0.074),0.979 (p=0.01),1.0 (p=0.007),0.958(p=0.014). The mTS showed no significant difference compared to IS, aTS or rTS.



Conclusion: In IMA, aTS and mTS might have prognostic value for recurrence. Prospective study with larger population would be necessary to validate the results.

Keywords: Postoperative recurrence, Tumor size, invasive mucinous adenocarcinoma

P1.09 PATHOLOGY
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P1.09-35 CLINICAL IMPACT OF SYSTEMATIC INFLAMMATION AND HISTOLOGIC GRADE IN NON SMALL CELL LUNG CARCINOMA (NSCLC)

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Background: Tumor grade is an important factor of cancer outcome. Systematic inflammation has been associated with tumorigenesis and tumor aggressiveness and prognosis in several human malignancies. Cancer cells create an inflammatory peritumoral microenviroment by releasing a number of cytokines. **Method:** In total, 100 patients (88 males) with histologically proven NSCLC and no signs of active infection were evaluated. Tumor grade was examined and systematic inflammatory response was assessed by circulating levels of C-reactive protein (CRP), albumin, ferritin, transferring and the modified Glasgow Prognostic Score (mGPS). Patients were followed up and survival data were subsequently collected. Associations with clinicopathological, histological parameters and patients' survival were studied. **Result:** Histological grade was associated with tumor size, the presence of pathological lymph nodes, organ metastases and advanced disease stage (p=0.010, p<0.001, p<0.001 and p<0.001, respectively). There was a trend of higher histological grade in adenocarcinomas compared to squamous carcinomas (p=0.263). High tumor histological grade was also significantly associated with elevated serum CRP levels (p<0.001), hypoalbuminemia (p=0.009), elevated ferritin levels (p=0.049), abnormal mGPS (p=0.006) and a trend for reduced transferrin levels (p=0.101). In multivariate analysis, histological grade, stage, ECOG performance status and mGPS were identified as independent prognostic factors for overall survival (Cox regression analysis, p=0.002, p=0.001, p=0.010 and p=0.019, respectively). **Conclusion:** Our data support the association of tumour grade with the presence of systemic inflammation; two well described negative prognostic factors for NSCLC. To our knowledge this is the first time that these factors are associated with each other giving more information about the prognosis in patients with NSCLC.

Keywords: mGPS, Tumor grade, systematic inflammation

P1.09 PATHOLOGY
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P1.09-36 CLINICAL SIGNIFICANCE OF CANNABINOID RECEPTOR CB2 EXPRESSION IN NON SMALL CELL LUNG CANCER (NSCLC)

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Background: Cannabinoid receptor CB2 expression has been identified to be high in various malignant neoplasms and it is involved in the pathophysiological mechanisms related to carcinogenesis. Lung cancer is an important health problem and new biomarkers are needed for better patients' stratification. This study was conducted to elucidate the clinical significance of cannabinoid receptor CB2 expression in NSCLC. **Method:** Cannabinoid receptor CB2 expression was evaluated immunohistochemically on Tissue MicroArrays (TMAs) of 79 tissue samples from NSCLC patients and it was correlated to clinicopathological parameters and overall survival (OS). **Result:** 79 NSCLC patients (48 adenocarcnomas and 31 squamous carcinomas) were studied. Enhanced cannabinoid receptor CB2 expression was observed in 20/79 (25.3 %) NSCLC patients. In particular, enhanced cannabinoid receptor CB2 expression was found in 9 out of 48 (18.8%) adenocarcinomas and in 11 out of 31 (35.5%) of squamous cell carcinomas. Cannabinoid receptor CB2 expression was significantly associated with sex, smoking history and histological type (p=0.019, p=0.022 and p=0.032, respectively). In adenocarcinomas, cannabinoid receptor CB2 expression was correlated with overall survival (log-rank test, p=0.031), while there was a trend for correlation with tumor size (p=0.091) and lymph node metastasis (p=0.074). However, in squamous carcinomas cannabinoid receptor CB2 expression was not found to be significantly correlated with any of clinicopathological parameters or survival. **Conclusion:** Cannabinoid receptor CB2 receptor may be involved in NSCLC malignant tranformation and growth particularly in adenocarcinomas. Therefore, cannabinoid receptor CB2 receptor could be considered as a potential biomarker or a therapeutic target in NSCLC. More studies needed to elucidate the role of this molecule in NSCLC.

Keywords: biomarker, Cannabinoid receptor CB2, Non Small Cell Lung Cancer (NSCLC)

P1.09 PATHOLOGY
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P1.09-37 TUMOR SPREAD THROUGH AIR SPACES (STAS) IN STAGE I LUNG SQUAMOUS CELL

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Background: Tumor spread through air spaces (STAS) has been reported as a form of tumor invasion having an unfavorable prognosis mainly in small lung adenocarcinomas, but the significance of STAS in lung squamous cell carcinomas is not well known. The aim of this study was to analysis STAS in stage I lung squamous cell carcinomas. **Method:** 39 completely surgically resected (lobectomy) stage I lung squamous cell carcinomas from 2005 to 2009 were included in this study. We examined all tumor edges to find floating tumor cells or clusters, STAS. A statistical analysis was performed to determine the impact of clinicopathologic parameters on STAS and to clarify the relationship between STAS and patient survival. **Result:** STAS was present in 18 of 39 cases (46.2%). There were no statistically significant associations between STAS and any clinicopathologic parameters including stage and lymph-vascular invasions. There was a significant association between presence of STAS and shorter recurrence-free survival (RFS) in univariate analysis (104.7 months with STAS, 145.5 months without STAS). In a multivariate

Cox proportional hazards model, STAS (p=0.06) couldn't reach a significant predictor of RFS. **Conclusion:** We found STAS about in half of resected stage I lung squamous cell carcinomas. Presence of STAS was predictive factor of worse RFS in univariate analysis, but not significant in multivariate analysis.

Keywords: Tumor spread through air spaces, STAS, Squamous cell carcinoma

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P1.09-38 PULMONARY EPITHELIOID HEMANGIOENDOTHELIOMA (EHE) WITH VON RECKLINGHAUSEN DISEASE

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Background: Malignant thoracic epithelioid tumors are an uncommon. The heterogenous group of tumors that include the low to intermediate grade epithelioid hemangioendothelioma(EHE) and epithelioid angiosarcoma under examination of the morphologic and immunohistochemical features. We here reported a rare case of multiple pulmonary epithelioid hemangioendothelioma with von Recklinghausen disease. **Method:** Case A 34–year–old male was admitted to our hospital with an abnormal shadow in the bilateral lung field. He has von Recklinghausen disease, and non-smoker. The laboratory data and physical examination are normal. A chest computed tomography scan showed multiple nodal lesions of 2 mm to 12 mm in diameter in the bilateral lung fields. **Result:** Thoracoscopic partial resection of the right middle lobe was performed. The tumor was well-circumscribed lesion. In the pathological findings, sections showed a proliferation of epithelioid tumor cells having oval-shaped and vesicular nuclei, prominent nucleoli and pale eosinophilic cytoplasm arranged in small nested or cord patterns. Intracytoplasmic vacuoles some of which contain erythrocytes were recognized. Mitotic figures were rarely seen. In the immunohistochemical examination, the tumor cells were positive for CD31 and CD34, but negative for D2-40, CAM5.2, Ber-EP4, alpha-SMA, desmin, S-100 protein, NSE, TTF-1, calretinin, claudin-4, CD36 and c-kit. RT-PCR analysis showed CAMTA1-WWTR1 fusions was negative. Those features were consistent with pulmonary epithelioid hemangioendothelioma. **Conclusion:** Pulmonary epithelioid hemangioendothelioma(EHE) is rare tumor and there is no report in the literature of EHE with von Recklinghausen disease. The behavior of this neoplasm is uncertain, so the methods of diagnosis and treatment will demand to do careful observation and further examination.

Keywords: von Recklinghausen disease, Malignant thoracic epithelioid tumors, Pulmonary Epithelioid hemangioendothelioma (EHE)

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P1.09-39 SPREAD THROUGH AIR SPACES PREDICTS A WORSE SURVIVAL IN PATIENTS WITH STAGE I ADENOCARCINOMAS > 2.0CM AFTER RADICAL LOBECTOMY

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Background: Spread through air spaces (STAS) has been reported a predictor for recurrence or metastasis for lung cancer patients after limited resection, however, the significance of STAS for patients with lobectomy remains inconsistent. The aim of this study was to evaluate the significance of Spread Through Air Spaces (STAS) in early lung adenocarcinomas after radical lobectomy and lymphadenectomy. **Method:** A total of 242 patients with lung adenocarcinomas less than 4cm (8th pStage I) were selected from the lung cancer patients surgically treated from January, 2009 to September, 2011. Pathological review focused on STAS, and recurrence or distant metastasis-free survival(DFS) and overall survival(OS) were compared between patients as stratified by STAS and tumor size. **Result:** STAS was observed in 33.47%(81/242) patients, which was significantly correlated with histological predominant subtype ($\chi2$=25.903, p=0.000) and differentiation grade($\chi2$=23.986, p=0.000).Patients with STAS (+) showed a comparable PFS(p=0.268) and OS rates(p=0.100) in all stage I cases, but a significant lower PFS(p=0.029) and OS(p=0.013) in tumors within 2.1~4.0cm. Multivariate analysis revealed STAS to be an independent worse prognostic factor in lung adenocarcinomas within 2.1~4.0cm, both for PFS(p=0.004) and OS(p=0.002) , while no significant difference was found in patients with tumors≤2.0cm(PFS, p=0.537; OS, p=0.448), after adjusting by other clinicopathological parameters as age, gender, smoking etc. **Conclusion:** Presence of STAS was a significant worse predictor for pStage I patients with lung adenocarcinoma>2.0cm who underwent radical lobectomy, while it is not significant in patients with tumor ≤2.0cm. These findings may be helpful in assessing postoperative therapy stratified by tumor size and STAS status.

Keywords: lung adenocarcinoma, Prognosis, Spread Through Air Spaces

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P1.09-40 METASTATIC ENDOMETRIAL SARCOMA PRESENTING AS A SPONTANEOUS PNEUMOTHORAX AND MASQUERADING AS A PULMONARY BLASTOMA.

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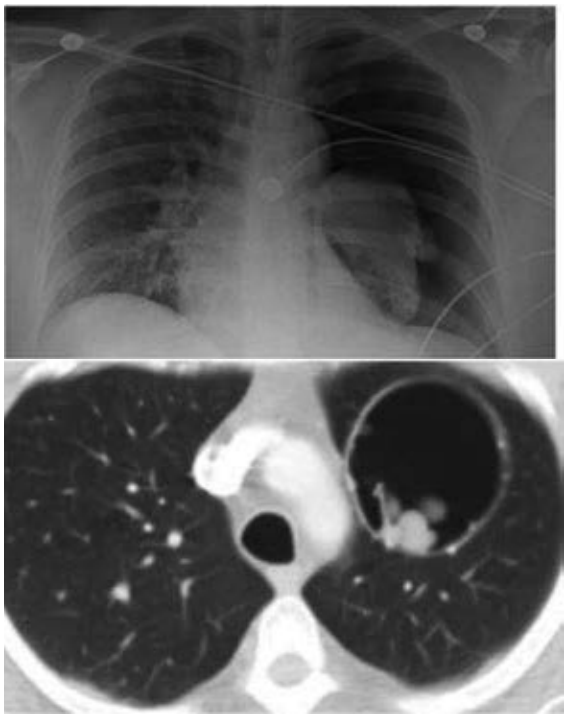
Background: For the proper evaluation of pulmonary cavitary lesions, it is essential to obtain an adequate assessment of the patient's clinical history. Imaging studies can be equivocal and adequate pathological diagnosis can also be challenging. This is particularly important in the case of metastatic lung tumors with extra-thoracic origin, such as certain gynecologic malignancies, which—owing to their late metastatic potential—can be noted years after removal of the primary tumor, causing a misdiagnosis. **Method:** We illustrate this scenario with an interesting case of an endometrial stromal sarcoma which presented as a cavitary lesion causing a spontaneous pneumothorax and initially diagnosed as a pulmonary blastoma. **Result:** 44 year old woman presented with a one day history of left sided chest pain and shortness of breath. The pain was sudden, sharp and associated with dyspnea. The patient denied any fevers, chills, cough, hemoptysis, weight loss, recent travel, sick contacts or tuberculosis. A chest X-ray demonstrated a large left-sided pneumothorax and a chest CT showed a left upper lobe cavitary lesion (Figure 1). Subsequently, a left upper lobe and lingual wedge resection were performe and biopsies of the cavitary lesion were sent. The initial pathological impression was that this was a pulmonary blastoma with heterologous leiomyosarcomatous differentiation. However, further history revealed that the patient had chronic anemia and menometrorrhagia secondary to uterine fibromas and had a total abdominal hysterectomy one year prior to presentation. This finding prompted a review of the pathological specimen and positive immunoreactivity to estrogen/progesterone receptors (ER+/PR+), and CD10+ provided the alternate diagnosis of a metastatic low-grade stromal sarcoma of endometrial origin. Patient followed with medical oncology and gynecology and is currently undergoing hormonal therapy.



Conclusion: This case highlights the importance of a proper correlation of clinical history alongside imaging studies and immunohistochemical findings in the diagnosis of certain lung lesions, in particular thoracic gynecological malignancies.

Keywords: Lung metastasis, Cavitary lesion, extrathoracic primary malignancies

P1.11 SCREENING AND EARLY DETECTION
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P1.11-01 THE NELSON TRIAGE ALGORITHM APPLIED TO A CHINESE BIOPSIED POPULATION: A PILOT STUDY

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Background: The Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) lung cancer screening study sequentially tests nodules' volume, growth and doubling time with an increasing screening interval length. For now, classification performances of NELSON are known only for a European population with specific eligibility criteria. We tested the NELSON trial triage algorithm on a cohort of biopsied Chinese patients. **Method:** Our study utilized a data subset from the NCT02693496 clinical trial. The data consisted of onsite prospective evaluations of 85 Chinese patients who underwent CTs within an average time interval of 259 days (Min=63; Max=1092). NCT02693496 readers applied the Chinese consensus low-dose CT management guidelines with referral to biopsy, when required. The eligibility criteria were: All genders; age: 18 to 90 years old; chest lesion <3cm. Smoking status was not considered. In our subset of 85 patients, 15 nodules from 15 patients were biopsied: 10 were confirmed malignant; of these, 3 were solid nodules (SN) and 7 were sub-solid nodules (SSN). Five biopsied nodules were confirmed benign. Of the whole cohort, 11.8% (10/85), were declared positive patients. The 75/85 others (88.2%) were declared negative by radiologists and/or pathologists. Using the Lesion Management Solution (LMS) platform (Median Technologies), we retrospectively re-processed the subset of images to analyze NELSON sensitivity at detecting malignant lung nodules. We used R CRAN software for statistics and Chi-Squared test for non-parametric comparison of two sample proportions. **Result:** We found 12.9% of patients (11/85) displayed no findings. There were 155 detected findings in the remaining 74 patients, which were documented as: 5.2% (8/155) benign as NODCAT I; 9.0% (14/155) pleural; 27.7% (43/155) SSN and 58.1% (90/155) SN. According to NELSON triage, five Patients were declared positive. In the biopsy-confirmed nodules group (10 patients), four were detected by NELSON, one at baseline. All patients displaying SNs were detected (3/3) whereas only one (1/6) patient displaying SSNs was detected. NELSON was better at detecting SNs (p=0.036). One patient with confirmed negative biopsy patient (1/5) was declared positive by NELSON with one SN and one SSN. Additionally, one SN in patient without biopsy was declared positive at baseline by NELSON triage algorithm. **Conclusion:** Prevalence of different nodule types in this Chinese population was different from the observations of the original European NELSON trial. The NELSON triage algorithm correctly classified patients with malignant SNs but misclassified most patients displaying SSNs. Further studies are needed to better evaluate SSNs by NELSON.

Keywords: CT screening, Clinical Epidemiology, nodule management

P1.11 SCREENING AND EARLY DETECTION
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P1.11-02 PATHOLOGIC COMPARISON OF PREVALENT VS. INCIDENT CT LUNG SCREEN DETECTED CANCER IN NCCN HIGH-RISK SUBJECTS: ARE THEY DIFFERENT?

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Background: CT lung screening (CTLS) detects two overlapping but potentially distinct groups of tumors. Prevalent tumors, found at baseline screening, are thought to be enriched with slow-growing, potentially indolent cancers while incident tumors, found on annual repeat scans, are thought to be more uniformly fast-growing and aggressive. Pathologically, squamous cell carcinomas, small cell carcinomas (SCC) and large cell neuroendocrine carcinomas (LCNEC) are uniformly fast-growing and aggressive while adenocarcinomas are more heterogenous in their growth-rates, behavior and histology. By comparing pathologic subtypes, I-ELCAP investigators reported a higher frequency of adenocarcinomas compared to squamous cell carcinomas in prevalent compared to incident tumors (ratio 8:1 vs. 3.4:1) and conversely a 4-fold lower frequency of SCC/LCNEC (7% vs. 30%, respectively). Based partly on these data, some worry about the risk of overdiagnosis in CTLS subjects undergoing baseline screening in which the proportion of slow-growing potentially indolent adenocarcinomas may be enriched. Current guidelines recommend screening specific high-risk subjects for which pathologic comparisons of prevalent and incident cancers have not been thus far described. **Method:** The pathology of 134 CTLS cancers detected at Lahey Hospital & Medical Center was reviewed, including 93 detected at baseline and 41 at annual repeat screening. All individuals met the NCCN Guidelines Lung Cancer Screening v1.2012 high-risk criteria, were asymptomatic, had no known metastatic disease and were free of lung cancer for at least 5-years. Detailed pathologic analysis was performed for 65 stage I resected adenocarcinomas whereas lineage alone was determined for the cytologically diagnosed tumors. **Result:** The proportion of adenocarcinomas to squamous cell carcinomas was similar in prevalent compared to incident tumors (ratio 2.6:1 vs. 3.1:1). Small cell carcinomas were only half as frequent among prevalent vs. incident cancers (5% vs. 12%). Among stage I adenocarcinomas, a similar proportion of prevalent vs. incident cancers exhibited a ≥5% solid pattern (32% vs. 30%), ≥5% micropapillary pattern (23% vs. 22%), ≥10% cribriform pattern (30% vs. 26%), intermediate/high mitotic grade (57% vs. 57%), angiolymphatic invasion (43% vs. 48%), and STAS (36% vs. 39%). Visceral pleural invasion was actually higher in the prevalent cancers (27% vs. 17%) however no statistically significant differences were observed. **Conclusion:** Pathologic comparison of prevalent vs. incident CTLS cancers among NCCN defined high-risk subjects reveals less variability than previously described by I-ELCAP. In particular, histologically indolent adenocarcinomas are not enriched in prevalent compared to incident tumors and thus the risk of overdiagnosis in baseline detected cancers may be less than once thought.

Keywords: Overdiagnosis, Screen

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P1.11-03 MICRORNA WITH ABILITY TO RECIPROCAL REGULATION OF DICER AND DROSHA – PLASMA EXPRESSION STATUS AND DIAGNOSTIC VALUE IN NON-SMALL CELL LUNG CANCER

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Background: Examination of microRNAs expression in plasma could be useful in screening and in early detection of non-small cell lung cancer (NSCLC). One of the most important enzymes in miRNA biogenesis are Dicer and Drosha. Disrupted expression of miRNA with ability to reciprocal regulation of Dicer and Drosha could participate in cancer development. **Method:** Plasma expression of miR-27-3p, miR-31, miR-182 and miR-195 were analysed in 138 Polish NSCLC patients (median age 65 years, 83 male and 55 female) and in 45 healthy people (median age 62 years, 28 male and 17 female). 57 (41.3%) NSCLC patient were in I-IIIA stage and 81 (58.7%) patients were in IIIB-IV stage. Relative expression of microRNAs between studied groups was compared using U Mann-Whitney test. For assessment of diagnostic accuracy (test sensitivity and specificity), the receiver operating curves (ROC) with area under curve (AUC) analysis were generated. **Result:** We demonstrated that plasma levels of miR-27-3p, miR-31 and miR-182 were significantly higher (p<0.000001, p=0.00008, p=0.006 respectively) and miR-195 significantly lower (p=0.000002) in NSCLC patients in comparison with healthy donors. Moreover, patients with early stages (I-IIIA) of NSCLC showed significantly higher expression of miR-27a-3p (p<0.000001), miR-31 (p=0.0003) and miR-182 (p=0.000003) than healthy persons. Expression of miR-195 was significantly lower in patients with early stages (I-IIIA) of NSCLC than in healthy donors (p<0.000001). AUC for miR-27a was 0.95 (94% sensitivity and 81% specificity, p<0.00001), for miR-31 was 0.71 (73% sensitivity and 61% specificity, p=0.001), for miR-182 was 0.77 (70% sensitivity and 79% specificity, p<0.00001) and for miR-195 was 0.82 (74% sensitivity and 80% specificity, p=0.00001).

Conclusion: Expression of miR-27a, miR-31, miR-182 and miR-195 could distinguish patients with NSCLC from healthy people. The examination of these microRNAs in plasma could be used in non-invasive lung cancer diagnosis. Deregulation of Dicer and Drosha expression by microRNAs could have oncogenic character.

Keywords: miRNAs, lung cancer, Biomarkers

P1.11 SCREENING AND EARLY DETECTION
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P1.11-04 SIZE MEASUREMENT VARIABILITY OF SOLID COMPONENT OF LUNG ADENOCARCINOMA

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Background: In the current TNM classification for lung cancer, the solid size is used for tumor diameter measurement as dense component. However, in daily practice, it is sometimes difficult to measure the solid size, so the variability between the observer may increase, and therefore it is presumed that the measurement variability between radiological and pathological size become large particularly in subsolid nodules. In this study, we investigate the interobserver variability and differences between the radiological and pathological tumor size in lung adenocarcinoma. **Method: Interobserver variability:** We assessed 47 cases of subsolid type lung adenocarcinoma operated in our department from January to December 2016. Six physicians including surgeons and radiologist measured the solid and total size using preoperative CT and assessed the interobserver measurement variability. Furthermore, we assessed the interobserver variability using 5 subclassified patterns of the tumor. **Radiological-pathological variability**: Radiological-pathological variability in measurement of solid size in adenocarcinoma using database of 554 surgical cases from January 2010 to Jun 2017 was investigated. We also assessed the stage migration using radiological and pathological T stage classified by only tumor size. **Result:** The mean interobserver variability of six observers of 47 cases was 9.7 mm in solid size, and 7.7 mm in total size. The tumor images were subclassified into the following 5 patterns: ①minimally invasive ②peribronchovascular ③spicula/atelectasis ④adjacent to cystic lesions ⑤pneumonia-like consolidation. To correct for differences in mean tumor diameter in each pattern, comparison was made using coefficient of variation (CV) calculated by SD/mean. The pattern of minimally invasive (①) became the largest value for CV in the measurement of solid size. The mean radiological-pathological variability of 554 cases was 5.9 mm in solid size, and 5.4 mm in total size. In cases of Tis, T1mi in T stage, and adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) in histological type, the CVs were larger than others. The comparison of radiological and pathological T stage, the accurate staging rate was 41.8%, and upstage were seen in 28.8% in all cases. **Conclusion:** Interobserver measurement variability of solid size of the lung adenocarcinoma was larger than those of total size. The difference between radiological and pathological invasion size tend to be larger in small-sized tumor as Tis and T1mi, and low-grade malignant potential lesions as AIS and MIA. Therefore, a careful consideration must be given to decide the management plan of these cases.

Keywords: measurement variability, solid size, lung adenocarcinoma

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P1.11-05 METABOLOMIC PROFILING FOR SECOND PRIMARY LUNG CANCER AMONG LUNG CANCER SURVIVORS

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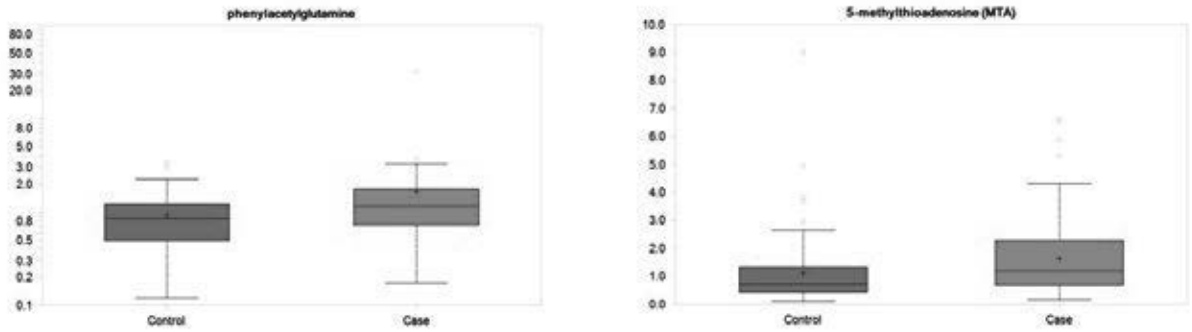
Background: Survivors of lung cancer(LC) have a high risk of developing second primary lung cancer(SPLC), the incidence of which is 4-6 times higher than that of initial primary lung cancer(IPLC). While national lung screening guidelines have been established for IPLC, no consensus guidelines exist for LC survivors. Furthermore, the factors that contribute to SPLC risk have not yet been established. The purpose of this study is to examine the potential of metabolomics to identify non-invasive blood-based biomarkers for SPLC screening. **Method:** We applied an untargeted metabolomics approach based on a liquid chromatography-tandem mass spectroscopy(UPLC-MS/MS) method to discover metabolic biomarkers using blood serum samples from the Boston Lung Cancer Study. Our study cohort consisted of 177 subjects diagnosed with IPLC between 1992 and 2012 and who survived >=5 years after the initial diagnosis. The cohort included 82 SPLC cases and 95 matched controls (i.e. IPLC patients without SPLC as of Dec, 2017) based on the age of initial diagnosis, sex, race, and smoking status. We applied random forest and Welch's t-test to identify metabolomic features associated with SPLC risk and to build a risk prediction model. **Result:** Our analysis detected 1008 named and 316 unnamed metabolites. The metabolites that were statistically significantly associated with SPLC risk (False Discovery Rate q-value<0.05) included 5-methylthioadenosine (MTA), phenylacetylglutamine, and umbelliferone sulfate, which showed 1.4-3.8 fold increases among SPLC cases versus controls (**Figure 1**). These metabolites were involved in amino acid, peptide, and xenobiotics pathways. The stratification by quintiles of estimated risk using the prediction model based on the metabolites showed that the observed incidence of SPLC was significantly higher in the fifth quintile(69.4%) versus the first-quintile(36.1%;P<0.05).

Figure 1. Top ranking metabolites (q-value < 0.05) with increased levels among SPLC cases versus controls. Phenylacetylglutamine (q-value=0.03 and p-value =0.0003) and 5-methylthioadenosine (MTA) (q-value=0.03 and p-value =0.0002) are involved in peptide and amid acid pathways respectively.



Conclusion: We identified potential metabolic biomarkers for SPLC among LC survivors. A risk-stratification approach based on metabolic biomarkers can be potentially useful for identifying high-risk LC survivors to be screened by CT.

Keywords: second primary lung cancer, lung cancer, metabolomics

P1.11-06 LUNG CANCER PROBABILITY IN NEW PERIFISSURAL NODULES DETECTED IN A LUNG CANCER SCREENING STUDY

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Background: In incidence lung cancer screening rounds, new lung nodules are a regular finding, with a higher lung cancer probability than baseline nodules. A substantial number of screen-detected nodules is classified as perifissural nodule (PFN). Previous studies showed that baseline PFNs and PFNs in clinical settings represent non-malignant lesions such as intrapulmonary lymph nodes. Whether this is also the case for incident PFNs is unknown. This study evaluates all newly detected nodules in the Dutch-Belgian randomized-controlled NELSON study with respect to perifissural classification and lung cancer probability. **Method:** All NELSON participants with a new solid nodule detected in screening round 2, 3 or 4 (1, 3, and 5.5 years after baseline, respectively), were enrolled in this substudy. Nodules were classified into three groups: intraparenchymal, vessel attached or fissure attached. Screening CT scans of participants with lung cancer based on a nodule classified as fissure attached, were re-evaluated by two radiologists (4 and 6 years of experience) to check whether this nodule was a typical, atypical or non-PFN. The fissure-attached cancers were matched based on size with benign cases (1:4), and the radiologists were blinded for the final nodule outcome. In case of discrepancy, a third radiologist (13 years of experience) arbitered. **Result:** 1,484 new nodules were detected in the second, third and final NELSON screening round in 949 participants (77.4% male, median age 59 [interquartile range: 55-63]). 1,393 nodules (93.8%) were benign based on 2 year follow-up or pathology; 96 of these (6.9%) were fissure attached. Lung cancer diagnosis was made in 74 new nodules in 74 participants (7.8% of participants with a new nodule). Nine lung cancers (12.1%) were fissure attached and re-evaluated by the radiologists. None of the fissure attached malignant new nodules was classified as a typical or atypical PFN. **Conclusion:** None of the lung cancers that originated from a new nodule in the NELSON study was classified as a typical or atypical PFN. Our results suggest that also in the case of a new PFN, it is highly unlikely that these PFNs will be diagnosed as lung cancer.

Keywords: Lung cancer probability, lung nodule, lung cancer screening

P1.11-07 UTILITY OF THE MAXIMUM CT VALUE IN PREDICTING INVASIVENESS OF PURE GGNS

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Background: In the current TNM classification of lung cancer, the pulmonary lesions presenting pure ground-glass nodules (GGNs) without solid component are classified as cTis tumor. However, some of them are pathologically diagnosed as invasive adenocarcinomas. This study aimed to predict the histological invasiveness using the computed tomography (CT) value in pure GGN lesions. **Method:** 138 patients underwent resection of pure GGNs between 2011 and 2016. The maximum diameter and CT value were measured using a computer graphics support system. We selected the axial section which showed the densest component of each GGN. The CT value was measured separately in several areas excluding portions of apparent vessels and bronchi manually. We analyzed the correlation between the CT value of pure GGNs and the histological diagnosis, such as atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and invasive adenocarcinoma (Ad). **Result:** The number of the patients with AAH, AIS, MIA and Ad was 6, 81, 45 and 6, respectively. 37% of the pure GGN lesions contained histologically invasive component and 4% of them were diagnosed as Ad. One tumor of Ad had lymphatic invasion, while there was no case with vascular invasion. 37 lobectomies, 38 segmentectomies and 63 wedge resections were performed and there was no recurrence. In comparison between the preinvasive lesions (AAH and AIS) and the invasive lesions (MIA and Ad), the latter was significantly correlated with the higher age of the patients (60 ± 9 years vs 67 ± 7 years), the larger total size (12 ± 5 mm vs 16 ± 5 mm), the higher maximum CT value (-388 ± 125 HU vs -208 ± 129 HU) and the presence of pleural indentation (odds ratio, 2.8). When the cut-off point of the maximum CT value in predicting histological invasiveness was set at -300 HU using the ROC curve analysis, the sensitivity, specificity, positive predictive value and negative predictive value were 80%, 77%, 67% and 87%, respectively. The 100% of Ad and the 78% of MIA were correctly estimated. **Conclusion:** Invasive adenocarcinoma and MIA accounted for 4% and 33% of the pure GGN lesions, respectively. The maximum CT value was correlated with the pathological diagnosis. It may be useful as a predictor of histological invasiveness. The threshold at -300 HU can be the basis of the computer-aided automatic diagnosis.

Keywords: GGN, invasiveness, CT value

P1.11-08 AI BASED MALIGNANCY PREDICTION OF INDETERMINATE PULMONARY NODULES: ROBUSTNESS TO CT CONTRAST MEDIA

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Background: Artificial Intelligence (AI) based malignancy prediction of indeterminate pulmonary nodules has been previously demonstrated to perform well on screen-detected nodules imaged with low-dose, non-contrast CT. This study aimed to assess the impact of contrast media on the classification performance of such a system. **Method:** A Convolutional Neural Network (CNN) was trained on the US National Lung Screening Trial (NLST), which contained only low-dose non-contrast screening images, selecting all nodules 6mm and greater in size (14761 benign nodules from 5972 patients; 932 cancer from 575 patients). A CNN classifier was trained using Deep Learning on this data to produce a malignancy score per nodule. For validation, an independent retrospective dataset of incidentally detected solid nodules was used. None of the patients had a cancer diagnosis within the past 5 years, and all had fewer than 5 nodules. The dataset contained 571 nodules from 505 patients, including 42 cancer from 39 patients. A CT was considered to be contrasted if the mode HU value within an ROI placed at the aortic arch was greater than 60HU. This resulted in two groups: the non-contrast group had 313 nodules from 276 patients (16 cancer from 14 patients); the contrast group had 258 nodules from 229 patients (26 cancer from 25 patients). The overall efficacy was assessed using Area-Under-the-ROC-Curve analysis (AUC) for each group. **Result:** The AUC on the non-contrast CT group was 0.96 (95% CI 0.93 to 0.98) and 0.95 (95% CI 0.90 to 0.99) on the contrast CT group. Further analysis revealed that excluding high contrast cases, where the HU in the aortic arch was greater than 300HU (40 nodules from 38 patients; 4 cancer), resulted in an AUC of 0.97 (95% CI 0.92 to 1.00). **Conclusion:** The CNN classifier seems to be robust to the presence of contrast media with only a moderate reduction in performance. Excluding cases with high contrast restored the performance, although, with only 38 nodules excluded by this, the result may be not statistically significant. These results indicate that a CNN developed to predict pulmonary nodule malignancy, that has been trained on low-dose, non-contrast enhanced CT images, may be used with CT images with moderate levels of contrast without retraining.

Keywords: pulmonary nodules, diagnosis, AI

P1.11-09 THE DELAY OF LUNG CANCER DIAGNOSIS DUE TO MISDIAGNOSING AS PULMONARY TUBERCULOSIS

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Background: Indonesia is a country with the second largest number of Tuberculosis (TB) cases in the world. Clinical symptom similarities of lung cancer to those of pulmonary TB can lead lung cancer patients to be diagnosed as pulmonary TB and receive Anti Tuberculosis Treatment (ATT) especially in TB endemic countries. The evaluation of ATT responses is often less stringent, resulting in delayed diagnosis of lung cancer. This study aimed to investigate the percentage of delayed lung cancer diagnosis due to misdiagnosing as pulmonary TB thus receiving ATT over one month. **Method:** A descriptive study was conducted in Dr. Moewardi Hospital, Solo Indonesia by using patients' medical record data from January 2014 to February 2016. **Result:** Of the 305 lung cancer

patients, 194 (63.6%) were males and 111 (36.4%) were females and the average age was 48 years old. History taking and Acid Fast Bacillus (AFB) smear revealed 93 (30.5%) patients were diagnosed as pulmonary TB and received ATT. Three (1%) were found to have lung cancer in conjunction with pulmonary TB with positive AFB while 90 (29.5%) lung cancer patients had been misdiagnosed as pulmonary TB and had been given ATT with the average duration of 3.26 months and the longest administration was 7 months. Based on the duration of ATT there were 22 (24.4%) and 68 (75.6%) patients receiving ATT for ≤ 1 month and > 1 month respectively. Of the 90 lung cancer patients who had misdiagnosis as pulmonary TB, there were 56.7% males, 94.4% aged over 40 years old and 62.2% smokers. The types of lung cancer were non-small cell lung carcinoma (NSCLC) consisted of 68 (75.6%) adenocarcinoma, 13 (14.4%) squamous cell carcinoma, 5 (5.6%) large cell carcinoma, and 2 (2.2%) neuroendocrine carcinoma. Two (2.2%) of the patients were small cell lung cancer (SCLC). Based on NSCLC staging there were 0% stage I, 0% stage II, 0% stage IIIa, 11.1% IIIb and 88.9% stage IV. The most common metastasis was pleural effusion (58.9%) followed by other organ (27.8%). **Conclusion:** Our study revealed that 29.5% lung cancer patients who were previously misdiagnosed as pulmonary TB, 75.6% of them received ATT over a month with the average duration of 3.26 months. This misdiagnosis resulted in the delay of lung cancer diagnosis.

Keywords: misdiagnosis, lung cancer, Pulmonary Tuberculosis

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P1.11-10 OPTIMIZING RADIOMICS FEATURES BY MINIMIZING BOUNDARY EFFECTS AND NORMALIZING WITH OPPOSITE LUNG TISSUE CHARACTERISTICS

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Background: For wide adoption of LDCT screening it is thought that CAD will likely by necessary. We hypothesize that CAD features that minimizes perimeter effects and normalizes nodule CT features using the lung parenchyma from the opposite lung will improve the ability to determine nodule malignancy. **Method:** We have developed a CAD system that includes lung tissue segmentation, nodule detection and feature extraction from the segmented nodule, the segmented nodule minus the perimeter transition pixels (Core), and the opposite lung parenchymal tissue. (See Figure 1). We use the Mann-Whitney U test to compare teh discriminating ability of individual features and combinations of features) extracted from the nodule, nodule core and nodule normalized by mirror region features.

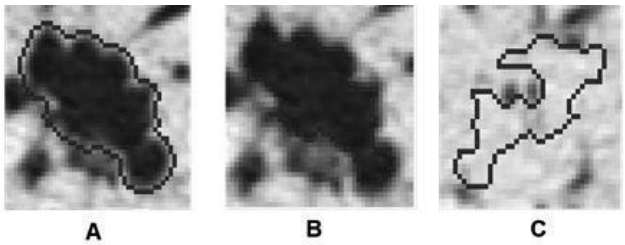

Figure 1: Example of a segmented nodule (A) nodule core, (B) and (C) the mirrored parenchyma region in the opposite lung (excluding blood vessels).

Result: In total, 34 early small suspect baseline nodules detected as part of the PanCan screening trial were used, these include 17 nodules proven to be cancer and 17 nodules that resolved on follow-up scans. The comparison of classification ability of features from nodules without edge vs. nodules with edge pixels reveals that the core features show better classification ability for 76 out of the 136 calculated features. Performing a leave-one-out LDA classifier cross-validation approach in using core features, gives an accuracy of 76% with only 1 feature through 3 features, and 82% with 4 features. However, repeating the same experiment for core plus edge features, shows accuracy of 67% with only 1 feature, 73% with 3 features, 79% with 4 features. Normalizing the core texture features by the texture features of the mirrored region in the opposite lung shows an improved classification ability for 52 out of the 89 texture features. **Conclusion:** In this study, the results suggest using the nodule core improves feature classification as does normalizing of the nodule by the mirrored region in opposite lung.

Keywords: Radiomics, Spiral CT, Early Cancer

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P1.11-11 COMPARING LUNG CANCER DIAGNOSED BY LOW DOSE CT (LDCT), INCIDENTAL LUNG NODULE PROGRAM (ILNP), AND NON-PROGRAM-BASED DETECTION

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Background: The aggregate 5-year survival of lung cancer patients is <20%, partly because most patients present with advanced disease. LDCT screening and algorithmic management of patients with incidentally-detected nodules are two methods for early detection, but rigorous evaluation is needed for effective implementation. We compared patients with lung cancer diagnosed via LDCT vs. ILNP vs. neither in a lung cancer-endemic US region. **Method:** We compared demographic, clinical, and treatment characteristics of patients diagnosed via LDCT and ILNP with those treated in a multidisciplinary program (MDP) who were not diagnosed through either early detection program. LDCT screening was implemented in 2015 using Medicare eligibility criteria. In the ILNP, navigators and a multidisciplinary team prospectively tracked patients with suspicious findings flagged by radiologists, using Natural Language Processing software. All patients were diagnosed within the same healthcare system from 2015-2018. Statistical comparisons used chi-square, Fishers Exact, and ANOVA. **Result:** Lung cancer diagnoses included 111 from 5,954 ILNP scans, 11 from 400 LDCT scans (1.9% v 2.8%, p=0.21), and 273 from MDC. An additional 40 (10%) LDCT scans were Lung RADS 3 or 4. Average ages were 70/68/68 years for ILNP/LDCT/MDC and patients were 43%/64%/48% male. African Americans were underrepresented in both early detection groups (23%/9%/36%; p=0.0111); Medicare patients were over-represented (83%/91%/42%, p<0.001). Active smoking was highest in LDCT (73%, 79 pack-year average), but similar between ILNP and MDC (39%, 50 pack-year average vs 36%, 63 pack-year average). Early detection cases were more frequently adenocarcinoma (61%/ 55%/48%; p=0.0595) with smaller lesions (2.2cm/1.0cm/4.2cm; p<0.001). Stage I/II cancers were more likely with early detection (71%/89%/42%; p<0.001), leading to substantially higher rates of surgical resection (75%/73%/31%; p<0.001). Median time from lesion detection to treatment initiation was similar between groups (61/74/58 days, p=0.48). 62% of patients with lung cancers diagnosed by ILNP and 57% by MDC were not eligible for LDCT screening. The most common disqualifying criteria were a 30 pack-year smoking history (unmet: 41% ILNP/ 41% MDC) and active smoking within 15 years (unmet: 41% ILNP/ 27% MDC). **Conclusion:** Lung cancers diagnosed by ILNP and LDCT had better prognosis than the MDC population, with smaller tumors, earlier stage, and more treatment with surgical resection. African Americans were underrepresented in these groups. Less than half of ILNP and MDC cases had enough smoking exposure to qualify for LDCT screening. ILNP is a critical component of early detection programs, reaching an element of the population that did not qualify for LDCT screening.

Keywords: screening; early detection; incidental nodule

P1.11 SCREENING AND EARLY DETECTION
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P1.11-12 INTERROGATION OF AN EXHALED MICRORNA PANEL FOR LUNG CANCER RISK ASSESSMENT

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Background: There is a need for non-invasive airway-based biomarkers in lung carcinogenesis for both risk assessment of the ex-smoker, and earlier diagnosis. Exhaled breath condensate (EBC) contains airway lining fluid molecules, including nucleic acids, presumably in part from epithelial cellular origins. MicroRNAs play important regulatory roles in many processes, including carcinogenesis. Here we further develop and begin validation of the detection of microRNAs in EBC from lung cancer patients and controls. **Method:** EBC was collected non-invasively, using a handheld commercial RTube® device in a clinical series of ambulatory subjects. We generated a 40 miR panel based on literature-derived microRNAs, bronchial brushed microRNA discovery by collaboration, and a lung parenchymal tissue discovery effort we have performed using

microRNA-seq on lung tumors and surrounding non-tumor tissue. The PCR primers were designed using our previously published RNA-specific RT-PCR technique. All samples were run twice with positive and negative controls. Calls was made of individual miR present or absent in a given EBC sample, by one of two replicates being positive. The data were analyzed by random forests. **Result:** We applied the panel to EBC from 177 individuals, 89 NSCLC predominantly early stage (I and II) cases and 88 controls of similar smoking history. We used an empirically-derived base clinical model that included age, smoking status, pack-years, quit-years, and underlying lung disease. MicroRNA signatures alone discriminated cases from controls with ROC-AUCs of 0.64-0.76. Both analyses revealed a small set of incrementally informative miRs (e.g., miRs-21**, 33b**, 96*,105*, `130b.3p*, 200a*, 200b**, 205, 212***, 221***, 345***, 767**, 944*, 1269a***, 1293*, 1910**, 3648*, 3662*, where number of '*' implies number of appearances in each of three models). Here some modest incremental case-control discriminant capacity was conferred by the respective microRNA signature over and above the base clinical model. The magnitude of the increment was typically 2-3% [RF AUC 0.84 clinical model=>0.86 clinical+microRNA (all lung cancer histologies, Welch p=1.33e-05); 0.82=>0.84 (adenocarcinomas, Welch p=3.13e-03); 0.84=>0.86 (NSCLC, Welch p=4.10e-05). Quantitative RT-PCR using this platform set-up was not sufficiently robust to further analyze. **Conclusion:** This new exhaled biomarker platform can yield case-control discriminant microRNA sets. albeit modest in incremental impact as formulated so far. Once quantified, further distilled and validated, our goal is to test this non-invasive biomarker approach to prospective cohorts for non-invasive lung cancer risk assessment, in order to non-invasively better select higher risk individuals to undergo effective CT screening.

Keywords: risk, biomarker, microRNA

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P1.11-13 NONINVASIVE DETECTION OF EARLY STAGE NSCLC EGFR MUTATIONS USING ELECTRIC FIELD INDUCED RELEASE AND MEASUREMENT (EFIRM)

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Background: The ability of liquid biopsy to detect circulating tumor mutations has proved especially valuable in the treatment of patients with NSCLC since well characterized variants inform small molecule chemotherapeutic options. EFIRM is a signal amplification technology that allows direct detection of mutations in native plasma and saliva without amplification or sequencing. Previously published work demonstrated a near perfect correlation between biopsy and EFIRM results for the Exon19 del and p.L858R mutations in *EGFR* in late stage NSCLC patients. In this study we investigated the performance of EFIRM in patients early stage (I and II) NSCLC patients. **Method:** Plasma samples were collected from 33 healthy controls with biopsy proven benign lung masses and 21 stage I and II NSLC patients with biopsy proven EGFR mutations The samples were immediately centrifuged and frozen. The samples were then blinded and sent for EFIRM analysis. **Result:** There were 12 biopsies positive for p.L858R (11 stage 1 and 1 stage II) and 9 positive for Exon 19 del (7 stage 1A, and 2 stage II). Using statistically derived cut-offs to optimize sensitivity and specificity, there were 2 false positives (both for p.L858R) in the controls yielding an overall specificity of 91% for the 2 SNP Mutation assay. The sensitivity was 92% for the p.L858R with only one negative in 12 samples in a patient with stage 1 and 77% for Exon 19 del with 2 negatives in 9 samples in a single patient each for stage 1 and 2. **Conclusion:** The preponderance of patients in this study had stage I NSCLC. The sensitivity of 94% and 77% respectively for the 2 most common mutations is remarkable for patients with Stage 1 lung cancer and a correspondingly low tumor burden and more importantly at a potentially curable stage. We are in the process of improving the technical performance of this assay and adding additional variants to the panel in order to increase clinical utility. These data are promising for the potential use of the EFIRM platform for the purposes of drug selection, disease recurrence, follow-up of indeterminate lung nodules from spiral CT screening programs, and / or population screening.

Keywords: early stage lung cancer, liquid biopsy, EGFR

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P1.11-14 RADIOLOGICAL PLEURA-TUMOR PROXIMITY IN PURE-SOLID CLINICAL STAGE I LUNG CANCER: ITS INFLUENCE ON LYMPH NODE METASTASIS AND RECURRENCE

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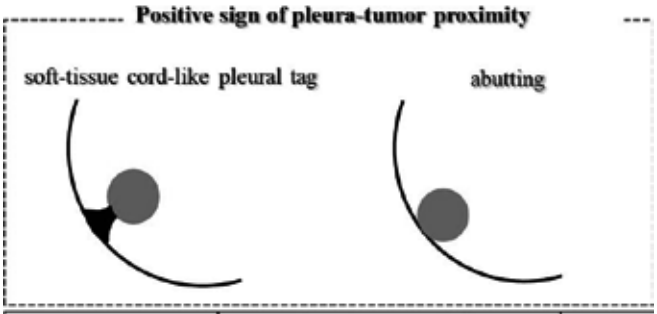
Background: Lymph node metastasis of lung cancer is an important factor for deciding on surgical indications. Radiological pure-solid lung cancer is a highly aggressive feature, even in small lesions, and it is generally difficult to evaluate lymph node metastasis based on preoperative clinical examinations. We focused on the radiological association between the tumor and pleura and assessed the influence of pleura-tumor proximity on the risk of lymph node metastasis and postoperative recurrence. **Method:** We retrospectively reviewed a consecutive series of 133 patients with clinical stage I lung cancer possessing pure-solid nodule on chest computed tomography who had undergone lobectomy with systematic lymph node dissection between January 2009 and December 2016. Figure shows the definition of positive pleura-tumor proximity. A multiple logistic regression analysis was used to identify the predictors for lymph node metastasis, and a multiple Cox proportional hazards model was used to identify the predictors for postoperative recurrence, with covariates of age, gender, performance status, resected side, pulmonary function, tumor size, pleural tag, pleura-tumor proximity, and maximum standardized uptake on positron emission tomography.



Pathological N status	Pleura-tumor proximity		P
	Present	Absent	
Positive	14 (23%)	7 (10%)	0.037
Negative	47 (77%)	65 (90%)	

Result: There were 89 men (mean age 70.7 ± 9.6 years). The mean tumor size was 22.9 ± 8.7 mm. Lymph node metastasis was found in 21 patients (15.7%), and postoperative recurrence was found in 24 patients (18%). According to the multivariate analysis, the age (p = 0.013) and positive pleura-tumor proximity (p = 0.036) were the independent predictive factors of lymph node metastasis, and the positive pleura-tumor proximity (p = 0.035) was an independent predictive factor of postoperative recurrence. **Conclusion:** Pleura-tumor proximity in radiological pure-solid lung cancer was associated with lymph node metastasis and postoperative recurrence. Such pleura-tumor proximity should therefore be taken into consideration in the therapeutic decision-making for stage I lung cancer possessing pure-solid nodules.

Keywords: lung cancer, computed tomography, radiological pure-solid tumor

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P1.11-15 APPLICATION OF LUNG-RADS VS. PAN-CAN NODULE RISK CALCULATION IN THE ALBERTA LUNG CANCER SCREENING STUDY

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Background: False positive or negative examinations and high early recall rates are important factors in the performance of lung cancer screening programs. How low-dose chest tomography (LDCT) scans are interpreted and classified may impact these metrics. **Method:** LDCT examinations for participants in the Alberta Lung Cancer Screening Study (ALCSS) were interpreted by chest radiologist with information entered in a synoptic report. Baseline scans were classified according to highest risk of malignancy nodule as per the PAN-CAN nodule risk calculator (NRC) and according to the Lung-RADS scheme. A positive scan was any baseline LDCT requiring any intervention beyond an annual screening examination (NRC nodule with ≥5% malignancy risk; Lung-RADS category ≥3). In the calculation of sensitivity, false negative scans could include reader error or classification errors (NRC <5% or Lung-RADS <3 but cancer present regardless of perceived appropriateness of resulting management). **Result:** Seven hundred and seventy-six participants in the ALCSS underwent LDCT screening and had no prior chest CT imaging on file. Median follow-up was 572 days (+/-205) with lung cancer confirmed in 16 (2.1%) participants. The early recall rate was 9.0% for NRC and 11.2% for Lung-RADS (p=0.044), with fair concordance between each approach (kappa 0.554). Sensitivity for malignancy was 87.5% vs. 87.5% (difference 0%, 95%CI -0.44%-0.44%) and specificity 92.6% vs. 90.4% (difference 2.2%, 95%CI 0.2%-4.3%) for NRC and Lung-RADS respectively. False negative screens were due to reader error (same case in both systems); and classification error (one different case for each system).

	Cancer +	Cancer -	Total
NRC +	14	56	70
NRC -	2	704	706
Lung-RADS +	14	73	87
Lung-RADS -	2	687	689
Total	16	760	776

Conclusion: Performance of both the NRC and Lung-RADS in the ALCSS was very good, with NRC resulting in a lower early recall rate. Application of the NRC demonstrated increased specificity over Lung-RADS without a change in sensitivity for lung cancer detection. Lung cancer program performance may be improved with the use of the PAN-CAN NRC classification.

Keywords: computed tomography, Screening, Early Detection

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P1.11-16 MODIFIED LUNG-RADS IMPROVES PERFORMANCE OF SCREENING LDCT IN A POPULATION WITH HIGH PREVALENCE OF NON-SMOKING-RELATED LUNG CANCER

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Background: We proposed a modification of the ACR Lung Imaging Reporting and Data System (Lung-RADS) to clarify the characteristics of subsolid nodules with categories 1–11, and to compare the diagnostic accuracy with Lung-RADS and National Lung Screening Trial criteria in an Asian population with high prevalence of adenocarcinoma. **Method:** We analyzed a retrospective cohort of 1978 consecutive healthy subjects (72.8% non-smoker) who underwent low-dose computed tomography from August 2013 to October 2014 (1084 men, 894 women). Lung-RADS categories 2 and 3 were modified to include subcategories of 2A/2B/2C and 3A/3B/3C, respectively. Clinical information and nodule characteristics were recorded. Receiver operating characteristic curves were used to compare diagnostic accuracy at different cutoffs. **Result:** Thirty-two subjects (30 nonsmokers) had pathology-proven adenocarcinoma spectrum lesions in the follow-up period (1.6 ± 0.5 years). Modified Lung-RADS, using modified Lung-RADS category 2C as cutoff, had an area under the curve (AUC) of 0.973 in predicting adenocarcinoma spectrum lesions (sensitivity of 100%, specificity of 89.3%), which was significantly higher than that of Lung-RADS (AUC = 0.815, P < .001) and National Lung Screening Trial (AUC = 0.906, P < .001). Furthermore, modified Lung-RADS showed an AUC of 0.992 in predicting invasive adenocarcinoma (sensitivity of 95%, specificity of 97.8%) when category 3B was used as cutoff. **Conclusion:** Modified Lung-RADS may substantially improve sensitivity while maintaining specificity for detection of adenocarcinoma spectrum lesions in an Asian population. Compared to Lung-RADS, it has enhanced ability to differentiate invasive from indolent adenocarcinoma by more refined subclassification of subsolid nodules using two cutoff values of category 2C and 3B. The effect of using modified Lung-RADS in clinical practice must be carefully studied in prospective large cohort studies.

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P1.11-17 DISCRIMINATING LESS INVASIVE LESIONS OF EARLY-STAGE LUNG ADENOCARCINOMA BY THREE-DIMENSIONAL COMPUTED TOMOGRAPHY ANALYSIS

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Background: In the revised TNM classification for non-small cell lung cancer, the clinical T factor is specified by the maximum diameter and by the diameter of the solid component for subsolid nodules. However, as radiological measurement of the solid part is sometimes difficult, errors can occur among observers. If less invasive lesions can be truly predicted using computed tomography (CT) images, it will be very useful for determining treatment strategies. Hence, we investigated the ability to detect less invasive lesions in pathologically early-stage adenocarcinomas by evaluating the whole tumor based on three dimensional (3D) images from high-resolution CT (HRCT). **Method:** Among patients who underwent lung resections for primary lung cancer between February 2014 and December 2016 in our institution, we retrospectively reviewed 127 patients with pathological stage 0 or IA adenocarcinoma. All the lesions were divided into two groups: the less invasive group comprised adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), and the invasive group comprised invasive adenocarcinoma. Radiological occupied lesion volumes (cm^3) were semi-automatically calculated using 3D-CT volumetry, which included the data of CT values and voxels. The following six factors were also evaluated using voxel-based histogram analysis (VHA): % solid (the ratio of the volume with CT values above -300 Hounsfield units to the whole CT value), mean CT values, variance, kurtosis, skewness, and entropy. Using multivariate logistic regression analysis, the relationship between these seven variables and pathological less invasive lesions were analyzed to prepare an optimal model for detecting the less invasive group. **Result:** Among 131 lesions, there were 39 lesions in the less invasive group (AIS/MIA = 16/23) and 94 in the invasive group. In univariate analysis, all the seven variables were significantly different between the two groups. Multivariate analysis using three variables revealed an odds ratio of 0.52 (95% confidence interval [CI]: 0.34-0.79, p = 0.002) for radiological lesion volume (cm^3), 0.94 (95% CI: 0.89-0.99, p = 0.016) for % solid, and 1.58 (95% CI: 1.11-2.23, p = 0.01) for kurtosis. The optimal cut-off values were less than 8.2% for % solid, less than 5.8 cm^3 for lesion volume, and greater than 3.6 for kurtosis. The area under the receiver operating characteristic curve was 0.92 (95% CI: 0.88-0.97) with the model, which achieved a 90% sensitivity and 84% specificity. **Conclusion:** Semi-automated objective discrimination of less-invasive lung adenocarcinomas can be achieved with high accuracy using VHA based on 3D-HRCT.

Keywords: early-stage lung adenocarcinoma, three-dimensional computed tomography, voxel-based histogram analysis

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P1.11-18 A CLASSIFICATION-BASED MACHINE LEARNING METHOD REVEALS EXOSOMAL MIRNA BIOMARKERS FOR PATIENTS WITH PULMONARY GROUND GLASS NODULE

J. Zhang[1], J. Xu[2], J. Su[1], R. Fu[1], J. Lin[1], B. Jiang[1], S. Dong[1], R. Liao[1], X. Yang[1], H. Qin[2], F. Li[2], L. Xiong[2], Y. Wu[1], W. Zhong[1]

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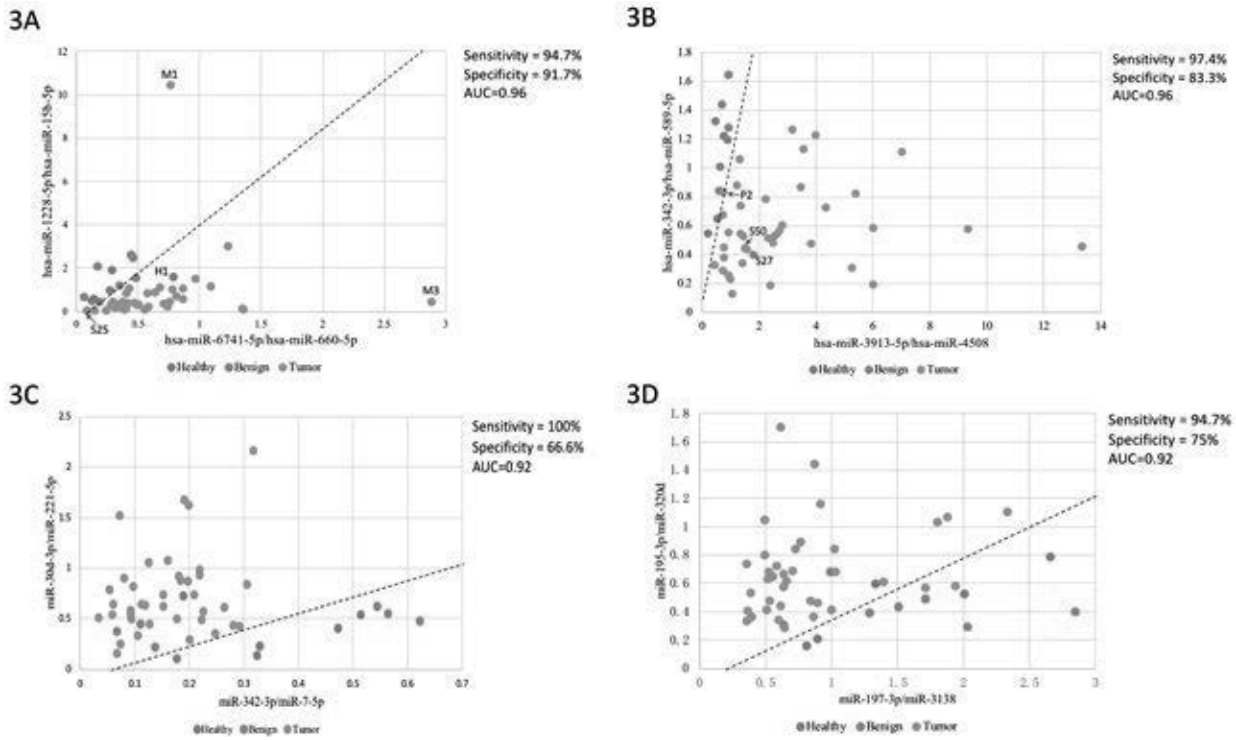
Background: Non-invasive detection of lung cancer is of critical importance but has proven challenging due to the rate of false-negative diagnosis with current tests. Plasma exosomes have been implicated as a non-invasive diagnostic source. However, little high throughput screening has been done in the early-stage lung cancer and problems such as bias of enrollment, less rigorous identification exists. This study aimed to reveal the plasma exosome-derived miRNA biomarkers for early-stage

lung cancer patients, especially those with ground glass nodule (GGN). **Method:** Pre-operative and paired post-operative plasma samples from patients with solitary pulmonary nodule and healthy volunteers were prospectively collected. Finally 38 malignant nodules, 7 benign nodules and 5 healthy volunteers were enrolled. The malignant nodules included 9 pure GGNs, 11 mixed GGNs and 18 solid nodules. Exosomes were collected from 1mL plasma and were isolated with 3D Medicine EV isolation kit. Exosomal miRNA profiling was performed using miRNA-seq. And an exosomal miRNA diagnostic model for patients with malignant nodules was constructed by using support vector machine (SVM). **Result:** In general, malignant nodules, benign nodules and healthy volunteers were indistinguishable based on overall clustering. Regarding to malignant nodules, pure GGNs and solid nodules could be separated under principal component analysis (PCA), and the mixed GGNs presented a transitional state between the pure GGNs and the solid nodules. Ultimately, a two-dimensional SVM diagnostic model for discriminating malignant and benign nodules was established. The optimal miRNA combination could reach an area under curve (AUC) of 0.96, with sensitivity and specificity of 94.7% and 91.7%, respectively. **Conclusion:** This preliminary analysis highlights the potential of exosomal miRNA based liquid biopsy for non-invasive detection of early-stage lung cancer. The SVM model seems could effectively distinguish pulmonary nodules, but needs further verified.



Keywords: liquid biopsy, Exosome, ground glass nodule

P1.11 SCREENING AND EARLY DETECTION
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P1.11-19 EXPRESSION OF TNFRII IN SERUM IS CORRELATED WITH THE SIGNIFICANT RISK OF SUBCENTIMETER LUNG ADENOCARCINOMA

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Background: With the rapid advances of low-dose computed tomography (LDCT) screening for lung cancer, the opportunity to detect subcentimeter non-small cell lung cancer (NSCLC) is gradually increasing. The results of many previous studies have shown that even subcentimeter NSCLCs are not always in the early stage. Thus, it is quite important for us to judge the possibility of malignancy for these patients, even the tumor size is less than 10mm. However, subcentimeter lung cancer is hard to diagnose only via biopsy and imaging features because of its tinny size. Chronic inflammation is well established as a hallmark in lung carcinogenesis. In our previous study, B lymphocyte chemoattractant (BLC), is found to be slightly associated with the risk of subcentimeter lung adenocarcinoma. The aim of the present study is to evaluate the correlation between TNF receptor type II (TNFRII) and the risk for subcentimeter lung adenocarcinoma, and the efficacy of diagnosing subcentimeter lung cancer after combining TNFRII and BLC. **Method:** Inflammatory biomarkers were measured in 71 subcentimeter lung adenocarcinoma patients and 71 age-, sex- and smoking-matched healthy controls by using the Luminex bead-based assay. **Result:** The mean (standard deviation or SD) age of patients was 56.01 (8.91) years, and 73.20% of them were female patients (n=52). Never smokers accounted for 85.96% of patients (n=57). The expression level of TNFRII is significantly down-regulated in subcentimeter lung adenocarcinoma patients compared with the healthy controls (P<0.001). And the results were validated by oncomine data mining analysis. Elevated levels of TNFRII were associated with an 89% reduced risk for subcentimeter lung adenocarcinoma. (OR=0.11, 95% CI: 0.04-0.30, $P=2.4*10^{-5}$). BLC was associated with a 2.70-fold (95% CI: 1.31-5.58, $P=7.0*10^{-3}$) increased risk of subcentimeter lung adenocarcinoma for the comparison of patients in the higher-level group with the lower-level group. To yield more information, the BLC/TNFRII ratio was created to examine their prediction for the risk of subcentimeter lung adenocarcinoma, and as expected there was a 35- fold increased risk for patients in the higher-level group relative to patients in the lower-level group. Further ROC curve analysis revealed

that TNFRII was a significant diagnostic biomarker for subcentimeter lung adenocarcinoma, with the area under the curve of 0.73 (95% CI: 0.65-0.82, P=2.0*10^{-6}). The sensitivity, specificity and accuracy were 0.75, 0.72 and 0.73, respectively. **Conclusion:** Our findings demonstrated that TNFRII was associated with the significant risk of subcentimeter lung adenocarcinoma, and could be a promising biomarker for accessorily diagnosing subcentimeter lung adenocarcinoma.

Keywords: lung adenocarcinoma, TNFRII, Risk

P1.12 SMALL CELL LUNG CANCER/NET
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P1.12-01 A SINGLE-ARM MULTI-CENTER PHASE II STUDY OF APATINIB IN PATIENTS WITH ES-SCLC AFTER SECOND/THIRD-LINE CHEMOTHERAPY

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Background: The survival of patients (pts) with extensive-stage small-cell lung cancer (ES-SCLC) was poor. And the standard treatment strategies have not yet been established for those who failed from second/third-line chemotherapy. Apatinib, a vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitor, has been shown anti-cancer activity and manageable toxicities in several solid cancers. **Method:** A single-arm multi-center phase II study was designed to determine the efficacy and safety of apatinib in pts with ES-SCLC after second/third-line chemotherapy (clinical trial information: NCT02945852). The inclusion criteria mainly included aged 18-75 years; pathologically confirmed SCLC; received chemotherapy with two or three regimens previously, including first-line platinum-based regimen. Pts were treated with afatinib 500 mg/day p.o. until tumor progression or lack of tolerability. One treatment cycle was 28 days long. The full analysis set included patients who received at least one cycle of treatment. Treatment interruptions or dose reductions were allowed when ≥grade 3 hematologic or grade 2 nonhematologic toxicities occurred. The primary endpoint is progression-free survival(PFS); secondary endpoint includes the safety of afatinib, overall survival (OS), objective response rate (ORR) and disease control rate (DCR). **Result:** As of Mar 2018, 40 pts from 3 institutions were recruited into the trial. Median age was 60 years, and 37 pts were male (92.5%). 17/40 (42.5%) pts experienced dose reduction or treatment interruptions. Followed up to Apr 26, 2018, the median during time of afatinib treatment was 80 days and 36 pts were eligible for assessing tumor responses. In the 36 pts, 8 (22.2%) pts achieved partial responses [PR], 20 (55.5%) pts achieved stable disease [SD] and 8 (22.2%) pts were assessed as progressive disease [PD]. The ORR was 22.2% (8 pts PR) and the DCR was 77.8% (8 pts PR, 20 pts SD). During the follow-up, a total of 25 pts died. The median PFS and OS was 86 days and 105 days, respectively. The most common adverse events were anemia (69.4%, 25/36), hand-foot syndrome (61.1%, 22/36), urine protein (55.6%, 20/36), hypertension (52.8%, 19/36) and fatigue (44.4%, 16/36). The related grade 3-4 toxicities included hypertension (47.2%, 17/36), hand-foot syndrome (5.6%, 2/36), Oral ulcer (5.6%, 2/36) and elevated aminotransferase (5.6%, 2/36). **Conclusion:** In this prospective phase II trial, apatinib showed encouraging durable response rates and survival in patients with ES-SCLC after second/third-line chemotherapy, with an acceptable safety profile.

Keywords: small-cell lung cancer, Apatinib, clinical trial

P1.12 SMALL CELL LUNG CANCER/NET
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P1.12-02 PHASE II STUDY OF AMRUBICIN MONOTHERAPY IN ELDERLY OR POOR-RISK PATIENTS WITH EXTENSIVE DISEASE OF SMALL CELL LUNG CANCER

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Background: Previous study indicated that an optional anti-cancer drug for the treatment in pretreated patients with small-cell lung cancer (SCLC) is amrubicin. However, no prospective studies have evaluated amrubicin in chemo-naive elderly or poor-risk patients with SCLC. Therefore, this study aimed to evaluate the efficacy of amrubicin as first-line chemotherapy for elderly or poor-risk patients with extensive-disease SCLC (ES-SCLC). **Method:** Patients with chemotherapy-naive ES-SCLC received multiple cycles of 40 mg/m^2 amrubicin for 3 consecutive days every 21 days. The primary endpoint was the overall response rate (ORR), and the secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety. **Result:** Between March 2011 and August 2015, 36 patients were enrolled in this study. Each patient received a median of four treatment cycles (range, 1–6 cycles). ORR was 52.8% [95% confidence interval (CI), 37–69%]. The median PFS and OS periods were 5.0 months (95% CI, 3.4–6.6 months) and 9.4 months (95% CI, 5.2–13.6 months), respectively. Neutropenia was the most common grade 3 or 4 adverse event (69.4%), with febrile neutropenia developing in 13.9% of patients. No treatment-related death occurred. At the time of starting second-line chemotherapy, 19 of 22 patients (86%) had significantly improved or maintained their performance status (PS) relative to their PS at the time of starting amrubicin monotherapy as first-line chemotherapy (P = 0.027). **Conclusion:** The results of the present study suggest that amrubicin could be considered as a viable treatment option for chemotherapy-naive elderly or poor-risk patients with ES-SCLC.

Keywords: Small Cell Lung Cancer, Elderly patients, Performance status, Amrubicin

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P1.12-03 A PROSPECTIVE STUDY OF APATINIB IN ADVANCED SMALL CELL LUNG CANCER PATIENTS FAILED FROM TWO OR MORE LINES OF CHEMOTHERAPY

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Background: Small lung cancer (SCLC), a highly malignant neoplastic, chemoresponsive disease. For SCLC patients who with worsening status after second-line treatment, there is currently no affirmative and widely accepted chemotherapy regimen. Apatinib is a novel oral multi-target small-molecule TKI mainly targeting the intracellular ATP-binding domain of VEGFR-2, which has a significant effect of anti-angiogenesis to suppress the growth of tumors. This study evaluated the efficacy and safety of Apatinib in SCLC patients who failed from second- or further-line chemotherapy. **Method:** Data was collected from the files of patients treated with Apatinib 500mg qd who diagnosed with advanced SCLC and failed from second or more lines of chemotherapy. Efficacy assessed after one cycles (4 weeks), then every two cycles (8 weeks) once again. The primary endpoint was PFS and the tumor response was determined according to the RECIST 1.1. PFS were graphed by Kaplan-Meier curves of progression-free survival. AEs were also evaluated and toxicity grade was determined based on CTCAE 4.0. **Result:** 22 patients were enrolled from November 10, 2016 to April 18, 2018, the number of patients that can be evaluated is 19. One patients obtained partial response, and 15 obtained stable disease, representing a DCR of 84.11%. Median PFS was 140 days (95% confidence interval [CI] 94.84–185.16). Although only one patient showed PR, all the patients' target lesions were reduced. A total of 46 AEs were reported during the trial, grade 3-4 AEs were hypertension (9.09%), leukopenia (4.55%) and proteinuria (4.55%) which most could be relieved by dose reduction.

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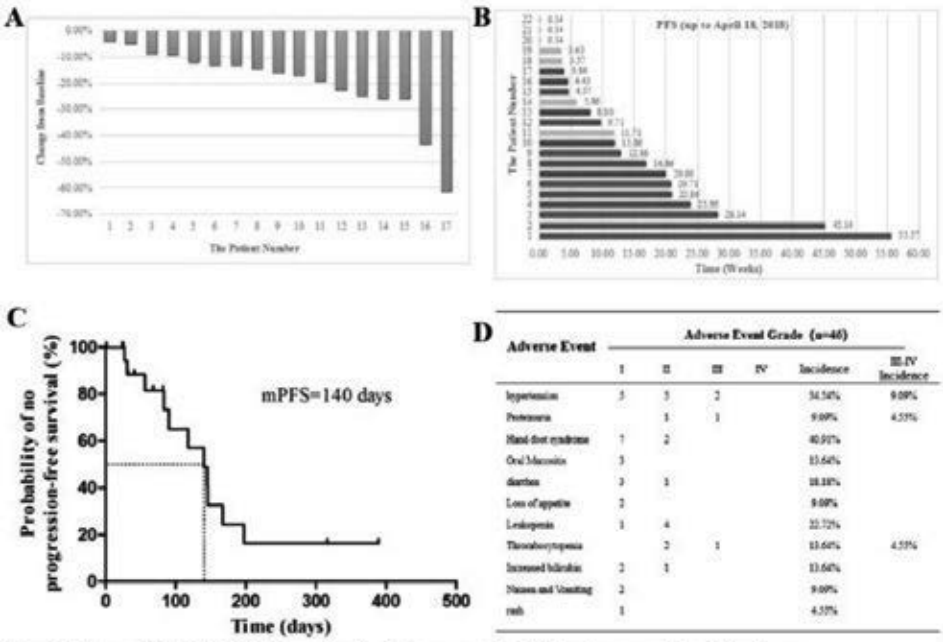

Figure 1. Efficacy and safety of Apatinib in advanced small cell lung cancer patients failed from two or more lines of chemotherapy
(A) Change of target lesion from baseline. Among 22 enrolled patients, 3 patients lost to follow-up, 2 patients have no target lesion. (B) The PFS of patients (up to April 18, 2018). Up to April 18 2018, 6 patients were lost to follow- up, 11 patients exclude from the trial due to progressive disease, another 4 patients are still on investigated as shown Figure B, (yellow bars= lost to follow-up, red bars= out of group, blue bars= on investigated). (C) Kaplan-Meier curves of progression-free survival. (D) Adverse Events.

Conclusion: In conclusion, Apatinib has a certain therapeutic effect in patients with advanced SCLC (third- or further-line). To further investigate the role of Apatinib in advanced SCLC patients, large sample and additional clinical trials are needed.

Keywords: small-cell lung cancer, Third- or further- line, Apatinib

P1.12 SMALL CELL LUNG CANCER/NET
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P1.12-04 A PH3 STUDY OF NIRAPARIB AS MAINTENANCE THERAPY IN 1L PLATINUM RESPONSIVE EXTENSIVE DISEASE SMALL CELL LUNG CANCER PATIENTS

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Background: Small cell lung cancer (SCLC) accounts for 15% of lung cancer, characterized by early dissemination and rapid development of chemo-resistant disease after platinum response (60-80%). Less than 2% of extensive disease SCLC (ED-SCLC) patients survive 5 years. The bi-allelic loss or inactivation of TP53 and RB1 is common in SCLC, the poly(ADP-ribose) polymerase-1 (PARP-1), a critical DNA damage repair enzyme, is highly expressed in SCLC, and SCLC is sensitive to platinum based chemotherapy, suggesting that the defect in DNA damage repair pathways plays an important role in SCLC. ZL2306/ Niraparib is a highly selective PARP-1/2 inhibitor which was exclusively licensed for development in China by Zai Laboratory from TESARO. In SCLC PDX model, niraparib demonstrated anti-tumor activities as monotherapy. In addition, niraparib demonstrated promising tumor growth inhibition in maintenance post platinum treatment in platinum sensitive SCLC PDX models. Clinically, in phase III NOVA study, niraparib demonstrated clear clinical benefit as maintenance treatment by significantly extending progression free survival in all platinum-sensitive recurrent ovarian cancer patients regardless gBRCA or HRD status which led to the approval by FDA and EMA in ovarian cancer. It is suggested that niraparib maintenance therapy could provide potential clinical benefit in platinum responsive SCLC. ZL-2306-005 is a randomized double-blind multi-center phase 3 study to evaluate the efficacy and safety of niraparib versus placebo as maintenance therapy in ED-SCLC patients who have had responses to platinum based chemotherapy. **Method:** Approximately 590 Chinese patients with histologically or cytologically confirmed ED-SCLC who have achieved either complete response or partial response to their platinum based chemotherapy to their newly diagnosed disease will be randomized (2:1) to 2 groups, receiving either ZL-2306 or placebo in ZL-2306-005 study. Patients need to complete 4 cycles of etoposide + cisplatin/ carboplatin. All patients will be stratified by gender, LDH level and history of prophylactic cranial irradiation. ZL-2306 will be started with 300mg PO QD for patients with a baseline body weight ≥77 kg and a baseline platelet count ≥150,000/μL, or 200 mg PO QD for patients with a baseline body weight <77 kg or a baseline platelet count <150,000/μL based on RADAR analysis in NOVA study. Patients will remain on treatment until disease progression or intolerable toxicity. The co-primary endpoints are PFS assessed by independent central radiologic review and OS; the secondary endpoints are PFS assessed by investigator, CFI, QoL, safety and tolerability. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: niraparib, small cell lung cancer

P1.12 SMALL CELL LUNG CANCER/NET
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P1.12-05 EFFICACY OF PERIOPERATIVE CHEMOTHERAPY FOR HIGH-GRADE NEUROENDOCRINE TUMORS

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Background: Large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung cancer (SCLC) are categorized as high-grade neuroendocrine tumors (HGNECs). There have been few studies to show the efficacy of perioperative chemotherapy for HGNEC as a single entity. **Method:** We retrospectively reviewed the medical records of patients who underwent tumor resection and were diagnosed with HGNECat Hyogo Cancer Center (Akashi, Japan) and Kobe University Hospital (Kobe, Japan) between January 2001 and December 2016. Overall survival (OS) was estimated by the Kaplan–Meier method. Multivariate analyses using a Cox proportional hazards model were performed to search for prognostic factors for HGNEC. Propensity score matching was performed to compare the OS between the treatment groups. **Result:** We identified 197 patients who underwent surgery and who were diagnosed with HGNEC. Forty-three patients were excluded for the following reasons: pathological stage 4 or incomplete resection (n=25), synchronous multiple cancers (n=14),

and insufficient medical records (n=5) We finally analyzed 153 HGNEC patients (LCNEC n=95, SCLC n=58). Seventy patients (LCNEC n=34, SCLC n=36) received perioperative chemotherapy. All of them received a platinum-based anticancer drug, and 80% received combined treatment with irinotecan or etoposide (n=56). The 5-year OS rates of the surgery plus chemotherapy and surgery alone groups were 75.5% and 34.7% (P<0.01), respectively. The HR for death in the surgery plus chemotherapy group was 0.34 (95% CI 0.20-0.56; P<0.01) in comparison to the surgery alone group. The multivariate analysis revealed that perioperative chemotherapy (HR 0.30, P<0.01), sublobar resection (HR 2.04, P=0.04), and lymph node metastasis (HR 3.54, P<0.01) were independently associated with survival. After adjustment for the patients' background characteristics by propensity matching, the 5-year OS rates of the surgery plus chemotherapy group were significantly higher than those of the surgery alone group (78.7% and 32.9%; P < 0.01). The HR for death in the surgery plus chemotherapy group was 0.33 (95% CI 0.15-0.68; p<0.01) in comparison to the surgery alone group. **Conclusion:** Surgical resection combined with perioperative chemotherapy was considered to be effective for HGNEC. Sublobar resection might increase the risk of death in HGNEC patients. Therefore if the general condition of the patient permits, perioperative chemotherapy should be performed, and the extent of resection in the treatment of HGNEC should be lobectomy or more.

Keywords: high-grade neuroendocrine tumor, perioperative chemotherapy, limited surgery.

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P1.12-06 PULMONARY NEUROENDOCRINE (CARCINOID) TUMORS: COMMNETS/NANETS ENDORSEMENT AND UPDATE OF THE ENETS BEST PRACTICE CONSENSUS

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Background: The lung is the most common single site of origin of neuroendocrine cancers, and lung neuroendocrine tumor (LNET) incidence and prevalence is rising. There is a lack of both LNET-specific data and up to date clinical guidance. Management of LNETs often relies on extrapolation from other tumor sites. The Commonwealth Neuroendocrine Tumour Collaboration (CommNETS) and North American Neuroendocrine Tumor Society (NANETS) sought to consider current data and provide updated guidance on LNET diagnosis and management. **Method:** The latest best practice consensus on LNETs was published by the European Neuroendocrine Tumor Society (ENETS) in 2015. A review of content and methods using the AGREE II Rigour of Development subscale (www.agreetrust.org) confirmed the quality of the ENETS initiative, providing a basis for endorsement and update. A systematic literature search was conducted and a 22 member, multidisciplinary CommNETS/NANETS expert panel endorsed or modified recommendations from a patient-centered perspective. All statements were graded using Oxford criteria (CEBM.net). **Result:** A total of 230 studies were identified for consideration by the panel. Recommendations were modified or added to reflect clinical data not available in 2015. Out of the 52 ENETS statements, 40% were endorsed, 58% were modified or updated, one was removed and four were added. Themes identified in the consensus update include new statements, practice changing modifications, augmented grades of recommendation and statement refinements, each addressing specialties ranging from epidemiology, pathology and diagnosis to treatment and follow-up (Table 1). The importance of LNET directed research and patient-centered care throughout the treatment trajectory is also emphasized, along with directions for future research. **Conclusion:** Ongoing collaboration is essential for future development of updated LNET clinical guidance and to direct research efforts in a patient-centered context. Our consensus update demonstrates international collaboration to develop guidance on clinical management of malignancies for which limited data are available.

Table 1. Themes in CommNETS/NANETS Lung NET Consensus Update

New statements	
Epidemiology	Highlights marked increase in the incidence and prevalence of lung NETs
Radiation Therapy	Guidance on use of palliative EBRT for patients with symptomatic locally advanced or metastatic disease
Medical Therapy	Recommendation of pre-surgical prophylaxis with SSAs for patients with carcinoid syndrome Indicates lack of benefit of anti-angiogenics in lung NET
Practice changing statement modifications	
Diagnosis	Indicates limited clinical value of chromogranin A in lung NET diagnosis and disease state characterization
Surgery	Indicates that cytoreductive surgery of the liver may be expanded to patients with non-aggressive tumors, including those with more limited extra-hepatic disease
Statements with augmented recommendations	
Surgery	The grades of recommendation for complete anatomic resection and systematic nodal dissection for peripheral tumors and for preference of lung parenchymal-sparing surgery over pneumonectomy were each augmented to Grade B
Medical Therapy	The grades of recommendation for PRRT and mTOR inhibitors statements were augmented to Grades B and A, respectively
Statement refinements	
Pathology	Refined to reflect new standards for classification (WHO 2015) and staging (UICC/AJCC 8th edition) Tailored to highlight need for endobronchial biopsy or surgical resection for sufficient sampling to differentiate TC from AC
Diagnosis	Radiological imaging statements were modified to simplify guidance and clarify differences in requirements for diagnostic compared to liver imaging, and to guide application of various nuclear imaging techniques Bronchoscopy statements were simplified to highlight efficacy and safety of bronchoscopy
Surgery	Surgery for localized disease statements modified to reflect equivalence of sublobar resection and lobectomy, especially for typical carcinoid tumors Endobronchial resection statements were revised to reflect need to limit procedure to high risk patients or as a bridge to surgery
Medical Therapy	Follow-up statement was revised to better define and direct post-treatment surveillance for lung NETs patients who receive medical therapy

AC; atypical carcinoid; EBRT, external beam radiotherapy; NET, neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; SSA; somatostatin analog; TC, typical carcinoid

Keywords: Consensus, Neuroendocrine tumor, Clinical management

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P1.12-06A ROVALPITUZUMAB TESIRINE MAINTENANCE THERAPY FOLLOWING 1ST LINE PLATINUMBASED CHEMOTHERAPY IN SMALL CELL LUNG CANCER

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Background: Small Cell Lung Cancer (SCLC) embodies 15-20% of lung cancers. Patients are staged with either limited or extensive disease (ED); the standard front-line treatment for the latter is chemotherapy with carbo- or cisplatin combined with etoposide or irinotecan. Response rates are high with limited duration. Recurrence may be attributable to chemo-resistant tumor initiating cells (TICs). Delta-like protein 3 (DLL3) is an inhibitory Notch receptor ligand identified as a novel target in SCLC TICs. DLL3 is highly expressed in SCLC but not normal tissue. Rovalpituzumab tesirine (Rova-T™) is an antibody-drug conjugate composed of a DLL3-targeting IgG1 monoclonal antibody tethered to a DNA cross-linking toxin. Rova-T has shown activity in recurrent/relapsed ED SCLC patients[1]. Given DLL3 expression in TICs, exploration of Rova-T front-line maintenance strategies in ED SCLC is warranted. The postulated mechanism of action of Rova-T and its clinical activity

indicate potential to improve progression-free and overall survival in this setting. **Method:** This is a Phase 3, randomized, double-blind, placebo-controlled, international study (NCT03033511, no patients enrolled yet as of 7 February 2017). Approximately 740 ED SCLC patients will be enrolled to include ~480 patients with high DLL3 expression. Eligibility: patients ≥ 18 years; histologically or cytologically confirmed ED SCLC with ongoing clinical benefit (complete/partial response or stable disease) after 4 cycles of 1st line platinum-based therapy; definitively treated CNS metastases allowed; > 3 but ≤ 9 wks between the administration of the last cycle of platinum-based chemotherapy and randomization; available tumor tissue for DLL3 expression testing; ECOG performance score 0-1. Patients will be randomly assigned 1:1 to receive 0.3 mg/kg Rova-T or placebo on Day 1 of each 6-wk cycle, omitting every 3rd cycle. Primary objectives: determine if Rova-T improves progression-free and overall survival. Secondary objectives: assess Rova-T antitumor activity by determining objective response rate, clinical benefit rate, duration of response, and changes in patient reported outcomes. 1. Rudin et al., Lancet Oncol, 2016. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Rovalpituzumab tesirine, small cell lung cancer, Phase 3

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P1.12-06B ROVALPITUZUMAB TESIRINE VS TOPOTECAN IN PATIENTS WITH ADVANCED SMALL CELL LUNG CANCER FOLLOWING 1ST LINE CHEMOTHERAPY

P. Komarnitsky, H. Lee, M. Shah, S. Wong, S. Gulbranson, J. Dziubinski, L. Caffrey, P. Tanwani, M. Motwani, F. Zhang

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Background: Small cell lung cancer (SCLC) represents ~15% of lung cancers. Standard therapy most often consists of a platinum-based therapy + a second agent (etoposide). Initial response rates are high but not durable. Treatment for relapsed patients is limited, but includes topotecan. However, efficacy of topotecan is suboptimal and there is a high unmet need in this population. Delta-like protein 3 (DLL3) is an atypical Notch receptor family ligand identified as a target in SCLC and neuroendocrine carcinomas (NECs). DLL3 is highly expressed in SCLC and NECs but not normal tissue. Rovalpituzumab tesirine (Rova-T™) is an antibody-drug conjugate composed of a DLL3-targeting IgG1 monoclonal antibody tethered to a toxic DNA crosslinker. Rova-T has antitumor activity in relapsed SCLC patients, and was well-tolerated[1]. Thus, we are investigating Rova-T vs topotecan as a 2nd line therapy in advanced SCLC. **Method:** This is a Phase 3, randomized, open-label, multicenter study (NCT03061812) to assess efficacy, safety, and tolerability of Rova-T vs topotecan. Approximately 411 patients will be enrolled and randomized 2:1 between 2 arms. Arm A regimen: 0.3 mg/kg Rova-T intravenous (IV) on Day 1 + 8 mg dexamethasone orally, twice daily on Day -1, 1 and 2 of a 42-day cycle; administered for 2 cycles with up to 2 additional cycles permitted. Arm B: 1.5 mg/m^2 topotecan (or per local label) IV on Days 1-5 of each 21-day cycle; administered until disease progression. Patient eligibility: ≥ 18 years; confirmed, advanced/metastatic SCLC with first disease progression following frontline standard therapy; DLL3-high tumor expression; ECOG 0-1; no prior exposure to a pyrrolobenzodiazepine-based drug or topotecan, irinotecan, or other topoisomerase I inhibitor. Efficacy endpoints include progression free survival, overall survival, objective response rate, duration of response, and patient-reported outcomes. 1. Rudin et al., Lancet Oncol, 2016. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Rovalpituzumab tesirine, Phase 3, topotecan

P1.12 SMALL CELL LUNG CANCER/NET
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.12-07 TIME TO THE END OF THORACIC RADIOTHERAPY AFFECTS TO SURVIVAL OUTCOMES GREATER THAN RADIATION DOSE IN LIMITED STAGE SMALL CELL LUNG CANCER

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Background: Early thoracic radiotherapy (TRT) concurrent with chemotherapy and radiation doses of 45 Gy given 1.5 Gy bid still has taken a seat as a standard treatment option for limited-stage small cell lung cancer (LS-SCLC). We aim to search the association between radiation parameters and survival outcomes in LS-SCLC patients who undertaken more than 45 Gy of TRT. **Method:** One hundred and one patients with LS-SCLC who completed TRT between August 2005 and March 2014 were reviewed retrospectively. Median age was 64 years (43-80) and male to female was 88 vs. 13. Stage IIIA was 30 and IIIB was 55, respectively. TRT was performed using 3-dimensional conformal radiation therapy (3DCRT) and delivered using 2Gy single fraction per day in 73.2% of patients. The median dose TRT was 50 Gy (45-65), and all patients received concurrent chemoradiotherapy. PCI was combined in 56 (55.4%) patients. **Result:** The median survival for all patients was 26.9 months. Local failure occurred in 41 patients (40.5%), and distant metastasis was noted in 54 patients (53.4%). The 3-year local control, progression-free survival (PFS), and overall survival (OS) rates were 52.0%, 29.5%, and 56.4%, respectively. On univariate analysis, the American Joint Committee on Cancer stage (p<0.001), timing of TRT (≤2 vs, >2 cycles, p=0.017), tumor response (CR vs. PR, p=0.015), the duration from the start date of chemotherapy to the end of TRT (SER) (≤70 vs >70 days, p=0.025), and PCI (p=0.003) were the significant predictors of OS and stage (p<0.001) and PCI (p=0.017) were the significant predictors in PFS. Multivariate analysis revealed that stage (hazard ratio [HR], 3.61; 95% CI, 2.15-6.07) was the only significant factor in PFS and stage (HR, 2.49; 95% CI, 1.56-3.98), SER (HR, 1.93; 95% CI, 1.22-3.07), PCI (HR, 0.52; 95% CI, 0.33-0.84), and tumor response (HR, 1.76; 95% CI, 1.12 – 2.77) were the significant predictors in OS. There was one fatal radiation pneumonitis. Grade 3 radiation pneumonitis and esophagitis was shown in 7 (6.9%) vs. 7 (6.9%) patients, respectively. Grade 3 and 4 leukopenia was shown in 30 (29.7%) vs. 11 (10.8%) patients and febrile neutropenia was 9 (8.9%) vs. 1 (0.9%) patients, respectively. **Conclusion:** SER less than 70 days was a significant predictors of OS in LS-SCLC patients who received more than 45 Gy of TRT concurrently with chemotherapy. We could not find any significant positive survival benefits of TRT dose or BED escalation in our patients groups.

Keywords: SER, concurrent chemoradiotherapy, limited-stage small cell lung cancer

P1.12 SMALL CELL LUNG CANCER/NET
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.12-08 THE EFFECT OF CISPLATIN VERSUS CARBOPLATIN ON CANCER OUTCOMES FOR SMALL CELL LUNG CANCER PATIENTS IN A POPULATION-BASED COHORT

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Background: Small cell lung cancer (SCLC) is associated with high rates of mortality and treatment involves chemotherapy. In non-small cell lung cancer, using cisplatin results in superior response and survival compared to carboplatin, but causes more toxicity. Little research regarding this drug choice in SCLC exists, but available studies suggest equivalent survival. Nevertheless, many oncologists continue to use cisplatin preferentially. **Method:** Using the population-based Manitoba Cancer Registry, we identified SCLC cases diagnosed from 2004 to 2013 in Manitoba and completed a retrospective chart review for those treated with chemotherapy. Demographics, tumour response, and treatment toxicity were compared between cisplatin and carboplatin treated groups. Overall survival (OS) and progression free survival (PFS) were evaluated using multivariate Cox proportional hazard methods. Likelihood of completing chemotherapy (at least 4 cycles) was assessed using multivariable logistic regression. **Result:** Of the 531 patients identified, 139 (26.2%) received carboplatin and 392 (73.8%) received cisplatin as part of first line chemotherapy. More patients who received carboplatin had poor performance status (13.7% v 7.4%), elevated LDH (58.3% v 42.3%), and extensive stage disease (69.8% v 54.1%), all p<0.01. Unadjusted median OS was 224 v 322 days for carboplatin and cisplatin. Multivariable adjusted analysis for OS using cisplatin patients not completing treatment as the reference comparator showed hazard ratios for carboplatin completers – 0.65 (0.43-0.98), cisplatin completers – 0.69 (0.47-1.00), and carboplatin incompleters – 1.00 (0.64-1.55), p = 0.13. For PFS carboplatin completers – 1.07 (0.60-1.90), cisplatin completers – 0.83 (0.51-1.36), and carboplatin incompleters – 0.96 (0.64-1.46), p = 0.59. There was not significant difference between carboplatin and cisplatin in likelihood of completing chemotherapy, when adjusted for other patient characteristics - 0.75 (0.47-1.22), p=0.26 Those treated with carboplatin had significantly less neutropenia (57.6% v 74.7%), nephrotoxicity (2.9% v 13.5%), neurotoxicity (0.7% v 12.0%), and nausea/vomiting (28.1% v 42.6%) associated with treatment, all p<0.01. **Conclusion:** In a real world, population-based setting, carboplatin appears to be an equally effective treatment option for SCLC, facilitating

equivalent survival while avoiding toxicity. Clinicians may wish to re-examine their preference for cisplatin.

Keywords: survival analysis, Chemotherapy Toxicity, Real-world data

P1.12 SMALL CELL LUNG CANCER/NET
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P1.12-09 THE EFFECT OF SITE OF FIRST CHEMOTHERAPY ON SMALL CELL LUNG CANCER PATIENT OUTCOMES

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Background: Small cell lung cancer (SCLC) ischaracterized by a rapid doubling time and high responsiveness to chemotherapy (CT) with a rapid relapse. Due to the sensitivity of SCLC to CT, it is one of the few malignancies treated in acutely ill patients admitted to hospital with a poor performance status (PS). However, there is little available information on the outcomes and toxicity experienced by patients with SCLC who require initial CT as an inpatient. **Method:** A retrospective cohort study was conducted evaluating patients consecutively diagnosed with SCLC in Manitoba from 2004 to 2013 treated with platinum-doublet CT. Patient demographics, staging, treatment, CT toxicities, Eastern Cooperative Oncology Group(ECOG) PS, treatment response, and survival were collected using the Manitoba Cancer Registry and chart review. Outcomes of progression free survival (PFS) and overall survival (OS) were evaluated based on site of first CT (inpatient versus outpatient) and PS. **Result:** 530 patients received CT for SCLC with 82 patients (15%) receiving their first CT as an inpatient. Sixty-three percent of inpatients received the full CT course, compared to 81% of outpatients, (p=0.0006). Outpatients had a greater likelihood of responding to CT (p=0.0043). Neutropenia, febrile neutropenia, thrombocytopenia, nephrotoxicity and fatigue were all experienced less often by the inpatient cohort, (p<0.0001), (p=0.0040), (p<0.0001), (p<0.0001) and (0.0068). For inpatients, OS at 12, 24 and 60 months was 22%, 9% and 7%, versus outpatient OS of 43%, 20% and 9%, (each p<0.0001). Median PFS and OS were longer for outpatients, 212 versus 161 days, (p=0.0035) and 321 versus 192 days, (p=0.0003). Patients with poorer ECOG PS had shorter PFS and OS; with a median PFS for PS 0, 1-2, 3-4 of 316, 203 and 147 days, (p<0.0001) and median OS for PS 0, 1-2 and 3-4 of 498, 303 and 179 days, (p<0.0001). On multivariate analysis, ECOG PS was an independent predictor of outcome, (p=0.0005) while site of first CT was not significant when ECOG PS was included, (p=0.3494). **Conclusion:** Although SCLC patients initially treated as inpatients had shorter PFS and OS, some experienced long term survival, including a 7% five-year survival. CT toxicities were not more common for inpatients. This validates that administration of CT in hospital can be considered as these patients may have a meaningful long-term response to therapy if properly selected. As previously identified in the literature, this data demonstrated that patients with poorer ECOG PS have shorter PFS and OS.

Keywords: small cell lung cancer, outcome, hospitalized patients

P1.12 SMALL CELL LUNG CANCER/NET
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P1.12-10 PATTERNS OF CURATIVE CHEMO-RADIOTHERAPY REGIMEN AND IMPACTS ON THE OUTCOME OF LIMITED STAGE SCLC IN A CANADIAN INSTITUTION: 2010 – 2015 DIAGNOSES

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Background: Curative intent chemotherapy and radiotherapy (ChemoRT) is the widely recommended treatment for limited stage (LS) small cell lung cancer (SCLC) follow by prophylactic cranial irradiation (PCI) in those who responded to the initial therapy. LS-SCLC is however characterized by high relapse rate with only about 20% surviving to 2 years. Our objective is to examine the characteristics, treatment patterns and overall survival of LS-SCLC for patients diagnosed within a 5-year period at the Tom Baker Cancer Centre, Canada, prior to wide adoption of emerging treatment options including surgery and immunotherapy in the curative and palliative settings respectively. **Method:** Using the Glans-Look Lung Research (GLR) database, we defined the clinical and demographic features of patients diagnosed with LS-SCLC from 2010 to 2015, determined the rate of systemic treatment uptake, and investigated the impact of PCI, curative intent, and palliative treatments on overall survival. We summarized our findings with descriptive statistics (including Fisher's Exact test) and Kaplan Meier survival curves using SPSS. Statistical significance was set at p value < 0.05 and 95% confidence intervals. **Result:** About a third (107/349, 31%) of patients diagnosed with SCLC from 2010 to 2015 were LS-SCLC, with median age of 67 years. Over the 5-year period, systemic treatments uptake rates and patterns fluctuates. Overall, > 50% received ChemoRT and 65% of the ChemoRT group also received PCI. Curative concurrent RT dose 45 – 55Gy, 25 fractions schedule was more common (55%). Few stage T1a-2a, N0-1 LS-SCLC had surgery (5%). Thirty eight percent of those who received initial curative intent treatments further received some palliative treatments for disease recurrence or progression {8% (2/26) initial Surgery ± Adjuvant & 92% (24/26) ChemoRT}. The median overall survival for the cohort was 24 months (p < 0.001). There were more than 50% survival at 60 months for patients treated with curative 15 fractions concurrent ChemoRT (p < 0.001). **Conclusion:** Most patients received ChemoRT while a few had surgery. Concurrent 15 fractions ChemoRT may offer better survival benefits than the 25 fraction schedule. The impact of PCI on LS-SCLC and other survival outcomes will be presented.

Keywords: Limited Stage SCLC, Chemo-radiotherapy, SCLC Overall Survival

P1.12 SMALL CELL LUNG CANCER/NET
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.12-11 2010 – 2015 EXTENSIVE STAGE SCLC DIAGNOSES IN A CANADIAN INSTITUTION: BASELINE CHARACTERISTICS THAT IMPACT ON THE OVERALL SURVIVAL

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Background: Small cell lung cancer (SCLC) represents only about 13 – 15% of lung cancers but has posed significant challenges due to minimal progress in therapeutics development prior to the recent advent of immunotherapy. Our objective is to establish baseline characteristics and overall survival of Extensive SCLC (ES-SCLC) based on the current conventional therapy for patients diagnosed within a 5 year period at the Tom Baker Cancer Centre, Canada. This information will be crucial in assessing the effectiveness of novel anti-immune checkpoint treatment strategies. **Method:** Using the Glans-Look Lung Research (GLR) database, we defined the clinical and demographic features of patients diagnosed with ES-SCLC from 2010 to 2015, determined the rate of systemic treatment uptake, and investigated the impact of prophylactic cranial irradiation and palliative treatments on overall survival. We summarized our findings with descriptive statistics (including Fisher's Exact test) and Kaplan Meier curves using the SPSS. Statistical significance was set at p value < 0.05 and 95% confidence intervals. **Result:** Among the 2010 to 2015 SCLC diagnoses, 68% (242/349) were ES-SCLC with median age of 68 years. Close to 90% received some form of palliative treatment. Chemotherapy (CT) was a major component of palliative treatments {89% overall, (190/214): 41% CT only, 22% CT & thoracic radiotherapy (RT) and 38% CT & RT-Other sites}. About a third (32%) of patients who received 1st line CT also had a 2nd line (range between 1 – 4 lines). Prophylactic cranial irradiation (PCI) uptake rates were 38% and 11% for CT only and CT & RT respectively. The median overall survival for ES-SCLC within the cohort was 7 months (p < 0.001). **Conclusion:** In contrast to advanced stage non-small cell lung cancers, there was high rate of sytemic treatment uptake for ES-SCLC. Overall however, < 20% (41/242) followed through with PCI. Other outcome findings will be presented and discussed.

Keywords: Extensive Stage SCLC, SCLC Treatment, SCLC Overall Survival

P1.12-12 A SYSTEMATIC REVIEW AND META-ANALYSIS OF EARLY AND LATE SURVIVAL FOLLOWING ANTI-CANCER THERAPIES FOR SMALL CELL LUNG CANCER

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Background: Treatments for small cell lung cancer (SCLC) have not changed significantly in contrast to non-small cell where it is more individually tailored. Current guidelines generally have a one size fits all approach to chemotherapy. We conducted the largest systematic review and meta-analysis in SCLC to evaluate early and median survival by different study factors. **Method:** We searched EMBASE and MEDLINE for randomized controlled trials and observational cohort studies which reported survival following platinum doublet chemotherapy for SCLC. We calculated overall survival at 30 and 90 days along with the median survival. **Result:** We identified 10,487 titles, 161 were included. Cisplatin + etoposide (n=87 (49.4%)), carboplatin + etoposide (n=36 (20.5%)) and cisplatin + irinotecan (n=23 (13.1%)) were predominantly reported. The commonly reported cause of death within 30 days was neutropaenic sepsis (n=27), disease progression (n=11) and cardiovascular (n=8). Across both stages 30-day survival was 98% (95% CI 98-99%) whilst 90-day was 95% (95% CI 94-96%). Thirty and 90-day survival showed similar patterns to study factors as median survival (summarised in *Table 1*). Limited stage median survival was 18.1 months (95% CI 17.0-19.1). Studies that administered thoracic radiotherapy and PCI had better survival than those that did not. Studies giving carboplatin + etoposide or included poorer PS (0-3) individuals had inferior survival. PCI timing did not show survival differences. Extensive stage median survival was 9.6 months (95% CI 8.9-10.3). This was augmented in studies that gave irinotecan + cisplatin and were conducted in Asia. There were no survival differences by cisplatin/carboplatin or median participant age.

Conclusion: Neutropenic sepsis accounts for the majority of 30-day deaths and was mostly reported with cisplatin + etoposide. Our findings broadly support guideline recommendations but suggest certain sub-populations e.g. Asian individuals, benefit from targeted treatment with irinotecan + cisplatin. Age should be re-considered as a treatment-deciding factor in extensive stage.

Keywords: Treatment efficacy, small cell lung cancer, Systematic review

Table 1: Median overall survival

Factor	Limited stage			Extensive stage		
	Median survival (months)	95% CI	I^2%	Median survival (months)	95% CI	I^2%
All	18.1	17.0-19.1	77.2	9.6	8.9-10.3	95.2
Quality /27						
Poor (0-9)	19.5	10.8-28.2	-	6.6	1.4-11.7	82.0
Moderate (10-14)	18.7	16.0-21.3	67.6	9.2	7.5-11.0	81.5
Good (15-19)	18.2	16.7-19.7	79.6	9.5	8.7-10.4	92.2
Very good (20-25)	17.9	16.0-19.7	77.1	10.1	8.5-11.7	96.8
Design						
RCT	19.1	17.3-21.0	85.2	9.9	9.4-10.3	73..1
Cohort	17.4	16.1-18.6	69.9	9.3	8.3-10.4	93.0
Chemotherapy						
Cisplatin+etoposide	18.5	17.1-19.9	77.3	9.4	9.0-9.9	64.0
Carboplatin+etoposide	15.7	14.0-17.5	67.1	8.8	7.3-10.3	93.6
Irinotecan+cisplatin	19.5	15.2-23.7	49.3	11.5	10.6-12.5	55.1
Platinum+etoposide	18.4	14.4-22.5	82.1	8.1	4.4-11.7	93.9
Topotecan+cisplatin	-	-	-	9.7	8.8-10.5	41.6
Platinum+etoposide/irinotecan	24.5	15.0-34.1	86.6	15.4	13.9-16.9	0
Thoracic radiotherapy						
Yes	18.1	17.4-19.6	78.3	8.9	7.3-10.4	94.9
No/ Not stated	11.7	9.1-14.3	0	10.0	9.1-10.8	95.3
Region						
Europe	15.7	14.5-16.9	62.7	8.5	7.3-9.7	94.6
North America	18.7	17.2-20.3	43.7	9.5	9.2-9.8	0
Africa	21.9	14.7-29.1	0	-	-	-
Asia	20.3	18.0-22.7	78.4	11.3	10.4-12.2	69.1
International	27.5	22.6-32.4	47.9	9.6	9.2-10.0	0
Australasia	16.0	12.7-19.2	0	7.1	3.6-10.6	93.1
South America	7.4	5.1-9.7	0	5.2	-2.9-13.3	92.9
Not reported	22.7	17.6-27.8	0	-	-	-
PCI						
Yes	19.7	18.5-21.0	75.7	9.4	9.0-9.8	12.7
No	13.6	10.5-16.6	81.1	9.1	6.7-11.6	96.3
Not stated	14.3	13.2-15.3	0	9.9	8.9-10.3	96.5
Timing of PCI						
<4th cycle	8.8	6.8-10.9	0			
4th-5th cycle	9.0	6.7-11.3	41.3			
≥6th cycle	9.3	8.4-10.2	38.2			
Not clear	9.5	9.0-10.0	7.8			
Included PS						
0-1	22.8	19.2-26.3	70.6	9.7	9.3-10.2	0
0-2	19.1	17.8-20.4	74.0	10.3	9.3-11.3	96.3
0-3	13.7	11.3-16.1	45.5	9.2	8.4-10.0	28.4
0-4	15.3	11.5-19.1	77.9	7.9	4.7-11.1	94.3
Not stated	16.1	13.5-18.6	63.7	8.3	6.6-10.0	81.8
Median participant age						
50-59	18.0	15.6-20.4	68.7	10.3	9.3-11.3	86.5
60-69	18.7	17.3-20.1	82.3	9.7	8.7-10.6	96.4
≥70	15.9	12.9-18.9	43.2	10.3	9.0-11.6	5.5
Not stated	16.1	12.6-19.7	64.4	8.3	6.6-9.9	83.0

P1.12-13 IMPACT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE ON THE SURVIVAL OF PATIENTS WITH EXTENSIVE-DISEASE SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) is a highly fatal lung malignancy. Cigarette smoking is an important cause of SCLC, and most patients have heavy smoking history. Also, smoking is an established risk factor of chronic obstructive pulmonary disease (COPD). Therefore, patients who are diagnosed with SCLC have high chance to coincide with COPD. However, the coincidence rate of COPD and SCLC are not known well. Moreover, the impact of COPD on the mortality of patients with SCLC, especially for patients with extensive diesase (ED) is not reported yet. Therefore, we conducted investigation of clinical features and survival differences between patients who were diagnosed with SCLC with COPD or patients without COPD. **Method:** We retrospectively reviewed medical records of patients who were diagnosed with SCLC-ED and received treatment between 2002 and 2016 at the Korea University Hospital. Among the 182 patients who were diagnosed with SCLC-ED and received palliative chemotherapy, 125 patients who had pulmonary function test report and previous or current smoking history were included. According to the global initiative for chronic obstructive lung disease (GOLD) classification, COPD was defined as FEV1/FVC <0.70. **Result:** Among 125 patients, COPD was present in 69 (55.2 %) patients. Among the patients with COPD, 48 (69.5%) patients did not know the COPD before the diagnosis of SCLC. Patients in the COPD group were older (mean age ± standard deviation, 68.9 ± 8.2 versus 65.6± 8.4 years; p=0.03). The mean FEV1(L) and predicted percent of FEV1 were 1.7L (67.9%) in COPD group and 2.9L (81.2%) in non-COPD group. Gender, body mass index, amount of smoking, ECOG performance status and neutrophil to lymphocyte ratio were not different between the two groups. Median overall survival of all patients was 8.6 months (95% confidential index [CI], 7.7-9.5). Median overall survival of the first-line chemotherapy between patients with COPD and patients without COPD was not statistically different (p=0.382). Median progression-free survival of the first-line chemotherapy between the two groups also were not different (p=0.372). In the analysis of COPD group, FEV1(L) and predicted percent of FEV1 did not affect survival among the patients with COPD (p=0.289). **Conclusion:** In conclusion, the presence of COPD at the diagnosis of SCLC-ED does not affect survival outcome in patients who were treated palliative chemotherapy. Even though the patients have severe obstructive pulmonary disease, active chemotherapy has to be considered with priority for the patients with SCLC-ED.

Keywords: small cell lung cancer, copd, survival

P1.12-14 SURVIVAL OF PATIENTS WITH SMALL-CELL LUNG CANCER UNDERGOING SURGICAL RESECTION

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Background: Small-cell lung cancer (SCLC) prognosis remains poor despite improvements in diagnosis and therapy. Current standard treatment for limited stage SCLC is concurrent chemo-radiotherapy, however recent retrospective studies indicate that surgery is an important treatment modality. We analyzed the overall survival and prognostic predictors of survival in patients who underwent surgical resection. **Method:** We reviewed the clinical course of 42 SCLC patients who had undergone complete surgical resection in our hospital between May 1989 and October 2017. Stages were determined or reclassified according to the eighth version of the TNM staging system. **Result:** The mean age at pulmonary surgery was 68.0 years, 37 (88.1%) patients were male, and 2 (4.8%) were never smokers. Preoperative diagnosis of cancer was achieved in 18 (42.9%) patients. The surgical procedures included wedge resection in 6 (14.3%) and lobectomy in 36 (85.7%). There were no perioperative deaths and major postoperative complications. Thirty-two patients (76.2%) received adjuvant chemotherapy and three patients (7.1%) underwent prophylactic cranial irradiation. Pathological stages were 2 cases in IA1, 5 in IA2, 1 in IA3, 6 in IB, 3 in IIA, 8 in IIB, 13 in IIIA, 3 in IIIB, 1 in IVA. The pathology of primary tumor demonstrated 30 (71.4%) pure SCLC and 12 (28.6%) combined SCLC. The overall 5-year survival rate was 57.2% after an average follow-up of 58.7 months. A significantly good survival was observed using univariate analysis in patients with female (p=0.048), preoperative normal serum level of CEA (p=0.013), normal serum level of SCC (p<0.001), pR0 resection (p=0.02), adjuvant chemotherapy (p<0.001), and histological pure SCLC (p=0.002). In preoperative factor, multivariate Cox proportional hazard model analysis revealed that overall survival was shorter in patients with increased SCC levels and cN1or 2. **Conclusion:** We conclude that pulmonary resection for early-stage SCLC is a safe and effective treatment strategy, and adjuvant chemotherapy may be useful in patients undergoing surgery in a practical management. Increased SCC levels and cN1 or 2 were identified as prognosis-related criteria for a poor prognosis of resected early SCLC.

Keywords: small-cell lung cancer, Surgery, Prognosis

P1.12-15 DISTINCTIVE CLINICAL CHARACTERISTICS OF SCLC IN NEVER-SMOKERS

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Background: Epidemiologic data suggest that 3% of patients with SCLCs are never-smokers. A large population study is required to describe the characteristics and outcomes of SCLC in never-smokers. Defining SCLC subgroups based on clinical characteristics, specifically smoking status, may lead to treatment advances in this historically recalcitrant cancer. **Method:** We performed a multicenter analysis using the Flatiron Health electronic health record-derived database, a nationally representative database comprising patient-level structured and unstructured data curated via technology-enabled abstraction. The cohort consisted of patients with clinician confirmed SCLC diagnosed on or after January 1, 2013. Genomic data from a clinico-genomic database developed by Flatiron and Foundation Medicine was used for a subset of patients that had received next-generation sequencing on the FoundationOne panel. Clinical and genomic characteristics were compared between smokers and never-smokers using descriptive statistics while the presence of other cancers was confirmed via chart review for never-smokers. Association of patient characteristics with overall survival was assessed using a univariate Cox proportional hazards model. **Result:** 103 of 4655 (2.2%) SCLC patients were never-smokers. Characteristics of these patients were: female 65%, male 35%; Asian 4.85%, Black 4.85%, White 62.1%; extensive-stage (ES) 68.9%, limited-stage (LS) 20.4%, unknown 10.7%. Compared with smokers (n=4552), never-smokers were more likely to be 80+ years (p=0.040), female (p=0.013), Asian (p<0.001), and present with ES (p=0.038). Based on univariate analyses, poor prognostic factors in never-smokers included sodium < 140 mEql/L (HR=1.95; p=0.028) and ES (HR=2.62; p=0.013). 26 (25%) patients had confirmed history of multiple primary malignancies. Three patients had prior history of organ transplant and two patients had history of pulmonary fibrosis. Survival of never-smokers (8.0 months for ES and 20.6 months for LS) appeared similar to historical data from smokers with SCLC. In the subset of 251 SCLC patients where tumor mutation data was available, never-smokers (n=18, 7.2%) were less likely to have a detectable alteration in TP53 (44.4% vs 95.3%; p<0.001) or RB1 (27.8% vs 76.8%; p<0.001). **Conclusion:** The never-smoker subgroup of SCLC patients has important clinical and genomic features that portend diagnostic, prognostic, and therapeutic opportunities. A high-frequency of other malignancies raises concern for neuroendocrine differentiation from other primary tumors. This series represents the largest reported data on SCLC in never-smokers.

Keywords: never smoker, small cell lung cancer

P1.12-16 MANAGEMENT OF ELDERLY SMALL-CELL LUNG CANCER PATIENTS IN A ROMANIAN TERTIARY CARE CENTER

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Background: Small cell lung cancer (SCLC) remains one of the most challenging conditions due to its poor prognosis and lack of effective

treatments. Although guidelines recommend aggressive treatment in elderly SCLC patients with good performance status, real-life data indicates that this patient subgroup is still undertreated. The aim of this analysis was to assess survival and management in elderly SCLC patients from North-East Romania. **Method:** We performed a retrospective analysis of all elderly patients diagnosed with SCLC and treated in the Regional Institute of Oncology Iasi (a territorial unit responsible for the diagnosis and treatment of cancer patients in Moldova) between 2012 and 2016. For each patient, we collected several types of data regarding patient status, tumor stage and management options that were correlated with overall survival. **Result:** We identified 41 patients diagnosed with SCLC and over 65 years old at the time of diagnosis. Average age was 69.63±3.98, with a median of 69 and a maximum of 78 years. The male to female ratio was 5.83:1, all patients were current or former smokers and performance status was 1 in 76.2% of cases. Most patients (57.1%) were diagnosed in stage IV and received doublet platinum-based systemic treatment in the first line setting. In the subgroup diagnosed with stage III disease, none of the patients received concurrent chemo-radiotherapy and less than half (35.29%) received sequential treatment. Although assessment after first-line treatment was available for less than half of the cases (39.02%), only one patient had progressive disease at that time-point (most were characterized as having a partial response). However, prophylactic cranial irradiation was performed in only 7.31% of cases. Second-line systemic treatment was initiated in 24.39% of cases – the preferred regimen was the CAV protocol followed by oral Topotecan. Overall survival was 11.17 months, with a maximum of 50 months and with statistically significant differences depending on stage and performance status. Age did not influence survival. **Conclusion:** Although elderly patients represent an important segment of the individuals affected by SCLC, they are sometimes undertreated and less aggressive management still seems to be the preferred approach despite good performance status and frequent response to first-line therapy. Most likely due to their age or because they delay seeking medical attention, elderly SCLC patients are more often diagnosed in metastatic stages. Our data for Romanian patients is mainly in accordance with available literature, although we found lower overall survival rates.

Keywords: small cell lung cancer, elderly

P1.12 SMALL CELL LUNG CANCER/NET
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.12-17 OVERALL SURVIVAL AND RECURRENCE AFTER SURGICAL RESECTION OF PURE AND MIXED LARGE CELL NEUROENDOCRINE TUMORS.

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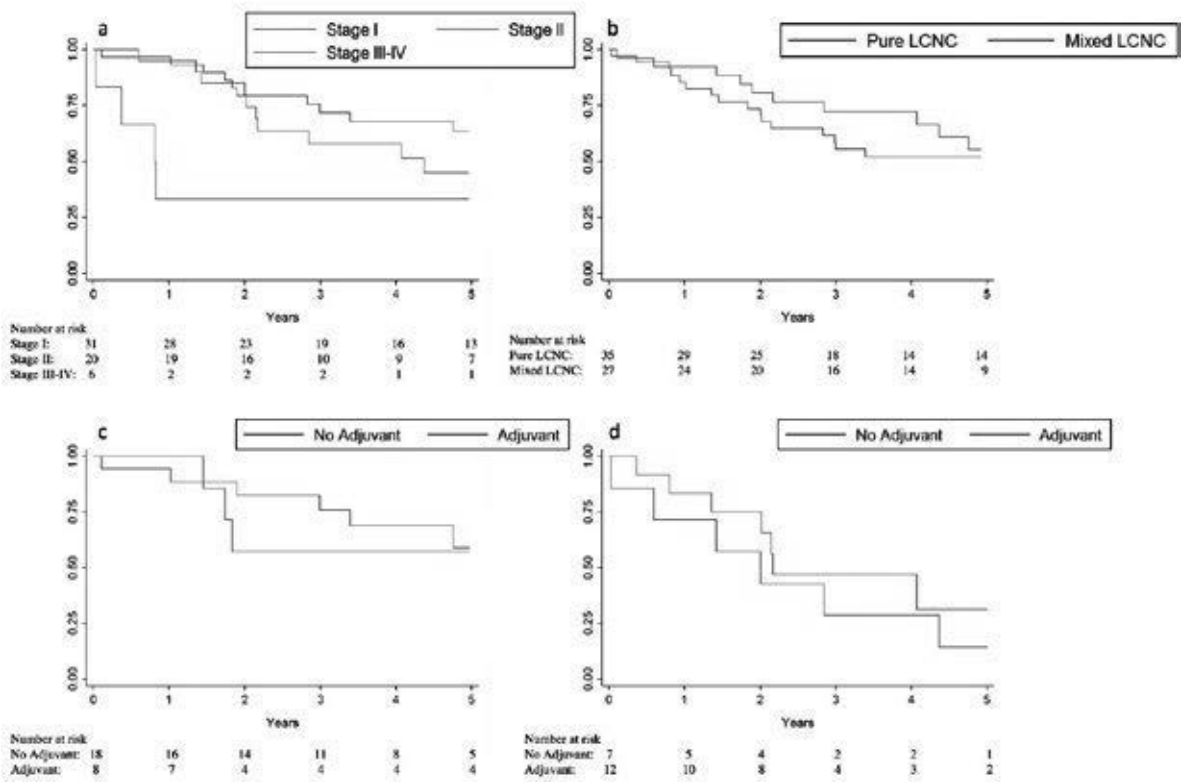
Background: Large-cell neuroendocrine carcinoma (LCNC) is an aggressive tumor with poor prognosis and undefined treatment. We performed a retrospective analysis on the outcomes of surgical resection and adjuvant therapy to assess the effectiveness of treatment. **Method:** Retrospective review of patients with LCNC who underwent surgical resection at a single-center tertiary care facility from 2002-2017. Survival times were assessed from day of surgery until death. A Kaplan-Meier method for overall survival (OS) and for recurrence was used and compared across prognostic factors using log-rank analysis and a Cox proportional hazard model. **Result:** Sixty-two patients were identified with a median follow up of 3.4 years. Of these, 26 (41.9%) were male and 56 (90.3%) were current or former smokers. The majority of patients underwent a lobectomy/segmentectomy (72.6%), while a smaller percentage (14.5%) underwent wedge resection, and the remainder pneumonectomy or bi-lobectomy (4.8%). Pathologically, 31 (54.4%) were stage I, 20 (35.1%) stage II, and 6 (10.5%) stage III-IV. Additionally, 35 (56.4%) represented pure LCNC while the remaining 27 (43.6%) had a mixed histology. Median OS for resected stage I disease was 11.3 years, decreased to 4.4 years in stage II disease, and was 0.8 years in stage III-IV disease (p = 0.01) (Figure 1). For those that recurred, median time to recurrence was 1.20 years for stage I and 1.15 years for stage II disease. Adjuvant therapy, type of resection, and tumor histology (pure vs. mixed) had no significant impact on OS on unadjusted or adjusted analysis.



Conclusion: LCNC is associated with early recurrence after surgical resection and poor survival for patients with stage III and IV disease. In patients with mixed histology survival and recurrence remain similar to those with pure LCNC tumors.

Keywords: survival analysis, Large cell neuroendocrine tumor, Surgery

P1.12-18 OUTCOME IN SMALL CELL LUNG CANCER PATIENTS WITH CEREBRAL RECURRENCE AFTER PRIOR PROPHYLACTIC CRANIAL IRRADIATION

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Background: Prophylactic cranial irradiation (PCI) is a standard therapy for both limited small cell lung cancer (SCLC) and extensive SCLC patients with good responses to first-line treatment. The aim of this study was to examine outcomes in SCLC patients in a single institution who underwent cerebral recurrence after prior PCI. **Method:** We retrospectively examined the medical records of 219 consecutive SCLC patients who had initially received PCI(25 Gray in 10 fractions) between June 2007 to June 2017. Data were analyzed with regard to age, sex, smoking status, treatment, disease stage, data of PCI, time to cerebral recurrence, site of cerebral recurrence, re-irradiation after cerebral recurrence and time to death. Survival was estimated by the Kaplan-Meier method. Multivariate analyses were performed by the log-rank and Cox's proportional hazard model test. **Result:** Of the 219 patients undergoing PCI, 180(82.2%) were LD-SCLC and 39(17.8%) were ED-SCLC. The median age was 59 years and the median follow-up time was 23.7 months. The median overall survival (OS) of all patients from the time of diagnosis was 39.0 months (95%CI, 29.6–48.4), in LD-SCLC it was 47.0 months (95%CI, 35.4–58.6), and in ED-SCLC it was 19.0 months (95%CI, 17.0–21.0). The difference was statistically significant with P=0.000. Forty-six patients (21.0%) were diagnosed with cerebral recurrence. 30(65.2%) of these presented with oligometastatic disease and 16(34.8%) had non-oligometastatic disease. Cox multivariate analysis identified disease stage (P=0.043) was the only significantly favorable prognostic factor for cerebral recurrence. The median survival time from PCI was 21.0 months (95%CI, 12.5–29.5), in oligmetastatic disease it was 35.0 months (95%CI, 19.0–51.0), and in non-oligometastatic disease it was 16.0 months (95%CI, 12.1–19.9). The difference was statistically significant with P=0.007. Meanwhile, the median time from PCI to cerebral recurrence was 11.0 months (95%CI, 9.5–12.5), in oligmetastatic disease it was 11.0 months (95%CI, 6.7–15.3), and in non-oligometastatic disease it was 10.0 months (95%CI, 8.4–11.6). There was no statistical significance between the two. Among forty-six patients with cerebral recurrence, 34 patients underwent re-irradiation using either Re-WBRT (11patients, 23.9%) or SRS /SRT (23patients, 50.0%), another 12 patients (26.1%) did not accept radiotherapy to brain. The median survival time from cerebral recurrence was 10 months (95%CI, 4.1-16.0) for re-irradiation and 4 months (95%CI, 2.3-5.8) for no radiotherapy group, respectively. The difference was statistically significant with P=0.000. **Conclusion:** PCI remains standard therapy for SCLC patients with good responses to first-line treatment. Cerebral recurrence is inevitable, however, cerebral re-irradiation after recurrence is proven to be beneficial for survival.

Keywords: small cell lung cancer, prophylactic cranial irradiation, recurrence

P1.12-19 CLINICO-PATHOLOGICAL CHARACTERISTICS AND TREATMENT OUTCOME IN SMALL CELL LUNG CANCER: A SINGLE INSTITUTIONAL EXPERIENCE

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Background: Lung cancer is one of the commonest cancer in the world with a high rate of mortality. Small cell lung cancer constitutes around 14% of all lung cancers. Literature on small cell lung cancer is scarce in literature. The aim of the study was to analyze clinical profile of patients with lung cancer and their treatment outcome. **Method:** This is a single institutional data review of patients treated between June 2011 and Dec 2017 with diagnosis of small cell carcinoma of lung. Patients were staged as either localized or extensive disease after appropriate staging work-up. Patients with localized disease were treated with concurrent chemo-radiation with platinum based chemotherapy. Those with extensive disease were treated with platinum based palliative chemotherapy. Clinic-pathological characteristics, treatment details and outcome were recorded in this study. Response assessment was done using RECIST criteria wherever applicable. Patients who received at least 1 cycle of palliative chemotherapy were included for survival analysis. **Result:** Total 128 patients were registered with median age of 62 years (range: 38-86), male:female ratio of 115:13. The ECOG performance status was 0 in 2, 1 in 30 (23%), 2 in 64, (50%) 3 in 29 (22%) and 4 in 3 patients. Ninety-percent (n=112) patients had smoking history and 20% (n=25) patients had symptom of superior vena cava obstruction at baseline. Eleven (9%) patients had localized disease at presentation. Sixteen (12.5%) patients had brain metastasis at presentation. Eighty-two (64%) patients took palliative chemotherapy and eight (10%) of them had localized disease. Chemotherapy regimen was – carboplatin only in 5 (6%), etoposide-carboplatin in 29 (35%) and cisplatin-etoposide in 48 (58%). Patients received median cycle number of 6 (range:1-6). Of the evaluable 58 (71%) patients, initial response was complete response in 2, partial response in 37, stable disease in 15 and progressive disease in 4. Fifteen patients received second-line chemotherapy on progression of disease. After a median follow-up of 6.7months (range: 0.3 - 36.6), median progression-free survival was 8.6 months.. After a median follow up of 12.5 months (range:0.3-36.6), median overall survival was 8.7 months. **Conclusion:** Small cell carcinoma in our series had high incidence of advanced stage (91%) and 10% patients were non- smoker. Only 64% patients received palliative chemotherapy and achieved high disease control rate (>90%) in the evaluable patients with median progression-free survival of 8.6 months and median overall survival of 8.7 months.

Keywords: chemotherapy, small cell, lung cancer

P1.12-20 OVERALL SURVIVAL WITH LURBINECTEDIN PLUS DOXORUBICIN IN RELAPSED SCLC. RESULTS FROM AN EXPANSION COHORT OF A PHASE IB TRIAL.

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Background: Lurbinectedin (PM01183, L) is a new anticancer drug that binds to DNA, inhibits transactivated transcription and modulates tumor microenvironment. Preclinical evidence of synergism was observed for PM01183 in combination with doxorubicin (DOX). **Method:** This multicenter, phase Ib clinical trial found impressive activity in second-line SCLC patients (ORR 67%). An expansion cohort with reduced dose (L 2mg/m^2+ DOX 40mg/m^2) was implemented to improve safety. SCLC patients <75 years with ECOG PS 0-1 and with no more than one prior chemotherapy line and stable brain metastases were included. DOX was interrupted after 10 cycles continuing with PM01183 alone. Primary G-CSF prophylaxis was not mandatory. **Result:** 27 patients treated. Males: 75%; median age: 64 (49-77) years; ECOG PS 0-1: 32%-68%; CNS involvement: 4%; bulky disease (>50 mm): 75%. 88% responded to 1st line (CR in 4%). Median chemotherapy-free interval (CTFI) was 3.5 months (m). 22% refractory (CTFI <30 days) 15% resistant (R) (CTFI 30-90 days) and 63% sensitive (S) (CTFI>90 days). Overall confirmed ORR was 37% (CR in 4%), and 53% (CR in 6%) in S patients. Overall median PFS was 3.4 m (95% CI, 1.5-6.2), being 1.5 m (95%CI, 0.8-3.4) in R pts, and 5.7 m in S patients. Overall survival (OS) data are summarized in the following table.

OS	Overall	Resistant	Sensitive
Overall (n=27)	7.9 m (95% CI: 4.9-11.5)	4.9 m (95% CI: 2.3-6.7)	11.5 m (95% CI: 6.0-16.6)
Excluding CTFI<-30days (n= 21)	10.2 m (95% CI: 6.0-12.1)	6.7 m (95% CI: 5.1-8.4)	11.5 m (95% CI: 6.0-16.6)
Data shown are median and 95% CI.			

Grade 4 neutropenia, anemia or thrombocytopenia appeared in 64%/0%/7% of patients, respectively, and febrile neutropenia (G3/4) occurred in 10%. Non-hematological toxicity was mild and mainly due to fatigue (G3=18%) and nausea (G3=7%). **Conclusion:** Lurbinectedin/DOX combination showed remarkable activity as second line in SCLC, especially in sensitive patients (CTFI>90 days). Activity is higher than that reported for CAV or topotecan. OS shows an outstanding improvement in this second-line setting, especially when excluding refractory pts. A phase III clinical trial (ATLANTIS, NCT02566993) is currently ongoing evaluating this combination in relapsed SCLC patients

Keywords: overall survival, Phae I, Small cells

P1.12-21 DEVELOPING A REAL-WORLD 3L COMPARATOR TO CHECKMATE 032: OVERALL SURVIVAL (OS) IN PATIENTS WITH SMALL CELL LUNG CANCER (SCLC)

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Background: In the US, no approved standard of care exists for the treatment of relapsed SCLC in 3L setting. This study describes 3L outcomes in US patients with SCLC and creates a matched real-world historical comparator to CheckMate 032, highlighting the relative benefit that nivolumab treatment may offer to patients. **Method:** Adult patients receiving 3L therapy for SCLC were selected from the Flatiron Health electronic health record (EHR) database (01Jan2011-30Sep2017). Index date was SCLC diagnosis. A matched cohort was constructed and evaluated based on Inclusion (I)/Exclusion (E) criteria of CheckMate 032. Patients were included if: pretreated with ≥1one platinum-containing regimen; ECOG score of 0 or 1; ≥2 months of continuous medical data. Patients were excluded if: treated with immunotherapy; had brain metastases; autoimmune disease (except type I diabetes); HIV; Hep B/ Hep C on/after diagnosis; on immunosuppressive doses of systemic corticosteroids. Kaplan-Meier curves were generated for patients with 3L SCLC from treatment initiation to death. Duration of therapy (DoT) was analyzed as time from start to end of 3L **Result:** 2,209 SCLC patients initiated 1L, of which 218(9.8%) received 3L treatment. 92 patients with SCLC matched I/E criteria as in CM 032. Mean age was 64 years; 53% were female; 68% were white; 99% had a history of smoking; and 94% of patients were treated in a community setting. Median follow-up exceeded 15 months. Median and landmark OS (1-year, 18-months, 2-year) and DoT including data for a subset of 3L patients, matched for I/E criteria to CheckMate 032 (n=92), are reported in the table.

Table: Overall Survival in Third-line SCLC Treatment

	Flatiron Electron Health Record		CheckMate 032
	All 3L Patients with SCLC (N = 218)	I/E Matched 3L Patients with SCLC (N = 92)	All 3L+ Patients with SCLC
Median OS (95% CI), months	3.8 (3.0, 4.2)	3.8 (2.8, 4.9)	[Data to be presented at conference]
1-year OS rate (95% CI), %	14.1 (9.3, 19.9)	11.2 (4.9, 20.4)	
18-month OS rate (95% CI), %	6.7 (3.4, 11.6)	7.5 (2.5, 15.9)	
2-year OS rate (95% CI), %	6.0 (2.9, 11.7)	7.5 (2.5, 15.9)	
Median DoT (SD), months	2.7 (2.6)	2.8 (2.2)	

Abbreviations: 3L, third-line; CI, confidence interval; DoT, duration of treatment; Exc, exclusion criteria; Inc, inclusion criteria; OS, overall survival; SCLC, small-cell lung cancer; SD, standard deviation

Conclusion: Poor survival among US patients treated for 3L SCLC emphasizes the need for more effective and tolerable therapies. In CheckMate 032, nivolumab demonstrated considerable activity in heavily pretreated patients when compared to real-world data and may represent a therapeutic option over available treatments.

Keywords: Small cell lung cancer, nivolumab, real world

P1.13-01 ANTI-EGF ANTIBODIES INCREASE THE EFFECT OF ALK AND MEK INHIBITORS IN ALK AND KRAS NSCLC AND CRC CELL LINES

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Background: Immunization against Epidermal Growth Factor (EGF) has demonstrated efficacy in a phase III trial including unselected NSCLC patients, and we have recently shown that antibodies generated by vaccination (anti-EGF VacAbs) potentiate the effects of TKIs in *EGFR*-mut cells growing *in vitro*. In this study, we aimed to determine if anti-EGF VacAbs show antitumor activity in *KRAS*-mutant (mut) and Anaplastic Lymphoma Kinase (*ALK*) translocated non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) cells, alone or in combination. **Method:** Anti-EGF VacAbs were generated in rabbits. Cell lines were treated with anti-EGF VacAbs alone and in combination with *ALK* TKIs, trametinib and standard chemotherapeutic agents in *ALK* translocated (H3122, E13;A20 (v1) and H2228, E6;A20 (v3)) and lung (A549 and H23) and colon (DLD1 and LS174T) *KRAS*-mut cell lines. Cell viability was analyzed by MTT, changes of total and phosphorylated proteins by Western blot and emergence of resistance by direct microscopic examination in low density cultures. **Result:** Anti-EGF VacAbs suppressed EGF-induced cell proliferation and inhibited *EGFR* phosphorylation signaling in all cell lines tested. In combination, the anti-EGF VacAbs significantly enhanced the antitumor activity of alectinib and crizotinib in H2228 cells and trametinib in A549, H23 and DLD1 cells. In these cell lines, the antibodies decreased Erk ½ and Akt phosphorylation. Finally, the addition of the anti-EGF VacAbs to the culture medium significantly delayed the emergence of resistant clones to alectinib and crizotinib in H2228 cells. In previous experiments, H2228 cells had shown a stronger dependency on the EGF/ EGFR pathway than H3122. Results for the combination with standard chemotherapy in *KRAS*-mut cell lines will be presented at the meeting. **Conclusion:** Anti-EGF VacAbs decreased cell proliferation and inhibited *EGFR* activation in lung and colon *ALK* translocated and *KRAS*-mut cell lines. In addition, they potentiated the effects of trametinib in *KRAS*-mut cells and TKIs in *ALK* translocated cells (v3), where they also prevented the emergence of resistance to alectinib and crizotinib. Two clinical trials are currently testing anti-EGF vaccination in advanced NSCLC; the Epical Phase I/II trial, in combination with *EGFR* TKIs in *EGFR*-mut patients; and the BV-NSCLC-002 Phase III trial, in combination with chemotherapy in *EGFR*-wt.

Keywords: EGF, Vaccine, Immunotherapy

P1.13-02 EXALT3: PHASE 3 RANDOMIZED STUDY COMPARING ENSARTINIB TO CRIZOTINIB IN ANAPLASTIC LYMPHOMA KINASE POSITIVE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Ensartinib (X-396) is a novel, potent ALK small molecule tyrosine kinase inhibitor (TKI). It is well-tolerated and has shown promising activity in NSCLC patients in a phase 1/2 study in patients that were both ALK TKI naïve and patients that received prior crizotinib, as well as those with CNS metastases. The safety profile of ensartinib appears to be different from other ALK TKIs. **Method:** In this global, phase 3, open-label, randomized study, approximately 270 patients with ALK+ NSCLC who have received no prior ALK TKI and up to one prior chemotherapy regimen will be randomized with stratification by prior chemotherapy

(0/1), performance status (0-1/2), brain metastases at screening (absence/presence), and geographic region (Asia /other), to receive oral ensartinib (225 mg, once daily) or crizotinib (250mg, twice daily) until disease progression or intolerable toxicity. Eligibility also includes patients ≥ 18 years of age, stage IIIB or IV ALK+ NSCLC. Patients are required to have measurable disease per RECIST 1.1, adequate organ function, and an ECOG PS of ≤2. Adequate tumor tissue (archival or fresh biopsy) must be available for central testing. The primary endpoint is progression-free survival assessed by independent radiology review based on RECIST v. 1.1 criteria. Secondary efficacy endpoints include overall survival, response rates (overall and central nervous system [CNS]), PFS by investigator assessment, time to response, duration of response, and time to CNS progression. The study has > 80% power to detect a superior effect of ensartinib over crizotinib in PFS at a 2-sided alpha level of 0.05. Phase 3 recruitment began in June, 2016 and currently has 98 active sites in 21 countries. The duration of recruitment will be approximately 28 months. This study is registered with ClinicalTrials.Gov as NCT02767804. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: crizotinib, ensartinib, ALK

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-03 ENSARTINIB TREATMENT BEYOND DISEASE PROGRESSION IN STAGE IV ALK+ NON-SMALL CELL LUNG CANCER

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Background: Anaplastic Lymphoma Kinase (ALK) positive non-small cell lung cancer (NSCLC) patients (pts) benefit from receiving ALK tyrosine kinase inhibitors (TKIs); however, despite initial activity, resistance invariably develops. Disease progression (PD) is sometimes limited to progression which occurs in only one or a few sites and may not occur systemically. Local treatment with radiation while continuing treatment with ensartinib may enable prolonged benefit beyond progression. **Method:** Patients who were ALK TKI naïve or had received prior ALK treatment received ensartinib 225mg QD until PD or unacceptable toxicity or investigator discretion. The primary endpoint was safety and tolerability, and the secondary endpoint was pharmacokinetic and preliminary biological activity. Tumor assessment was performed locally every 8 weeks. Post-progression treatment with ensartinib was allowed if the investigator felt the patient was still receiving benefit from ensartinib. Cycles were approximately every 28 days, and radiation therapy after Cycle 1 for isolated CNS metastases was permitted if there was no evidence of progressive disease elsewhere. Post-progression treatment data were captured and analyzed. **Result:** As of the data cut-off (May 01, 2018), 12 pts with progression continued ensartinib treatment post progression (67% with progression only in the CNS, 75% of which had CNS lesions at baseline and 33% with progression only outside the CNS). Of the 12 pts, half of the patients were ALK TKI naïve and half had received at least one prior ALK TKI. Six pts received radiation therapy at the time of initial progression. The initial median Progression Free Survival (PFS) of the 12 pts with post progression treatment was 15.7 months and median secondary PFS (date of initial progression to the date of second progression or end of treatment) was 5.7 months for a combined duration of therapy of 23.8 months. A significantly longer duration of continued therapy was observed in patients who received radiation treatment than those who did not 8.6 mos vs 3.5 mos. The secondary PFS was longer in treatment naïve pts than in pts who received a prior ALK TKI, 7.7 mos vs 5 mos. After the initial progression, excluding lesions treated with radiation therapy, secondary stable disease was observed in 92% of patients. No new or additional safety risk was identified in the pts post progression. **Conclusion:** Ensartinib may have clinical benefit in selected patients with NSCLC if continued post-progression. Secondary PFS was longer in patients treated with radiation therapy. Ensartinib was generally well tolerated in these patients treated post progression.

Keywords: ALK, ensartinib, post-progression

P1.13 TARGETED THERAPY
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P1.13-04 INTEGRIN β3 INHIBITION ENHANCES THE ANTITUMOR ACTIVITY OF ALK INHIBITOR IN ALK REARRANGED NSCLC

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Background: Anaplastic lymphoma kinase (ALK)-positive cancers are sensitive to small molecule ALK kinase inhibitors, but most cases experience failure following treatment. Hence, additional drug targets and combination therapeutic treatments are needed. We investigated gene expression that is regulated by the expression of ALK and explored its roles in cancer progression and therapeutic implication. **Method:** We screened ALK-rearranged non-small cell lung cancer (NSCLC) cases using immunohistochemistry and fluorescence in situ hybridization, and then conducted multiplex gene expression analysis. We also performed a clinicopathological analysis to validate the findings. Additional cellular experiments, including inhibition and migration assays, and in vivo lung cancer model studies were performed. **Result:** Among patients with ALK-rearranged NSCLC, integrin β3 (ITGB3) was one of the overexpressed genes in comparison with that in ALK-negative NSCLC (P = 0.0003). ALK and integrin β3 expression were positively correlated, and we discovered that high integrin β3 mRNA expression was associated with metastasis and more advanced tumor stages (P <0.005; P < 0.05). Furthermore, we found that inhibition of both ALK and integrin β3 led to increased drug sensitivity in vitro and in vivo (both P < 0.05). **Conclusion:** We discovered a positive correlation between ALK and integrin β3 expression levels in ALKrearranged NSCLC. Our findings suggest that high integrin β3 expression in ALK-rearranged NSCLC is associated with tumor progression and a worse prognosis. This demonstrates the prognostic value of integrin β3 and provides a rationale for combination treatment with ALK and integrin β3 inhibitors in patients with ALK-rearranged NSCLC.

Keywords: ALK-rearranged NSCLC, ITGB3, multiplex gene expression analysis

P1.13 TARGETED THERAPY
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P1.13-05 INTEGRIN β3 INHIBITION ENHANCES THE ANTITUMOR ACTIVITY OF ALK INHIBITOR IN ALKREARRANGEDNSCLC

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Background: Anaplastic lymphoma kinase (ALK)-positive cancers are sensitive to small molecule ALK kinase inhibitors, but most cases experience failure following treatment. Hence, additional drug targets and combination therapeutic treatments are needed. We investigated gene expression that is regulated by the expression of ALK and explored its roles in cancer progression and therapeutic implication. **Method:** We screened ALK-rearranged non-small cell lung cancer (NSCLC) cases using immunohistochemistry and fluorescence in situ hybridization, and then conducted multiplex gene expression analysis. We also performed a clinicopathological analysis to validate the findings. Additional cellular experiments, including inhibition and migration assays, and in vivo lung cancer model studies were performed. **Result:** Among patients with ALK-rearranged NSCLC, integrin β3 (ITGB3) was one of the overexpressed genes in comparison with that in ALK-negative NSCLC (P = 0.0003). ALK and integrin β3 expression were positively correlated, and we discovered that high integrin β3 mRNA expression was associated with metastasis and more advanced tumor stages (P < 0.005; P < 0.05). Furthermore, we found that inhibition of both ALK and integrin β3 led to increased drug sensitivity in vitro and in vivo (both P < 0.05). **Conclusion:** We discovered a positive correlation between ALK and integrin β3 expression levels in ALK rearranged NSCLC. Our findings suggest that high integrin β3 expression in ALK-rearranged NSCLC is associated with tumor progression and a worse prognosis. This demonstrates the prognostic value of integrin β3 and provides a rationale for combination treatment with ALK and integrin β3 inhibitors in patients with ALK-rearranged NSCLC.

Keywords: ALK-rearranged NSCLC, ITGB3, combination therapy

P1.13-06 FIRST-LINE LORLATINIB VERSUS CRIZOTINIB FOR ADVANCED ANAPLASTIC LYMPHOMA KINASE-POSITIVE (ALK+) NON-SMALL CELL LUNG CANCER

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Background: Lorlatinib and crizotinib are oral tyrosine kinase inhibitors with activity against ALK and ROS1 fusion proteins. Crizotinib is well tolerated and has superior efficacy compared to chemotherapy for treatment of patients with advanced *ALK*+ non-small-cell lung cancer (NSCLC). However, resistance to crizotinib can develop, and the central nervous system (CNS) is often a site of disease relapse. Second-generation ALK inhibitors, ceritinib and alectinib, have demonstrated activity in crizotinib-naive or resistant treatment settings, and alectinib has been shown to have superior progression-free survival (PFS) compared to crizotinib as first-line therapy. Lorlatinib is a selective, CNS-penetrant ALK inhibitor that has potent activity against ALK and kinase domain resistance mutations, including the difficult-to-treat G1202R mutation.Lorlatinib has shown clinical activity in patients previously treated with crizotinib and other ALK inhibitors, including patients with progressive CNS metastases. This study aims to determine if lorlatinib is superior to crizotinib in prolonging PFS in treatment-naïve patients and to identify candidate biomarkers predictive of clinical efficacy or treatment resistance. **Method: Trial Design** This global, multicenter, open-label phase 3 study will enroll ~280 treatment-naïve patients. Eligible patients must be aged ≥18 years, have Eastern Cooperative Oncology Group performance status of 0–2 and ≥1 measurable extracranial target lesion not previously treated with radiotherapy. Patients with asymptomatic brain metastases are eligible. Patients will be randomized (1:1) to lorlatinib 100 mg once daily or crizotinib 250 mg twice daily and stratified by presence of brain metastases (yes/no) and ethnicity (Asian/non-Asian). Treatment will continue until disease progression, patient refusal, or unacceptable toxicity. Crossover between treatment arms will not be permitted. The primary endpoint is PFS based on blinded independent central review (BICR) using RECIST v1.1. Secondary endpoints include PFS based on investigator assessment, overall survival, objective response (OR) by BICR and investigator assessment; intracranial (IC) OR (periodic magnetic resonance imaging will be performed for central nervous system evaluation), IC time to progression, duration of response and time to response all by BICR; tumor tissue and peripheral blood circulating free DNA biomarker assessment, adverse events and patient-reported health-related outcomes as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 EORTC (QLQ-C30) and EORTC Lung Cancer Module (QLQ-LC13), and the 5-level EuroQol 5-dimension questionnaire (EQ-5D-5L). The first patient was screened on April 14, 2017. This study is registered with ClinicalTrials.gov as NCT03052608. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: lorlatinib, ALK-positive NSCLC, tyrosine kinase inhibitor

P1.13-07 EPITHELIAL-MESENCHYMAL TRANSITION INDUCED THE ACQUIRED RESISTANCE TO ALK INHIBITOR BRIGATINIB IN LUNG CANCER CELLS HARBORING WITH ALK FUSIONS

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Background: The ALK inhibitors, such as crizotinib and alectinib show a great response to patients with non-small cell lung cancer (NSCLC) harboring ALK fusions. However, the acquired drug resistance is also known as important issues in the treatment with the specific molecular targeted agents, such as EGFR-TKI as well as ALK-TKI. The mechanisms of acquired resistance to ALK-TKI are reported previously, bypass tract signals of EGFR or MET, and Epithelial-mesenchymal transition (EMT). Novel generation ALK inhibitor brigatinib is promising for NSCLC harboring ALK fusions, however, the precise mechanism of the acquired resistance to brigatinib is not fully understood. To elucidate for the novel acquired resistance to brigatinib, we here conducted the cell-based experiments using ALK fusion NSCLC cells. **Method:** We established ALK fusion NSCLC cells H3122 (variant 1 E13;A20) and H2228 (variant 3 E6;A20) with the acquired resistance to brigatinib by step-wise methods. ALK inhibitor sensitivity and signal transduction in H3122 and H2228 cells were examined in vitro. **Result:** H3122-brigatinib resistance cell (H3122-BR) and H2228-brigatinib resistance cell (H2228-BR) indicated the cross-resistance to other ALK inhibitors alectinib, crizotinib and lorlatinib. Furthermore, morphological change was observed to spindle shape, and additionally shows decreasing of E-cadherin and increasing of vimentin which are marker of EMT by the western blotting analysis. Moreover, some of these resistant cells cultured with drug-free medium for 4weeks were reversed the sensitivity to ALK-TKIs and cell formation backed to parental cells. **Conclusion:** We demonstrated that EMT elicited the acquired resistance to ALK-TKIs under the exposure of brigatinib treatment in ALK fusion NSCLC cells. Further experiments are needed to overcome this drug resistance induced by EMT.

Keywords: epithelial-mesenchymal transition, ALK, Acquired resistance

P1.13-08 DISTRIBUTION, DIFFERENCES IN CLINICAL CHARACTERISTICS AND RESISTANCE MECHANISM OF ALK VARIANTS IN CHINESE LUNG CANCER PATIENTS.

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Background: ALK rearrangements are established targetable drivers in NSCLC. Recent reports indicate differential progression-free survival to ALK inhibitors according to specific EML4-ALK variant. **Method:** A total of 172 unique Chinese lung cancer patients with tumors harboring ALK rearrangements (ALK+) were enrolled in the study from 2016 to 2018. ALK+ were detected by Ventana, FISH, or next-generation sequencing based ER-Seq method, which enables simultaneously assess single-nucleotide variants, insertions/deletions, rearrangements, and somatic copy-number alterations across at least 59 genes (59-1021). Tissue biopsy was the first choice for NGS mutation profiling, and ctDNA or pleural effusion testing was used as an alternative. **Result:** Of these 172 cases, the median diagnosis age was 50 (range 24-78), 58% were female, 90% was NSCLC. Of the 147 ALK+ cases detected by NGS, we identified 65 (44%) EML4-ALK v1 (E13; A20), 18 (12%) EML4-ALK v2 (E20; A20), 43 (29%) EML4-ALK v3 (E6; A20), 13 (9%) other EML4-ALK, and 8 (5%) non-EML4-ALK rearrangements. 2 new fusion genes were found in non EML4-ALK rearrangements (SRBD1-ALK (EX20; EX20) and CLIP4-ALK (EX9; EX20)), and the CLIP4-ALK patient's tissue was also ALK positive by Ventana. V1 found a higher proportion of pleural effusion at baseline than non-v1 (12% v.s.5%). Mutation profiling by NGS were performed after disease progression in 55 patients treated with crizotinib. mPFS was 8.1 months, no significant difference existed between v1 and v3 (P=0.69). But the presence of known ALK resistance mechanisms was significantly higher in v3 as compared to non-v3 (67% v.s. 27%, P=0.038). **Conclusion:** Next generation sequencing allows for detection of the specific ALK fusion partner and variants, increases the understanding of the biology of ALK+ NSCLC, and may have value to foretell potential mechanisms of resistance.

Keywords: ALK variants, lung cancer, resistance mechanism

P1.13-09 EFFICACY AND TOLERANCE OF OSIMERTINIB IN REAL WORD SETTING: RESULTS OF THE FRENCH EARLY ACCESS PROGRAM (EXPLORE T790M GFPC STUDY).

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Background: Based on the Phase III AURA3 trial, osimertinib a third-generation EGFR TKI is approved in France in EGFR T790M-positive advanced NSCLC whose disease have progressed on or after first or second generation EGFR TKI. Objective: to assess efficacy and tolerance of Osimertinib in real world setting. **Method:** Retrospective, multicentric study including T790M-positive advanced NSCLC receiving osimertinib from 07 April 2015 to 27 April 2016 in French early access program. Overall survival (OS) and progression free survival PFS) were analyzed in the whole population, in the subgroup of patients with cerebral metastasis at osimertinib initiation and according to the number of previous treatment lines (1 versus 2 or more). **Result:** The analysis included 205 patients treated in 52 centers; mean age 69.5 ± 11.1 years, female 68.8%, adenocarcinoma 97.5%, EGFR mutations exons 19/21: 66.5%/ 30.5%, never smokers 71.5 %, PS 0-1/2/ 3-4: 54%/18,8%/27.2%, stage IV: 87.4%,presence of cerebral metastasis at osimertinib initiation: 43.7% . EGFR T790M mutation diagnosis have been done by liquid biopsy in 34.4 % or on tissue re-biopsy in 65.6%. Patients received a median of 2.8 ± 1.5 lines of treatment before osimertinib initiation. All patients received a first or second generation EGFR TKI before osimertinib. Osimertinib has been used in second line setting in 18% of cases and in third line or more setting in 82%. Median PFS was 12.4 (CI 95%: 10.1-15.1) months in the whole population, 9.7 (CI 95%: 7.7-13.5) in patients with cerebral metastasis and 15.8 (CI 95%: 11.9-17) months in patients without cerebral metastasis, (p : 0.2). PFS was not significantly different according to the use of osimertinib as second or third line of treatment: 12.6 (CI 95%: 6.7-17.5) vs 12.4 (CI 95%: 9.7-15.3) months, respectively. Median OS since osimertinib initiation was 20.5 (CI 95%: 16.9-24.3) months, 23.06 [18.56;27.83] and 18.00 [12.16;22.21] months in patients without and with cerebral metastasis, respectively. OS was not significantly different according the use of osimertinib as second or third line of treatment: 17.5 (CI 95%: 11.6;27.8) vs 21.7 (CI 95%: 17.3;24.3) months (p=0.4). A new biopsy was performed at disease progression on osimertinib in 50 patients: data will be presented. **Conclusion:** Efficacy of Osimertinib in real world setting appears similar to that observed in clinical trials in patients with EGFR T790M mutation in ≥2nd line. Clinical trial information: Supported by an academic grant from Astra Zeneca

Keywords: osimertinib, egfr mutation, treatment

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P1.13-10 AURORA KINASE A DRIVES THE EVOLUTION OF RESISTANCE TO THIRD GENERATION EGFR INHIBITORS IN LUNG CANCER

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Background: Paradigm defining for precision medicine, EGFR inhibitors are a major breakthrough in the treatment of EGFR-mutant non-small cell lung cancer (NSCLC). Although these EGFR-TKI therapies often elicit profound initial therapeutic responses, their effects are transient due to residual disease. This residual disease and subsequent disease progression occurs through tumor evolution and molecular drivers behind the formation, maintenance and evolution of residual disease and acquired resistance have remained elusive. Although in many cases pre-existing clones with bona-fide genetic resistance have been identified, majority of patients have undetectable resistance causing genetic alterations suggesting that non-genetic alterations may drive altered cell state and signaling associated with EGFR inhibitor resistance. Furthermore, in the case of osimertinib now used in first line setting, mechanisms of acquired resistance have been ill defined and no effective second line therapies exist. **Method:** Using EGFR mutant lung cancer cells we developed eight distinct in vitro models of acquired resistance to 3rd generation EGFR-TKI inhibitors, osimertinib and rociletinib. We examined the efficacy of drug combinations in vivo using both cell line xenografts and PDX models of EGFR TKI resistance. We measured the level of staining of the candidate biomarker, TPX2, in patients progressing on first and third-generation EGFR TKIs. **Result:** Chemical screens in acquired resistant cell lines revealed that Aurora kinase inhibitors are highly synergistic when combined with third-generation EGFR inhibitors. Resistant cells harbored heightened activation of AURKA caused by upregulation of its co-activator protein TPX2. In *in-vitro* and *in-vivo* models of acquired resistance the combination induced potent cell death by reactivating BIM-mediated apoptosis. We found that tumors from the majority of patients progressing on first and third-generation EGFR TKIs harbored high levels of TPX2, indicating that AURKA is likely activated and driving resistance in a significant fraction of EGFR-mutant lung cancers. Tracking the kinetics of AURKA activation, we found that AURKA activity is required for the formation and maintenance of residual drug tolerant cells, precursors of acquired resistance. Either single agent EGFR-TKI, the AURKA inhibitor MLN8237 or the combination enhanced the magnitude of response and forestalled the emergence of resistance in vitro as compared to monotherapies. The combination robustly induced tumor regressions in an EGFR L858R PDX tumor model generated from a residual disease surgical specimen. **Conclusion:** This synthetic lethal interaction between EGFR TKIs and Aurora kinase inhibitors has important clinical implications for the development of better treatment strategies using EGFR-TKIs and suggest a new paradigm for preventing the emergence of resistance.

Keywords: Acquired resistance, EGFR, Tyrosine kinase inhibitors

P1.13 TARGETED THERAPY
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P1.13-11 PRO-CTCAE TOXICITIES IN ADVANCED NSCLC PATIENTS WITH EGFR MUTATIONS: A REAL WORLD ASSESSMENT

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Background: The Patient Reported Outcomes of the CTCAE (PRO-CTCAE) tool has not been evaluated in a real-world study of EGFR-mutation positive patients treated with TKIs/chemotherapies. We evaluated its role in capturing clinically-significant toxicities. **Method:** A longitudinal observational study evaluated common EGFR-TKI toxicities using PRO-CTCAE, measured on a five-point scale (1=no symptoms to 5=very severe symptoms) in outpatients with EGFR-mutated (EGFRm) advanced NSCLC. **Result:** Toxicity information was collected for 709 follow-up visits (encounters) from 232 patients. Median age was 64 (range:29-96), 161 (69%) were female and 124 (53%) were Asian. 85 (37%) already had brain metastases at first encounter. 485 encounters were observed from patients stable on treatment, and 187 from patients progressing or with documented progression on their current treatment. 24 patients were treated with osimertinib (97 encounters, 97% in second/subsequent-line), 136 with gefitinib (324 encounters, 95% in first line therapy), 42 were receiving other EGFR-TKIs (118 encounters, 53% in second/subsequent-line), and 29 with chemotherapy (73 encounters, 96% second/subsequent-line). The table below summarizes the treatment-related PRO-CTCAE toxicities self-graded as moderate-to-very-severe by EGFRm patients.

Proportion of patients reporting highest grade of toxicity as grade 3-5, by PRO-CTCAE

	Gefitinib	Osimertinib	Other EGFR TKI	Chemo-therapy
Diarrhea	17%	18%	24%	8%
Constipation	12%	4%	12%	16%
Decreased ap-petite	10%	7%	14%	26%
Nausea	6%	3%	4%	24%
Vomiting	1%	2%	3%	16%
Fatigue	18%	12%	23%	42%
Numbness and Tingling	6%	7%	10%	16%
Skin Rash	23%	12%	20%	9%
Visual Disorders (includes dry eye)	4%	0%	3%	4%
Total PRO-CT-CAE Score, MEDIAN [IQR]	4 [0,16]	0 [0,15]	6 [0,17]	10 [0,21]

Conclusion: Osimertinib therapy had the most favorable self-reported toxicity profiles of all the therapies in EGFRm patients, followed by gefitinib. Chemotherapy generated the greatest toxicities. The use of PRO-CTCAE was well-accepted by patients in a clinical setting. This confirms trial data supporting favorable toxicities with osimertinib compared to other therapies for EGFRm NSCLC patients.

Keywords: EGFR-mutated NSCLC, Targeted therapy, toxicity

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P1.13-12 EGFR THERAPY IN ASCL1 POSITIVE LUNG ADENOCARCINOMA

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Background: Greater than 40% of lung adenocarcinomas (LUAD) contain no known driver mutations from point mutation or structural variance analysis. Recently, we discovered that 15-20% of LUAD have abnormally high levels of ASCL1, a key regulator of neuroendocrine differentiation in the lung. ASCL1 in these tumors orchestrates the expression of a network of genes that affect the behavior of tumors and their microenvironments and provide opportunities for treatment that has largely been understudied. The goal of this study was to explore potential therapeutic options in these tumors. **Method:** Bioinformatics analyses used public and internally generated expression data from LUAD. In vitro co-immunoprecipitation and cytotoxicity assays were used to determine the interaction between proteins and the sensitivity to EGFR blockers gefitinib and lapatinib. These drugs were also tested in patient derived xenograft (PDX) models from cisplatin resistant brain met LUAD with (A^+AD) and without (A^-AD) ASCL1 expression. **Result:** Our data demonstrated that ASCL1 acts upstream of RET and promotes chronic over-expression of the oncogene in A^+AD. In vitro experiments revealed a strong interactions between wild type EGFR and RET in A^+AD which rendered these tumors vulnerable to treatment by EGFR blockers. Furthermore, while EGFR inhibitors blocked tumor growth in the A^+AD PDX model, they were completely ineffective in the A^-AD PDX model. EGFR therapy also markedly changed key regulators of the tumor microenvironment in favor of anti-tumor immunity. Analysis of TCGA data identified some overlap between A^+AD and other LUAD subtypes, such as *KRAS* or *EGFR* mutant tumors. Further meta-analysis in a compendium of microarray data in stage-1 LUAD from multiple institutions demonstrated that high expression of wild type RET was significantly associated with a poor overall survival. Furthermore, high expression of EGFR (or its ligand TGFA) and RET imparted an aggressive phenotype in A^+AD with overall survival similar to small cell lung cancer. Notably, *EGFR*, *TGFA*, and *RET* did not have any prognostic value in A^-AD. **Conclusion:** Our data provide strong evidence that patients with A^+AD may benefit from a multipronged treatment strategy that include EGFR therapy even in the absence of mutations in *EGFR*.

Keywords: ASCL1, lung adenocarcinoma, RET EGFR

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P1.13-13 POTENT ANTI-TUMOR EFFECT OF GANETESPIB IN ACQUIRED EGFR-TKI RESISTANCE NSCLC CELLS

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Background: Non-small cell lung cancer (NCSLC) harboring epidermal growth factor receptor (*EGFR*) mutation shows favorable response to EGFR-tyrosine kinase inhibitors (EGFR-TKIs). However, almost all these patients eventually acquire resistance to EGFR-TKIs, and novel therapeutic strategies to overcome the acquired resistance have been required. The 90-kDa heat shock protein (HSP90) is a chaperon protein expressed at high levels in cancer cells and involved in folding or stabilization of client proteins essential for cancer cell growth and survival. Ganetespib (STA-9090) is one of the second-generation HSP90 inhibitors with potent anti-tumor effect on NSCLC cells. In this study, we evaluated the anti-tumor effect of ganetespib in EGFR-TKI sensitive and acquired resistance NSCLC cell lines. **Method:** We treated 4 *EGFR*-mutant NSCLC cell lines (HCC827, HCC4006, HCC4011 and PC-9), and 5 experimentally established EGFR-TKI (gefitinib) resistance cell lines with ganetespib. The EGFR-TKI resistant mechanism consisted of *EGFR* T790M second mutation, *MET* amplification, epithelial-to-mesenchymal transition (EMT) and cancer stem cell-like properties. We determined cell proliferation by MTS assay and calculated the IC50 values. We also performed Western blotting to investigate downstream signaling pathway alterations. **Result:** The IC50 values in parental NSCLC cell lines ranged from 1.3nM to 15nM, and those in acquired EGFR-TKI resistance NSCLC cell lines ranged from 0.87nM to 25nM, which suggests potent anti-tumor effect of ganetespib. In addition, this effect was observed regardless of the resistant mechanisms, including EMT. Ganetespib effectively suppressed the expression of downstream pathway molecules in all examined cell lines including acquired EGFR-TKI resistance NSCLC cell lines. Also, ganetespib effectively induced apoptosis in parental and acquired EGFR-TKI resistance NSCLC cell lines with *EGFR* T790M mutation or *MET* amplification. **Conclusion:** Ganetespib exhibited potent anti-tumor effect in acquired EGFR-TKI resistance NSCLC cell lines regardless of the resistant mechanisms, suggesting that ganetespib could be a promising therapeutic option in the treatment of NSCLC with acquired EGFR-TKI resistance.

Keywords: HSP90 inhibitor, drug resistance

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P1.13-14 THE MOLECULAR LANDSCAPE OF LUNG ADENOCARCINOMAS WITH ACTIVATING EGFR GENE MUTATIONS DETERMINED BY TARGETED-SEQUENCING

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Background: The analysis of *EGFR* activating mutations and *ALK* rearrangement is a routine procedure in qualification of NSCLC patients for molecularly targeted therapy. Targeted sequencing, as a type of NGS, allows more comprehensive analysis of low-frequency variations in suppressors and oncogenes that are commonly mutated in solid tumors. In the following study we analyzed a molecular landscape of NSCLC patients harboring *EGFR* activating mutations who response for EGFR TKIs. **Method:** The studied group included 19 Caucasian patients (7 male and 12 female, median age 65±12 years, 4 current smokers, 12 non-smokers and 3 former-smokers) with lung adenocarcinoma. 12 (63%) deletions in exon 19, 4 (21%) substitutions Leu858Arg in exon 21, 2 (11%) insertions A763_Y764 in exon 20 and 1 (5%) substitution Thr790Met in exon 20 of *EGFR* gene were detected using real-time PCR technique. Four non-smoking patients (median age 65±12 years) with lung adenocarcinoma and wild-type (wt) of *EGFR* gene were a control group. The DNA for the analysis was isolated from FFPE tissue or cellblocks and the mutational landscape was evaluated using Illumina's TruSight Tumor 26 panel on miSeq platform (Illumina, USA). **Result:** The targeted sequencing confirmed lack of *EGFR* gene mutations in control group and the presence of *EGFR* mutations in 84% (16/19) of patients with these mutations confirmed in routine diagnostics - all deletions in exon 19 and substitutions in exon 21 were confirmed. Targeted sequencing did not identify rare mutations in exon 20. NGS compared to real-time PCR technique achieved 86,95% accuracy with 84,21% of sensitivity and 100% of specificity or PPV and NPV values reached 100% and 57,10%, respectively. The targeted sequencing allowed to identify 166 variants in 25 out of 26 genes covered by the analysis. The most frequently mutated suppresors were *TP53*, *MSH6* and *APC* (38%; 19% and 17% respectively) and oncogenes were *MET*, *PDGFR* and *EGFR-AS1* (31%, 14% and 13% respectively). The frequency of particular variants was significantly higher in smokers than in non-smokers (p=0,0002; χ^2=16,94). U-Man Whitney test showed that the median number of genetic alternations in *EGFR* mutated group was significantly higher than in wt *EGFR* group (p=0.0091; median: 17 vs 11 respectively). **Conclusion:** The targeted sequencing allowed to detect the most common activating mutations in *EGFR* gene and numerous variants both in suppressors and oncogenes. NGS showed too low sensitivity for detection of rare *EGFR* mutations. The molecular landscape was more unpredictable and varied in smokers compare to non-smokers.

Keywords: targeted-sequencing, EGFR-TKIs, NSCLC

P1.13-15 DETECTION OF EGFR MUTATIONS IN CFDNA AND DEVELOPMENT OF RESISTANCE

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Background: Peripheral blood sampling for T790M in patients (pts) failing initial EGFR-TKIs is now standard practice. The value of longitudinal sampling in pts is unknown. **Method:** A study of cell free (cf) DNA analysis in pts with *EGFR* mutated(m) non-small cell lung cancer (NSCLC) is ongoing at the Princess Margaret Cancer Centre. The ThermoFisher Oncomine™ lung assay detecting single nucleotide variants and indels to a limit of 0.05-0.1% variant allele frequency (VAF) was used. Patient clinical details and outcomes were collected prospectively. **Result:** From Oct 2016-Feb 2017, 73 pts with *EGFR*m NSCLC enrolled and first blood samples were analysed. Most (92%) had mutations in del19 or L858R, including 1 pt with del19/S768I. Uncommon *EGFR*m were present in 6 (G718X, L861Q, exon20ins). Detectable levels of cfDNA were found in 50 pts (68%). Of 64 pts either starting an EGFR-TKI (n=11,17%), receiving a TKI without progression (PD) (23, 36%) or with PD on a TKI (30, 47%), the presence of the primary *EGFR*m (n=39, 61%) strongly associated with pre-1st TKI or PD, p=0.03. Of 53 pts receiving a TKI, the presence of T790M in 31 (58%) associated with PD (p=0.04). Where pts had no radiologic PD evident, the median progression free survival (PFS), taken from blood draw, was 2.1 months (mths) versus 10 mths (HR 2.22, 95% CI: 0.89-5.54 p=0.08) when the primary *EGFR*m was detected. If T790M was present in cfDNA, the median PFS was 3.0 months versus 9.7 mths, (HR 4.59, 95% CI: 1.43-14.73 p=0.005). In univariable regression analyses the %VAF of the primary EGFRm correlated with PFS (HR 1.15, 95%CI: 1.02-1.29, p=0.02) with a trend in the %VAF of T790M (HR 1.16 95% CI:0.99-1.37, p=0.08). T790M was detected in 3 of 4 pts with T790M -ve tissue, and other co-occurring EGFRm were found in 10 pts including K745R in a pt receiving first-line osimertinib. TP53 (n=10), KRAS (1), PI3KCA(1) and ALK(2)gene mutations were also detected. Interestingly, in 1 pt receiving chemotherapy with T790M+ disease, both the primary EGFRm and T790M were detected in blood at the time of PD. **Conclusion:** In addition to the emergence of resistance mutations, the presence of the primary *EGFR*m in pts receiving EGFR-TKIs may associate with a shorter PFS and therefore may be useful in longitudinal analyses of cfDNA to direct therapy.

Keywords: cfDNA, EGFR mutations, resistance

P1.13-16 THE DIAGNOSTIC ACCURACY OF CIRCULATING TUMOR DNA FOR THE DETECTION OF EGFR-T790M MUTATION IN NSCLC: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: This meta-analysis aims at evaluating the diagnostic accuracy of circulating tumor (ct) DNA for the detection of epidermal growth factor receptor (EGFR)-T790M mutation in patients with EGFR-positive advanced non-small cell lung cancer (NSCLC) who progressed to prior EGFR-tyrosine kinase inhibitors (TKIs). **Method:** Data from published studies collecting matched blood and tumor tissue samples from patients with EGFR-positive advanced NSCLC who progressed to prior EGFR-TKI were collected by searching in PubMed, Cochrane Library, American Society of Clinical Oncology, European Society of Medical Oncology and World Conference of Lung Cancer meeting proceedings. Studies which evaluated both sensitivity and specificity of plasma-based EGFR-T790M mutation testing by ctDNA analysis were included and pooled sensitivity and specificity with 95% confidence intervals (95% CIs) were calculated. **Result:** A total of twenty-one studies, with 1639 patients, were eligible. The pooled sensitivity of ctDNA analysis was 0.67 (95% CI: 0.64-0.70) and the pooled specificity was 0.80 (95% CI: 0.77-0.83). The positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 2.67 (95% CI: 1.86-3.82) and 0.46 (95% CI: 0.38-0.54), respectively. The pooled diagnostic odds ratio (DOR) was 7.27 (4.39-12.05) and the AUC of the sROC curve was 0.77. Subgroup analysis by different detection platforms showed that sensitivity, specificity and AUC of ctDNA analysis by real-time (RT)-PCR were: 0.61 (95% CI: 0.57-0.65), 0.82 (95% CI: 0.77-0.87), and 0.70; sensitivity, specificity and AUC of ctDNA analysis by digital (d) PCR were: 0.72 (95% CI: 0.68-0.76), 0.73 (95% CI: 0.67-0.79), and 0.77; sensitivity, specificity and AUC of ctDNA analysis by by next-generation sequencing (NGS) were: 0.87 (95% CI: 0.76-0.95), 0.89 (95% CI: 0.82-0.94), and 0.88, respectively. **Conclusion:** The ctDNA analysis represents a promising, non-invasive approach to detect and monitor the T790M mutation status in patients with EGFR-positive advanced NSCLC, with NGS emerging as the most accurate detection platform. Development of standardized methodologies and clinical validation are recommended.

Keywords: ctDNA, T790M, EGFR

P1.13-17 MULTICENTRE PHASE II TRIAL OF FIRST-LINE AFATINIB IN PATIENTS WITH SUSPECTED/CONFIRMED EGFR MUTANT NSCLC: CTDNA & LONG-TERM EFFICACY

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Background: Efficacy of afatinib in EGFR mutant patients with comorbidities *or* those with suspected EGFR mutations unfit for chemotherapy is poorly explored. We evaluated afatinib in this population, with serial plasma ctDNA to investigate the role of molecular EGFR genotyping and monitoring. **Method:** Phase-II trial enrolled NSCLC patients with comorbidities precluding chemotherapy, and either (i) EGFR-mutation, PS 0-3, or (ii) suspected EGFR-mutation (tissue unavailable/failed genotyping), never/former-light smoker, adenocarcinoma, and PS 0-2. Afatinib (40mg daily) given until progression/toxicity. Blood samples obtained at baseline and 12-weekly until discontinuation; plasma ctDNA performed using InVisionSeq™ (amplicon-based NGS). **Result:** 39 patients recruited (14 UK centres). Median age 72 years; 27 PS 0-1/12 PS 2-3. 21 patients (54%) had known tissue EGFR-mutations. Additional 8 patients with unknown tissue status (8/17;47%), were ctDNA EGFR-mutant, making 74% EGFR-mutant in total (29/39). Combined tissue and ctDNA data identified 21 patients with common mutations (exon 19/L858R), 8 with rare mutations (exon 18/20), and 10 suspected only. Corresponding median PFS of these cohorts were 10.2/3.9/5.3 months, with 6-month PFS of 71/38/50% all exceeding the 30% target; median OS were 24.8/5.7/11.4 months (p<0.001). Therefore, all patient groups benefitted; known EGFR-mutants having best outcomes. In April 2018, 5/39 patients survived >36 months, including 4/39 progression-free (median follow-up 33 months, maximum 55). Patients with ctDNA mutation clearance during afatinib treatment had substantially improved outcomes compared to those without clearance (Figure). 40% (4/10) of mutant cases who discontinued after 3 cycles because of progressive disease developed an exon 20 *EGFR*-mutation.

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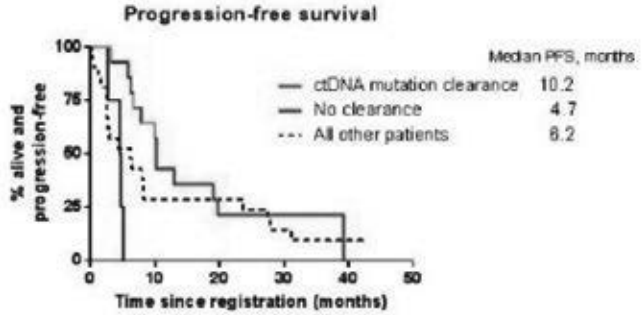

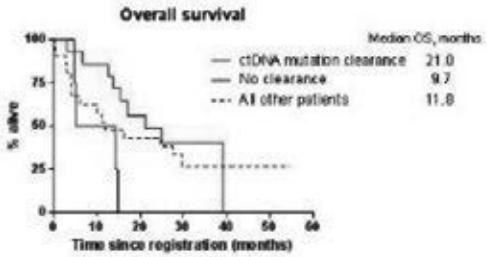

Figure. PFS and OS according to whether or not patients had ctDNA EGFR mutation clearance (i.e. baseline values became undetectable during serial measurements) whilst on afatinib (p<0.001 PFS and p=0.01 OS for the comparison of n=14 with clearance versus n=4 without clearance). 'All other patients' consists of 6 with mutations at baseline but did not have samples at 2 timepoints to assess clearance, and n=15 without mutations.

Conclusion: Patients unsuitable for chemotherapy with confirmed/suspected EGFR-mutations by tissue or ctDNA benefit from afatinib. Serial ctDNA is a potentially useful stratification and monitoring tool; amplicon-based ctDNA analysis can identify EGFR mutations when tissue is unavailable. Exon 20 mutations were observed at acquired resistance. ctDNA clearance during afatinib treatment is strongly associated with better PFS/OS.

Keywords: progression free survival, NSCLC, EGFR mutation

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-18 EXPLORING THE RESISTANCE MECHANISM OF OSIMERTINIB AND MONITORING THE TREATMENT RESPONSE USING PLASMA CTDNA IN CHINESE NSCLC PATIENTS

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Background: Osimertinib (AZD9291; Tagrisso) is a third generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) known to be effective for patients harboring the EGFR-T790M variant, which is accounts for more than half of the acquired resistance mechanisms to the first generation EGFR-TKIs. However, limited osimertinib resistance-mechanism was reported. Study on potential osimertinib-resistance mechanisms in advanced NSCLC is necessary. **Method:** This study enrolled eight T790M-positive (tissue validated) patients, treated with osimertinib after first generation EGFR-TKI (Erlotinib, Gefitinib, Icotinib) resistance and progressed rapidly. Serial plasma samples were collected until disease progressed. Plasma DNA was extracted and sequenced by target-capture deep sequencing of 1021 previously annotated genes related to solid tumors. Clonal EGFR T790M mutation was defined if mutation was in the cluster with the highest mean variated allele frequency with PyClone, and otherwise subclonal EGFR T790M mutation. Molecular tumor burden index (mTBI) was calculated with the mean variant allele frequency of mutations in trunk clonal population. **Result:** The median progression-free survival (PFS) of these eight rapidly-progressed patients was 3.82 months [95% CI 2.05-5.01] .Targeted capture sequencing of pretreatment ctDNA showed all of the eight patients (100%) were EGFR-positive (Exon19del [n=6] and L858R [n=2]), and seven patients (88%) harbored EGFR T790M mutation, except for the only one patient (P006) who showed an extremely low level of ctDNA. During the Osimertinib treatment, five patients (63%) had osimertinib resistance-related mutations: EGFR C797S (in cis position), G724S, KRAS G12D, PIK3CA E542K, EGFR amplification, and ERBB2 amplification. Among them, two patients had more than one resistance mechanisms: patient P034 had EGFR G724S, KRAS G12D and EGFR amplification, simultaneously; patient P013 had amplification in both EGFR and ERBB2. Other potential resistance mechanisms were identified including EGFR T751I and K754E mutations in P002 and ERBB2 S603 in P013. Notably, the only one patient (P004) who had not been detected to have any known osimertinib resistance mechanism but progressed in 3 months, was demonstrated to harbor a subclonal EGFR T790M mutation by analysis of ctDNA clonal structure. Serial ctDNA monitoring showed mTBI increased when disease progressed in 88% (7/8) patients, except P006, whose mutation were negative at second (stable disease) and third (progressed disease) therapeutic evaluations due to the extremely low level of ctDNA. **Conclusion:** This study presented comprehensive the resistance mechanism of osimertinib progressed rapidly in ctDNA including multiple mechanisms co-occurred in same patient. Serial monitoring of plasma ctDNA may be a promising approach to explore resistance mechanism and monitored the treatment response of third generation EGFR-TKI.

Keywords: plasma ctDNA, non-small cell lung cancer, Resistance

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-19 TREATMENT CESSATION FOR IMPROVED DETECTION OF EGFR-MUTATED CIRCULATING TUMOR DNA IN ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC)

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Background: First/second generation EGFR-tyrosine kinase inhibitors (EGFR-TKI) are eventually met with therapeutic failure in EGFR-mutated (EGFRm) aNSCLC, but post-progression continuation of therapy can delay the need for second line therapy by a median of ~ 3 months. In this context, osimertinib was shown to be effective in T790M mutated EGFR, which occurs in > 50% of cases. T790M detection within circulating tumor DNA (ctDNA) is convenient but has suboptimal sensitivity. The goal of this study is to determine whether temporary cessation of the TKI - beyond initial progression - would allow for increased plasma detection of EGFR mutations. **Method:** EGFRm aNSCLC patients who were still on first/second generation EGFR-TKI beyond initial progression were enrolled. TKI was withheld on day 0. Blood samples were drawn and the NCCN-FACT FLSI-17 questionnaire v2 was administered on days 0 and 6±1. Semi quantitative measurements of EGFR mutations within plasma samples were obtained using the cobas® EGFR Mutation Test v2. Descriptive statistics were reported and paired t-test was used to compare differences in ctDNA yield and quality of life after TKI cessation. **Result:** 33 patients were enrolled in 2017. Baseline characteristics and relevant study results are summarized in Table 1. Temporary TKI cessation was safe with no tumor flares reported - questionnaire scores indicate a trend towards improved quality of life one week after TKI cessation. The yield of detection was significantly higher after TKI cessation, but only for the baseline sensitizing mutation.

Table 1	
Age, Median - years (range)	71(46 - 87)
Gender, female n (%)	25 (75.8)
Median time to progression on first/second generation TKI, months (range)	9.76 (0.3 - 46)
Median time from initial progression to study enrollment, months (range)	1.03 (0.25 - 7.57)
NCCN-FACT FLSI-17 questionnaire - Questionnaire score day 1 - Questionnaire Score day 6/7	 - 45.81±10.78 - 48.41±9.91 (p=0.08)

Baseline EGFR sensitizing mutation	
- Overall detection of ctDNA, n (%)	
- Detection within ctDNA on only one of the two test dates, n (%)	**- 21 (63.6)**
Semi quantitative index of detected ctDNA	**- 6 (28.5)**
- Day 1	**- 5.2±6.2**
- Day 6/7	**- 6.1±6.4 (p=0.04)**
T790M EGFR mutation	
- Overall detection of ctDNA, n (%)	
- Detection within ctDNA on only one of the two test dates, n (%)	**- 21 (63.6)**
Semi quantitative index of detected ctDNA	**- 6 (28.5)**
- Day 1	**- 5.2±6.2**
- Day 6/7	**- 6.1±6.4 (p=0.04)**

Conclusion: Our data suggest that TKI cessation can lead to increased shedding of ctDNA in sensitive cells. However, drug withdrawal may not impact the shedding of ctDNA in resistant clones. Irrespective of drug withdrawal, a strategy of repeat testing appears to increase the sensitivity of ctDNA detection and would likely produce more clinically relevant outcomes in comparison with one-time testing.

Keywords: Circulating Tumor DNA, EGFR mutation, Tyrosine kinase inhibitors

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-20 MET PROTEIN EXPRESSION AND ACTIVATION DURING TARGETED THERAPY IN EGFR MUTATED LUNG ADENOCARCINOMA

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Background: In EGFR mutated (EGFRm) lung adenocarcinoma (ADC) the tyrosine kinase (TK) receptor MET is involved in acquired resistance to anti-EGFR treatment. We analyzed MET protein expression and activation in EGFRm lung ADC treated with TK inhibitors (TKI). **Method:** Patients with advanced EGFRm lung ADC, treated at the Oncology Department - San Luigi Hospital, who underwent tissue biopsy for diagnosis and tissue re-biopsy at disease progression for T790M test (after a negative liquid biopsy) were selected. c-MET (clone SP44) and phosphorylated (p-) MET (Tyr1234/1235, D26) expression was analyzed by immunohistochemistry and evaluated as H-Score (HS). **Result:** Tumor tissues from 18 advanced EGFRm patients (12 female and 6 male; mean age 59 years) were available. On April 2018, 10 patients were alive and 8 were died. 11/18 (61%) cases harbored a T790M point mutation (T790M+) detected at tissue re-biopsy. At the baseline tumor tissue, lower c-MET expression levels were found in T790M+ (mean HS value= 135, range 40-250) compared to the T790M negative (T790M-) group (mean HS value= 226, range 100-300) (p=0.02). Furthermore, in T790M+ patients p-MET was expressed in 2/11 cases (18%, HS values=5 and 60) while in the T790M- group p-MET was expressed in 3/7 (43%, HS values=5, 240 and 240) cases (although with no significant p value). After first line TKI treatment, in the T790M+ group c-MET expression (mean HS value=140, range 5-300) was augmented in 7 and reduced in 4 cases, while p-MET was positive in 2/11 cases (HS values of 300 and 30). No significant differences in survival were found. In the T790M- group the c-MET mean HS value was 152 (range 30-300) and the 4/7 cases with higher c-MET expression levels (HS> 152) had a significant shorter PFS (p=0.02, HR=0.3, median survival: 7.5 vs 24 months). Furthermore, in this group p-MET positivity was maintained in the same 3 cases (with HS values= 240, 180, 10) and the two patients with higher MET activation had short PFS (9 and 6 months) at first line TKI treatment. **Conclusion:** Our preliminary analyses suggest that a strong expression of basal c-MET receptor in advanced EGFRm ADC may predict a T790M negative status at disease progression. Furthermore MET higher expression and activation may play a role in acquired resistance to TKI, although a limited number of cases have been analyzed. Thereby, we propose to monitor MET status along treatment and to reconsider MET-directed therapies for a well-selected subset of EGFRm lung ADC patients.

Keywords: lung adenocarcinoma, EGFR targeted therapy, MET

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-21 CLINICAL EFFICACY AND SAFETY OF APATINIB COMBINED WITH EGFR - TKIS IN ADVANCED NON-SMALL CELL LUNG CANCER WITH EGFR - TKIS RESISTANCE

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Background: Acquired resistance to EGFR-TKIs frequently occurs in advanced non-small cell lung cancer (NSCLC) patients with sensitizing EGFR mutations. Previous studies have shown that apatinib (a TKI against VEGFR-2) combined with EGFR-TKIs might improve the survival of EGFR-TKIs resistant NSCLC patients. We conducted this trial to investigate the efficacy and safety of apatinib combined with EGFR-TKIs compared with traditional chemotherapy for EGFR-TKIs resistant NSCLC patients. **Method:** This prospective study enrolled advanced NSCLC patients who acquired resistance to the EGFR-TKIs therapy. Patients received apatinib combined with EGFR-TKIs (apatinib in start dose of 250 mg+pior EGFR-TKIs dose) or chemotherapy (pemetrexed or vinorelbine with platinum). Efficacy was evaluated every 6 weeks based on RECIST 1.1. This study was registered on Chinese Clinical Trail Registry, and the registration number was ChiCTR-OIN-17012051. **Result:** From Mar 2017 to May 2018, 24 patients were enrolled, including 18 patients received apatinib combined with EGFR-TKIs, 6 patients received chemotherapy. In the apatinib group, 83.33%(15/18) patients were available evaluated. The objective response rate was 20% (3/15) and the disease control rate was 100% (15/15). All patients have different degrees of lesion shrinkage. Till May 1, 2018, the median duration of apatinib group treatment was 187 days, and the median PFS has not researched. The most common adverse events in the apatinib group were hypertension, proteinuria, weakness. Five (27.78%) grade 3 hypertension, 3 (16.67%) grade 3 proteinuria and 1 (5.56%) grade 3 diarrhea were observed. Two patients who failed treatment with osimertinib received osimertinib combined with apatinib, got lesions decreased after one cycle. One of the two patients was treated as fifth line treatment. Two patients with brain metastases in the apatinib group got metastases lesions decreased. Two progressive patients got lesions decreased after apatinib dose increasing to 500mg. Of the 7 patients receiving chemotherapy, 6 patients were available evaluated. The objective response rate was 16.67%(1/6) and the disease control rate was 100% (6/6). Major adverse reactions were digestive tract reaction and myelosuppression. **Conclusion:** Apatinib combined with EGFR-TKIs may provide a new therapy strategy for NSCLC patients with acquired EGFR-TKIs resistance. Both drugs are oral, which is advantageous in improving the patient's quality of life and the compliance of therapy. Further study with lager samples are needed to validate our findings. Moreover, We will further explore the correlation between genetic mutations, biomarkers and therapeutic efficacy.

Keywords: Apatinib, EGFR - TKIs resistance, Non-small cell lung cancer

P1.13 TARGETED THERAPY
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P1.13-22 CLINICAL FEATURES AND OUTCOMES OF NSCLC PATIENTS WITH UNCOMMON EGFR MUTATIONS TREATED WITH EGFR-TKIS

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Background: Non-small cell lung cancers with common epidermal-growth factor receptor (*EGFR*) mutations (exon 19 deletion and exon 21-point mutation L858R) are known to greatly benefit from *EGFR*-tyrosine kinase inhibitors (TKIs). However, much less is known about the treatment responses of *EGFR* mutations such as L861Q, G719X and double *EGFR*mut$^+$ carriers. In this study, we report clinicopathological and treatment outcomes of patients harboring such *EGFR* mutations and treated with *EGFR*-TKIs. **Method:** Between 2009 – 2015, 233 *EGFR*mut$^+$ NSCLC patients treated at two Alberta-based cancer centres, Tom Baker Cancer Centre (Calgary) and Cross Cancer Institute (Edmonton) were screened retrospectively via the provincial cancer registry and the Glans-Look Lung Cancer Database. Clinicopathological and treatment outcomes were analyzed. Overall survival was assessed using the Kaplan-Meier method and compared using the log-rank test. Outcomes of single versus double *EGFR*mut$^+$ carrier sub-groups were compared using Fisher's Exact test. **Result:** 42/233 (18%) patients harbored uncommon *EGFR* mutations: 14/42 (33%) carried single rare *EGFR*mut$^+$ and 11/42 (26%) carried double *EGFR*mut$^+$, meanwhile 41% couldn't be specified. Most frequently detected uncommon single *EGFR* mutations were G719X (12%)

and L861Q (17%). **Table 1** summarizes clinical characteristics and TKI efficacy amongst uncommon *EGFR* mutations. Compared to single *EGFR* mutants, double *EGFR* mutation carriers were older (median age 71yrs vs 69 yrs), have a smoking-history (73% vs 50%), experienced longer median OS and PFS (15 and 12 months $p < 0.001$, vs. 9 and 3 months $p = 0.0014$ respectively), and were also more likely to continue with a TKI beyond initial-TKI-PD (82% vs 28%).

Table 1. TKI outcome efficacy analysis in uncommon *EGFR*mut⁺ carriers (n=24/42)

Uncommon *EGFR* Mutation Exon Category	Uncommon *EGFR* mutation	Age (yrs)	Smoking History (Y, N)	Primary -TKI Disease Stage	Primary TKI (Gefitinib, Erlotinib)	Systemic treatment post primary-TKI	Radiotherapy received post primary-TKI initiation (Y, N)	PFS (m)	OS (m)
Exon 18	G719X (1)	67	No	IV	Gefitinib	Pemetrexed/Cisplatin	No	1.6	9
	G719X (2)	67	Yes	IV	Erlotinib	Pembrolizumab	Yes	5.2	18
	G719X (3)	70	Yes	IV	Gefitinib	Afatinib	No	No data	28
	G719X (4)	86	No	IV	Gefitinib	None	No	30.3	45
	G719X (5)	85	No	IV	Gefitinib	NA	NA	NA	3.6
Exon 20	Ex 20 insertion	57	No	IV	Erlotinib	NA	NA	No data	No data
	S768I	52	No	IB	Gefitinib	None	No	10	13
Exon 21	L861Q (1)	80	No	IV	Gefitinib	Cisplatin/Vinorelbine	No	4	18
	L861Q (2)	84	No	IV	Gefitinib	No data	No data	No data	10
	L861Q (3)	53	No	IIIB	Gefitinib	None	No	3	4
	L861Q (4)	68	No	IV	Gefitinib	None	No data	No data	2
	L861Q (5)	88	Yes	IV	Gefitinib	None	Yes	4	15
	L861Q (6)	83	Yes	IV	Gefitinib	None	Yes	3	5
	L861Q (7)	63	No	IV	Gefitinib	Cisplatin/Vinorelbine	Yes	2	10
Double *EGFR*mut⁺ carriers	19Del + L858R (1)	50	No	IV	Gefitinib	Erlotinib	Yes	2	9
	19Del + L858R (2)	81	Yes	IV	Gefitinib	Pemetrexed	No	9	16
	19Del + L858R (3)	83	Yes	IV	Gefitinib	None	No	9	42
	19Del + L858R (4)	71	Yes	IIIB	Gefitinib	None	Yes	13	15
	19Del + L858R (5)	59	Yes	IV	Gefitinib	None	Yes	2	6
	19Del + L858R (6)	69	Yes	IV	Gefitinib	Cisplatin/Vinorelbine	No	16	20
	19Del + L861Q	54	Yes	IV	Gefitinib	Cisplatin/Gemcitabine	No	5	16
	S768I + G719X (1)	51	Yes	IV	Gefitinib	None	No	1	1
	S768I + G719X (2)	78	Yes	IIIA	Gefitinib	None	No	35	59

Conclusion: Retrospective real-world data illustrating the experience and outcomes of uncommon *EGFR* mutation carriers was explored in this study. Additionally, our results, although limited by cohort-size, highlights that tumor responses from TKI treatments vary amongst uncommon *EGFR*mut⁺ carriers, with most favorable survival responses observed in double *EGFR* mutants.

Keywords: uncommon EGFR mutants, double EGFR mutation carriers, Targeted therapy

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-23 TP53 MUTATIONS AS MECHANISMS OF PRIMARY AND ACQUIRED RESISTANCE TO TYROSINE KINASE INHIBITORS IN PATIENTS WITH EGFR-MUTATED NSCLC

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Background: Around 80% of patients with non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations usually respond to tyrosine kinase inhibitors (TKIs). We previously demonstrated that *TP53* mutations are associated with primary resistance to TKIs in patients with *EGFR*-mutated lung adenocarcinoma (ADC) treated with a first-line TKI. In the present study we investigated whether *TP53* mutations are modulated by TKIs, evaluating its status before and after TKI treatment. **Method:** Thirty-five patients with EGFR-mutated lung ADC treated with a first-line TKI and who subsequently underwent re-biopsy after disease progression were considered. Tumor tissue was available for evaluation before and after TKI treatment for all patients. *EGFR* and *TP53* mutation analyses were performed by Sanger Sequencing or Next Generation Sequencing methods. The different mutations were evaluated in relation to disease control rate (DCR) [complete response (CR), partial response (PR) or stable disease (SD)] and objective response rate (ORR) (CR, PR). **Result:** Of the 35 patients, 14 (40%) showed a TP53 mutation, 12 in exons 5-8 (5 in exon 5, 2 in exon 6, 2 in exon 7 and 3 in exon 8) and 2 in other exons (1 in exon 2 and 1 in exon 4) of the gene. The group was treated with a first-line TKI and data on response and follow-up were available for 30 patients. Of these, 11 were treated with gefitinib, 11 with erlotinib, 6 with afatinib and 2 with dacomitinib. Overall DCR and ORR were 90% and 77%, respectively. With regard to TP53 mutations, DCR and ORR were 94% and 83%, respectively, in *TP53* wt patients, and 83% and 66% in *TP53* mutated cases. All 30 patients underwent re-biopsy at progression and 20 (67%) showed T790M mutation in tumor tissue. Of the 10 T790M-negative patients, 5 (50%) had a *TP53* mutation which was not present at baseline in 2 cases. Among the patients who were *TP53* wild type at baseline, 4 (22%) showed a mutation at disease progression. Data on progression free survival and overall survival are currently being evaluated. **Conclusion:** *TP53* mutations were associated with a lower response to TKIs in *EGFR*-mutated patients and may have been acquired during TKI treatment, independently of the T790M mutation.

Keywords: TP53, EGFR, TKIs

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-24 EGFR-KDD IS RARE AND DEMONSTRATES VARIABLE ANTI-TUMOR RESPONSE TO TYROSINE KINASE INHIBITORS IN EAST ASIAN NSCLC POPULATION

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Background: The kinase domain duplication of epidermal growth factor receptor (EGFR-KDD) has been identified and implicated to be oncogenic in non-small cell lung cancer (NSCLC). However, its frequency and clinical outcomes in lung cancer patients are largely uncertain. **Method:** We conducted a multi-center record review of 8064 East Asian NSCLC patients who underwent genetic testing using next-generation sequencing (NGS) targeting the whole exons of *EGFR* gene as well as introns involved in *EGFR-KDD* and gene rearrangements. Patients' demographic and clinical data, including age, gender, histology type, pathological stage, and their responses to tyrosine kinase inhibitor (TKI) treatments were analyzed. **Result:** *EGFR-KDD* was identified in 11 patients, which is approximately 0.012% of the total NSCLC population reviewed (*N*=8064), and also consists of 0.05% of all patients with *EGFR* aberrations (*N*=2289). Nine patients were identified with the canonical *EGFR-KDD* form involving the duplication of exon 18 throughout exon 25, while the remaining two cases harbor *EGFR* exon 14-26 and exon 17-25 duplication, respectively, which have not been previously described. Importantly, all these patients were not identified with any other co-existing known driver mutations, highlighting the potential oncogenic role of this alteration. Three out of five patients with exon 18-25 KDD who received TKI treatments showed partial anti-tumor responses to the therapy, while the other two patients progressed shortly. Our data further indicated that *EGFR* T790M mutation and *EGFR* amplification may represent the major resistance mechanisms against targeted therapy in tumors bearing *EGFR-KDD*. **Conclusion:** *EGFR-KDD* is rare in East Asian NSCLC population with different duplication variants. Tyrosine kinase inhibitors demonstrated variable anti-tumor efficacy in patients harboring *EGFR-KDD* alteration.

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-25 EFFICACY AND SAFETY OF OSIMERTINIB IN EGFR T790M-POSITIVE ADVANCED NSCLC PATIENTS WITH BRAIN METASTASES (APOLLO STUDY)

L. Xing[1], Y. Pan[2], Y. Shi[3], Y. Shu[4], J. Feng[5], W. Li[6], L. Cao[2], L. Wang[7], W. Gu[8], Y. Song[9], J. Yu[1]

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Background: Osimertinib has demonstrated promising efficacy in T790M-positive NSCLC patients with central nervous system (CNS) metastases, but there is limited data on Chinese patients. We aim to investigate the efficacy and safety of osimertinib in T790M-positive advanced NSCLC patients with brain metastases and to explore the dynamic genetic changes as well as drug penetration in CNS with paired cerebrospinal fluid (CSF) and plasma samples. **Method:** In this single arm, multi-center, prospective trial (NCT2972333), patients with confirmed EGFR T790M positive by Cobas, advanced NSCLC with brain metastases, who had progressed following first-generation EGFR-TKI treatment, received osimertinib 80 mg qd. The primary endpoint was overall progression free survival (PFSo). Paired CSF-plasma samples were collected at baseline, 6 weeks after treatment and disease progression and analyzed by NGS. **Result:** Thirty-eight eligible patients were enrolled and 12 paired CSF-plasma samples were collected. Baseline characteristics and efficacy results are summarized in Table 1. Median PFSo (60% maturity, 23/38) was 8.4 months (95% CI 5.8-11.0). Adverse events of grade 3 or higher were reported in 39.5% patients. Analyzed in 12 paired samples, the median CSF penetration rate of osimertinib was 31.7% (range 19.8-57.7%), with a median CSF concentration of 10.83nM (range 5.2-30.3nM). T790M mutation was detected in 83% (10/12) of plasma and 17% (2/12) of CSF samples at baseline, with a concordance rate of 8.3% (1/12). Median PFSo was prolonged in patients with EGFR sensitizing mutation clearance at week 6 compared with those with persisting EGFR mutations (not reached vs 2.83 months; HR 0.09, 95% CI 0.02-0.54; p<0.01). Table 1. Baseline characteristics and efficacy

Patients characteristics	N=38		
Age, median (range), years	63 (38-74)		
CNS metastases, No (%): brain metastases (BM) / leptomeningeal metastases (LM) / other	35 (92.1%) / 2 (5.3%) / 1 (2.6%)		
Histology, No (%): adenocarcinoma	38 (100%)		
EGFR mutations, No (%): T790M with Ex-19del / L858R	22(57.9%) /16 (42.1%)		
Sample type for T790M confirmation No (%): Blood / Tissue	27 (71.1%) / 11 (28.9%)		
Lines of anti-tumor therapy, No (%): 1 / 2 / ≥3	13 (34.2%) / 3 (7.9%) / 22 (57.9%)		
Efficacy	Overall	Extracranial	Intracranial
Median PFS (months, 95% CI)	8.4 (5.8, 11.0)	10.2 (7.5, 14.0)	10.9 (6.1, NA)
Objective response rate (ORR)	42.4%(14/33)	39.4%(13/33)	71.9%(23/32)
Disease control rate (DCR)	90.9%(30/33)	90.9%(30/33)	96.9%(31/32)
Median Duration of Response (DoR) (months, 95% CI)	8.1 (3.4, NA)	11.1 (5.6, 11.1)	8.3 (5.8, NA)

Conclusion: Osimertinib demonstrated promising efficacy, good blood brain barrier penetration and manageable tolerability in EGFR T790M-positive Chinese advanced NSCLC patients with brain metastases. NGS analysis revealed genetic heterogeneity between plasma and CSF samples and longitudinal genetic analysis may be beneficial to predict the efficacy of osimertinib.

Keywords: (5): T790M, osimertinib, Cerebrospinal fluid

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-26 FIRST-LINE CONTINUAL EGFR-TKI PLUS LAT DEMONSTRATED SURVIVAL BENEFIT IN EGFR-MUTANT NSCLC PATIENTS WITH OLIGOPROGRESSIVE DISEASE

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Background: The effect of local ablative therapy (LAT) for oligoprogressive epidermal growth factor receptor (EGFR) mutation non-small cell lung cancer (NSCLC) remains undetermined. This study aimed to investigate the survival benefit of addition of LAT to EGFR-TKIs in EGFR-mutant NSCLC patients with oligoprogression during TKI therapy. **Method:** Patients with stage IIIB/IV EGFR mutant NSCLC who had oligoprogressive disease during the first-line EGFR-TKI therapy from March 2011 to February 2016 were identified. The primary research point were progression-free survival1 (PFS1), defined as time of initiation of TKI therapy to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 defined progress disease (PD) or death and PFS2, defined as time of initiation of TKI therapy to off-TKI PD. The second research piont inclued

overal survival (OS) and safety. **Result:** A total of 206 patients were included. The median follow-up time was 42 months (20.0-69.6 months). The median PFS1, median PFS2 and median OS for the related cohort were 10.7 months (95% CI, 10.1-13.3 months), 18.3 months (95% CI, 17.4-19.2 months) and 37.4 months (95% CI, 35.9-38.9 months) respectively. Survival rates of 1 year, 2 years and 3 years were 94.1%, 78.9%, and 54.7%, respectively. Multivariate analysis revealed that female, EGFR exon 19 mutation, one metastatic lesion, partial or complete response to prior EGFR TKIs therapy were the independent prognostic factors. No unexpected toxicities were observed. **Conclusion:** The current study suggested that the addition of LAT to EGFR-TKI could provide satisfactory survival benefit for EGFR-mutant NSCLC patients with oligoprogression during first-line EGFR-TKI treatment.

Keywords: Oligoprogressive disease, Local ablative therapy, EGFR-TKI

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-27 A RANDOMIZED STUDY OF CONCURRENT VS SEQUENTIAL ALTERNATING EGFR-TKIS AND CHEMOTHERAPY FOR ADVANCED NSCLC WITH EGFR MUTATIONS

H. Yong[1], L. Hui[1], L. Fang[1], L. Dong[1], X. Ling[1], W. Qiang[1], X. Peng[1], H. Hua[1], Y. Yang[2], G. Ping[2], K. Cui[2], W. Wu[2], C. Yu[2], L. Huo[3], X. Qiang[4], S. Xi[5], C. Jin[6]

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Background: EGFR-TKIs have been accepted as the standard first-line treatment for EGFR-mutated NSCLC, and EGFR-TKIs in combination with chemotherapy are found to achieve PFS benefits. However, the optimal sequence of EGFR-TKIs and chemotherapy remains controversial until now. This study aimed to compare the efficacy and safety of concurrent versus sequential alternating EGFR-TKIs and chemotherapy for treatment-naive advanced nonsquamous EGFR-mutated NSCLC. **Method:** A multicentre, open-label, parallel, randomized controlled trial was performed. Eligible participants were randomly assigned into Group A (n = 36) and Group B (n = 59). Subjects in Group A were concurrently given EGFR-TKI and platinum-based doublet chemotherapy on day 1, every 3 weeks for 4 to 6 cycles, followed by maintenance therapy with EGFR-TKIs, while patients in Group B received EGFR-TKI alone, and platinum-based doublet chemotherapy was given upon disease progression. Chemotherapy regimens included selected cisplatinum (75 mg/m^2) or carboplatin (AUC 5.0) plus pemetrexed (500 mg/m^2) or paclitaxel (175 mg/m^2) on day 1 of a 21-day cycle. All subjects were administered orally with erlotinib 150 mg QD (n = 40), gefitinib 250 mg QD (n = 30) or icotinib 125 mg TID (n =19), until disease progression or intolerance to adverse events. The primary endpoint was PFS, and the secondary endpoints were OS and safety. **Result:** At a median follow-up of 18 months, 53.4% of patients had progressive disease and 23.2% died. Median PFS was 15.0 months (95% *CI*, 9.9 to 20.1 months) for the concurrent regimen and 17.5 months (95% *CI*, 14.4 to 20.5 months) for the sequential alternating regimen (P = 0.614). In addition, administration of EGFR-TKIs alone achieved 12.0 months PFS (95% *CI*, 9.3 to 14.8 months), which was comparative to the concurrent regimen (P = 0.508). Drug-related grade 3 or 4 adverse events didn't occur. **Conclusion:** This interim analysis demonstrates that concurrent EGFR-TKIs and chemotherapy achieves comparative PFS to sequential alternating EGFR-TKIs and chemotherapy and EGFR-TKIs monotherapy for treatment-naive advanced nonsquamous non-small-cell lung cancer with sensitive EGFR mutations.

Keywords: advanced NSCLC, Targeted therapy, EGFR mutations

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-28 THE FUNCTIONAL MDM4 GENETIC POLYMORPHSIM AS PROGNOSTIC BIOMARKER FOR ADVANCED LUNG ADENOCARCINOMA PATIENTS' SURVIVAL TO EGFR-TKIS THERAPY

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Background: As a mostly used epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), gefitinib significantly prolongs survival of lung adenocarcinoma patients with sensitizing *EGFR* mutations. However, more than 10% of *EGFR* mutation-positive patients do not respond and a substantial fraction of responded patients progress after 8-12 months' treatment. Identification of new biomarkers associated with EGFR-TKIs prognosis would have great clinical potential for individualized treatments. The objective of this study is to investigate associations between the functional *MDM4* genetic variant and survival of lung adenocarcinoma patients treated with gefitinib, especially in the patients with active *EGFR* mutations. **Method:** In this study, a total of 384 patients with stage IIIB or IV lung adenocarcinoma were recruited between January 2009 and June 2013. All patients were treated with gefitinib orally at a daily dose of 250 mg as 1st-line monotherapy. *MDM4* rs4245739 A>C genotypes were determined using the MassArray system (Sequenom Inc., San Diego, USA). Dual luciferase reporter gene assays were used to evaluate the function of *MDM4* rs4245739 genetic variant in lung adenocarcinoma cell lines A549 and H1299. The differences of patient clinical characteristics and different reporter gene assays were calculated using student's t test or χ^2 test. The genotype effects on PFS or OS was estimated using the Kaplan-Meier method and a comparison between survival curves was done with log-rank test. Multivariate Cox regression analysis assessed prognostic factors for PFS or OS. A P value of less than 0.05 was used as the criterion of statistical significance, and all statistical tests were two-sided. **Result:** Among 384 patients, *EGFR* mutations were positive in 181 patients (47.1%). Median progression-free survival (PFS) and overall survival (OS) for all patients with the rs4245739AC genotype were significantly longer than that of the AA carriers (PFS: 22.9 vs. 10.9 months, P < 0.001; OS: 27.3 vs. 16.5 months, P = 0.003). Notably, in the *EGFR* mutation-positive subgroup, individuals with *MDM4* rs4245739AC genotype showed 14.1 months prolonged PFS (28.8 months vs. 14.7 months; P = 0.022) and 12.2 months prolonged OS (31.4 months vs. 19.2 months; P = 0.047) compared to the AA group. In support of this, reporter gene assays showed that the rs4245739A allele leads to significantly increased *MDM4* expression in lung adenocarcinoma cells compared to the C allele (P < 0.05). **Conclusion:** *MDM4* rs4245739 genotypes may act as prognostic biomarker for patients' survival to gefitinib therapy and offer help to patient-tailored treatment strategy in lung adenocarcinoma patients with *EGFR* mutations.

Keywords: functional MDM4 genetic variant, EGFR-TKIs treatment, Prognostic Biomarker

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-29 OVERALL RESPONSE RATE OF NINTEDANIB AND DOCETAXEL IN COMBINATION WITH THE NUTRACEUTICAL USE OF SILIBININ IN ADVANCED NSCLC

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Background: The bioactive flavonolignan silibinin, the main component of standardized extracts from the seeds of the milk thistle herb *Silybum marianum*, has been shown to exhibit significant anticancer activity in preclinical models. Silibinin is a direct inhibitor of pSTAT3, a signal transducer and key transcription factor that is associated with chemoresistance in cancer cells. Our group has shown that oral administration of the silibinin-containing nutraceutical Legasil® could represent the first silibinin formulation with proven clinical benefit as an adjunct cancer treatment in patients with brain metastases. Nintedanib is an orally administered, small-molecule triple angiokinase inhibitor of VEGF1–3, PDGFa and b, and FGFR1–3. The LUME-Lung 1 trial showed that nintedanib significantly extended progression-free survival (PFS) and overall survival (OS) in patients with NSCLC adenocarcinoma when added to docetaxel chemotherapy, with no differences in response rate. **Method:** Patients with stage IV NSCLC who failed ≥1 prior treatment were eligible for nintedanib/docetaxel combination. We present retrospective data analysis regarding patients that received nintedanib/docetaxel with or without combination with up to 5 capsules (630 mg)/day of Legasil®. **Result:** Fifty-nine patients were enrolled in the study: median age, 60y (range: 43–79); male, 46 (78%). All the cases had adenocarcinoma histology. All patients had received first line therapy and 13 (22%) patients had >2 prior lines of treatment. A higher overall response rate (ORR) was observed in the group receiving Legasil® supplementation: ORR 55.5% *versus* 22%, p=0.02. No statistically significant differences in the median PFS were observed in the two arms: 2.34 months (95% confidence interval [CI] 1.83–2.91) for nintedanib/docetaxel combination

(n=41) *versus* 4.99 (95%CI 0.94–9.05) for nintedanib, docetaxel and Legasil® triple combination (n=18) (p=0.241) at the data cut-off of January 2018. In the control group (n=41), ORR was greater in patients with known *KRAS* (n=8) or *EGFR* (n=3) mutations: 45% *versus* 13%, p=0.028. **Conclusion:** The inhibition of pSTAT3 with silibinin may increase tumor responses to nintedanib/docetaxel combination. In addition, patients with known *KRAS* or *EGFR* mutations may show higher tumor responses to nintedanib/docetaxel combination.

Keywords: silibinin, pSTAT3, nintedanib

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-30 NEUTROPHIL-TO-LYMPHOCYTE RATIO AS A PROGNOSTIC FACTOR AND ITS RELATIONSHIP TO NSCLC PATIENT OUTCOMES IN THE REVEL TRIAL

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Background: Neutrophil-to-lymphocyte ratio (NLR) reflects underlying levels of systemic inflammation and has prognostic importance in solid tumors. Higher baseline NLR is an independent negative prognostic factor in advanced non–small cell lung cancer (NSCLC) and may indicate more aggressive disease. An exploratory analysis from REVEL demonstrated benefits of ramucirumab(RAM)/docetaxel(DOC) in NSCLC patients with rapidly progressing and refractory disease. We investigated the relationship between pretreatment NLR, prognosis and response to RAM/DOC. **Method:** Pretreatment NLR was analyzed by dividing absolute neutrophil count by absolute lymphocyte count from peripheral blood. Multiple NLR cutoffs ≥4 were evaluated for prognostic significance by analyzing overall survival (OS), progression-free survival (PFS), and objective response rate (ORR). Kaplan-Meier analysis and Cox proportional hazards regression model were used for analyzing OS and PFS, and Cochran-Mantel-Haenszel test for ORR. **Result:** Pretreatment NLR was determined for 1224 REVEL patients (n=611 RAM/DOC, n=613 placebo [PBO]/DOC), among whom 51%, 40%, and 32% had NLR ≥4, 5, and 6, respectively. Baseline characteristics were balanced between arms in NLR subgroups and the REVEL intent-to-treat (ITT) population. Patients with higher NLR values had worse OS, PFS, and ORR compared to the ITT population. For all NLR cutoff values, OS, PFS and ORR were improved in patients treated with RAM/DOC compared to patients receiving PBO/DOC (Table). Efficacy and safety outcomes across high NLR subgroups were consistent with those in the ITT population.

Table: Efficacy outcomes by pretreatment NLR

	REVEL ITT Population		NLR ≥4		NLR ≥5		NLR ≥6	
	RAM + DOC	PBO + DOC	RAM + DOC	PBO + DOC	RAM + DOC	PBO + DOC	RAM + DOC	PBO + DOC
	(n=628)	(n=625)	(n=305)	(n=322)	(n=242)	(n=247)	(n=200)	(n=192)
Median OS, months (95% CI)	10.5 (9.5, 11.2)	9.1 (8.4, 10.0)	9.3 (7.8, 10.3)	7.1 (6.1, 8.3)	8.4 (7.0, 10.1)	6.6 (5.4, 7.8)	7.5 (6.2, 9.7)	6.2 (5.2, 7.7)
Unstratified HR (95% CI)	0.86 (0.75,0.98)		0.84 (0.70, 1.00)		0.79 (0.64, 0.97)		0.81 (0.65, 1.01)	
Median PFS, months (95% CI)	4.5 (4.2, 5.3)	3.0 (2.8, 3.9)	4.0 (3.2, 4.5)	2.8 (2.4, 3.0)	3.5 (3.0, 4.2)	2.7 (2.0, 3.0)	3.3 (2.9, 4.1)	2.6 (1.7, 2.8)
Unstratified HR (95% CI)	0.76 (0.68, 0.86)		0.82 (0.70, 0.97)		0.86 (0.72, 1.04)		0.85 (0.69, 1.05)	
ORR (CR + PR), % (95% CI)	22.9 (19.7, 26.4)	13.6 (11.0, 16.5)	20.7 (16.3, 25.6)	10.2 (7.2, 14.1)	20.2 (15.4, 25.9)	10.5 (7.0, 15.0)	17.0 (12.1, 22.9)	10.9 (6.9, 16.2)
p-Value	<0.001		0.0007		0.0067		0.1707	

CI, confidence interval; CR, complete response; DOC, docetaxel; HR, hazard ratio; ITT, intent-to-treat; NLR, Neutrophil-to-lymphocyte ratio; ORR, objective response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PR, partial response; RAM, ramucirumab.

Conclusion: In this exploratory analysis of REVEL, higher pretreatment NLR was an independent prognostic factor indicating poorer survival outcomes. Treatment benefit with RAM/DOC was preserved in patients with elevated NLR and was consistent with REVEL ITT results. NLR is an inexpensive and reproducible blood test and may provide a simple way to identify patients with more aggressive disease who can benefit from treatment with RAM/DOC in second-line NSCLC.

Keywords: second-line NSCLC, ramucirumab, Neutrophil-to-lymphocyte ratio

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-31 SAFETY AND TUMOUR HYPOXIA MODIFYING EFFECT OF BUPARLISIB WITH RADIOTHERAPY IN NSCLC: A PHASE I DOSE ESCALATION STUDY

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Background: The Ras/PI3K/Akt pathway plays an important role in determining intrinsic and extrinsic tumour radiosensitivity. Buparlisib (BKM120) is a highly specific pan class-1 PI3K inhibitor. Pre-clinically, this class of agents radiosensitises tumours by direct effects on intrinsic radiosensitivity and by reducing tumour hypoxia. We therefore assessed the safety and determined the maximum tolerated dose (MTD) of buparlisib in combination with radiotherapy in patients with NSCLC and investigated its effect on tumour hypoxia. **Method:** BKM120 was a single centre, open-label, dose-escalation and dose-expansion phase 1 trial. Patients with advanced stage NSCLC received 2 weeks of oral buparlisib. Palliative thoracic radiotherapy (20Gy in 5 fractions) was delivered during the second week of treatment. ^{18}F-fluoromisonidazole (FMISO) PET scans were used to assess tumour hypoxic volume (HV) before and after 1 week of buparlisib treatment. HV was defined as the volume with a tumour-to-blood F-MISO uptake ratio ≥ 1.4. **Result:** From June 2013 to August 2017, 21 patients were recruited. 11 patients were registered to the dose escalation phase with 9 evaluable for MTD analysis: 3 in Cohort 1 (50mg OD), 3 in Cohort 2 (80mg OD) and 3 in Cohort 3 (100mg OD). No DLT was reported therefore 100mg OD was declared the MTD and 10 patients received this dose in the expansion phase. Of all patients who received buparlisib (n=21), 1 SAE (Grade 3 hypoalbuminaemia) was possibly related to buparlisib (5%). The most common buparlisib-related AEs were fatigue (8.3%) and nausea (3.3%). 93.9% of all AEs with any relation to buparlisib were ≤ Grade 2. There was no reported radiotherapy associated toxicity. 15 patients were evaluable for tumour hypoxia imaging analysis. Median change in HV in Cohort 1 (n=3), Cohort 2 (n=3) and Cohort 3 combined with the expansion cohort (n=9) was 7%, -18% and -20%, respectively. **Conclusion:** This is the first clinical trial of a specific PI3K inhibitor with concurrent radiotherapy in NSCLC. This combination was found to be safe and well-tolerated. This study provides clinical evidence that PI3K inhibition rapidly reduces tumour hypoxia and therefore warrants further trials combining this class of agents with radiotherapy.

Keywords: Tumour hypoxia, NSCLC, Radiotherapy

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-32 COMPARISON BETWEEN IMMUNE-MEDIATED PNEUMONITIS AND PNEUMONIA IN PATIENTS TREATED WITH PD-1/PD-L1 THERAPY

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Background: Immune-mediated pneumonitis (IMP) is an uncommon but potentially fatal toxicity of anti–programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1) therapy for non-small cell lung cancer. The purpose of study was to compare clinical and radiographic findings between IMP and pneumonia by pathogen. **Method:** From 2014 to 2017, a total of 154 patients who received anti–PD-1/PD-L1 therapy were identified. Among these, IRP developed in 9 (5.8%) and pneumonia in 30 (19.5%), which were confirmed through multidisciplinary approach. CT findings (reticulation, consolidation, ground glass opacity [GGO], interlobular septal thickening, micro- [<10mm] and macro-nodules [≥10mm], bronchial wall thickening, bronchiectasis, pleural effusion, and lesion distribution/bilaterality) and clinical features (symptom, smoking history, cancer staging, laboratory findings, underlying disease, prior radiotherapy history) were compared between IRP and pneumonia. Grade and outcome of IRP were also investigated. **Result:** In chest CT, diffuse reticulation (44.4% vs.0%, P=0.02), patchy/diffuse GGO (100% vs. 50%, P=0.01), and interlobular septal thickening (66.7% vs. 10%, P=0.002) were significantly more frequent in IRP than in pneumonia, whereas macronodule (0 vs. 36.7%, P=0.033) was significantly more common in pneumonia than IRP. IRP significantly showed peripheral location (77.8% vs. 16.7%, P=0.001) and bilateral distribution (44.4% vs. 3.3%, P=0.007). However, there were no significant differences in clinical findings between IRP and pneumonia. Among the IRP patients, 66.7% (6 of 9) of cases were grade 3, and 66.7% improved with drug holding/steroid therapy. The median onset duration of IRP from the first prescription was 126 days (range, 40-669), the median time for improvement was 43 days (range, 21-45), and the median time to death due to IRP was 18 days (range, 11-55). **Conclusion:** Several CT findings including diffuse reticulation, patchy/diffuse GGO, and interlobular septal thickening with bilateral and peripheral distribution were more frequent in IRP than pneumonia by pathogen. Clinical findings were overlapped.

Keywords: immune-mediated pneumonitis, lung cancer, Immunotherapy

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-33 EX VIVO 2*2*2 TUMOR TISSUE EXPLANT CULTURE FOR PRECISION MEDICINE IN IMMUNOTHERAPY AND TKI PROGRESSORS IN LUNG CANCER

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Background: Lung cancer is one of the leading causes of cancer mortality worldwide. Despite of remarkable progress made in the lung cancer therapy, an unmet need is there in tailoring the appropriate patient specific therapy due to a variety of treatment options. Our aim was to develop a high-throughput drug screening method of tumor ex-vivo analysis (TEVA) which can predict patient-specific drug response and thus can be used for personalized cancer treatment. **Method:** Freshly operated tumor tissue samples from non small cell lung carcinoma (NSCLC) patients were received from Soroka Medical Center, Israel and implanted in NSG mice to form PDXs. We developed a method that enabled us to cut the PDXs into 2*2*2mm tissue explants and then treated with clinically relevant drugs (Genomics/proteomics suggested) in 48 well plates for 24 hours. TMA blocks were prepared and IHC was performed. Parameters, such as Ki67, TUNEL and respective signalling molecules (pMAPK, pPRAS40) were chosen to predict the drug response *ex vivo* and a score was given to each drug based upon those parameters. **Result:** 8 NSCLC patients have been enrolled so far. Implantation rate was 75%. 15 drugs combinations have been developed to test the most common conditions, i.e. progression on EGFR TKIs, progression on immunotherapy and progression on chemotherapy. Preliminary results indicate a potential role for MET blockade in immune-resistant as well as in EGFR progressors. We also observed that the TEVA score correlated with the genomics/proteomics based drug results. **Conclusion:** Overall, this low cost, fast, relatively simple and efficient method can bypass the necessity of drug validation in mice and can be used for multiple drug screening to select a precise patient specific drug. The method is feasible and expose ways to overcome acquired resistant to novel drugs.

Keywords: Immunotherapy, Tumor ex vivo analysis, TKIs

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-34 CHANGES IN RADIOMIC FEATURES BETWEEN BASELINE AND TWO WEEKS POST-NIVOLUMAB TREATMENT ARE PREDICTIVE OF PATHOLOGIC COMPLETE RESPONSE

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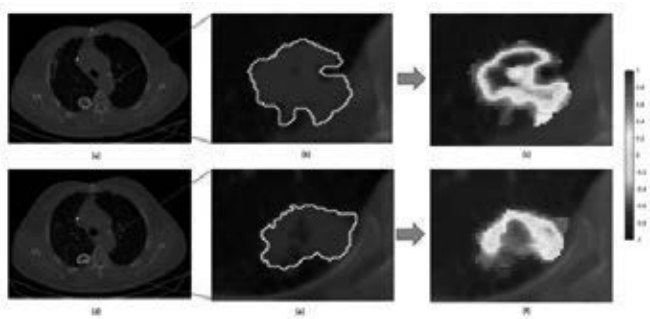
Background: Programmed cell death immune checkpoint inhibitors have been approved by the FDA to treat stage III unresectable NSCLC or Stage IV metastatic lung adenocarcinoma. However, the response rate to such therapy is limited to 19%. Currently, there are no clinical biomarkers to identify patients who are likely to derive benefit from Nivolumab. Our aim was to explore whether changes in intratumoral and peritumoral radiomic texture features between baseline and 2-week post-treatment CT scans could predict immunotherapy response. **Method:** Surgical biopsy specimens (pre-treatment) and CT scans from 73 NSCLC patients with pre- and 2-week post-Nivolumab treatment were acquired. Patients with an objective response (complete/partial) per RECIST after two cycles of Nivolumab were defined as "responders" and patients with progressive disease were defined as "non-responders". 454 intra-tumoral texture, 24 shape features and 7426 features from annular rings (15 annular rings

each, 2mm each) outside the expert-annotated nodules were extracted from the baseline and post-treatment scans. Besides, 76 features quantifying compactness of tumor infiltrating lymphocytes (TILs) were extracted from the surgical specimens. A linear discriminant analysis(LDA) classifier was trained using the most predictive features identified on the discovery set(n=29) and validated on the test set(n=44). To investigate the radio-pathomic associations, a pairwise Spearman correlation was performed between each radiomic and TIL feature. **Result:** A combination of 6 intra-tumoral, 3 peri-tumoral and 1 shape delta radiomic feature yielded an AUC of 0.93±0.085 within the discovery set and a corresponding AUC = 0.91 within the validation set. Lymphocyte density was found to be negatively(r=-0.5) correlated with a peritumoral Gabor feature from the first annular ring. **Conclusion:** Change in texture features extracted from baseline and post-Nivolumab treated CT scans were predictive of pathological response. Association of these texture features with TIL compactness may provide a deeper understanding of immune response and corresponding imaging phenotypes.



A segmented tumor regions and heat map of Haralick (entropy) feature in the pre- and post-treatment CT scans from non-responder group. (a) and (d) are the segmented CT scans from a responder in the pre- and post-treatment CT scans, respectively. (b) and (e) are the enlarged segmented tumor region from the CT scans. (c) and (f) showed the heat map of Haralick entropy texture features. It may be observed that eccentricity of non-responder tumor has increased after therapy

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-35 HYPOXIA MAPPING USING OXYGEN-ENHANCED MRI IN LUNG CANCER

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Background: Oxygen deprivation (hypoxia) is associated with worse non-small cell lung cancer (NSCLC) outcomes and predicts poor response to NSCLC treatments, including radiotherapy. There is an unmet need to develop non-invasive hypoxia biomarkers. We report the first preclinical and clinical evidence that oxygen-enhanced MRI (OE-MRI) can map and quantify therapy-induced change in NSCLC hypoxia. **Method:** In the preclinical study, radiation-induced changes in OE-MRI were first examined in a Calu-6 xenograft model of NSCLC. Tumours received a single 10Gy fraction of radiotherapy (*n*=9), chemoradiotherapy (5 x 2Gy fractions plus cisplatin; *n*=6) or control (*n*=9). Mice were imaged longitudinally using a multi-parametric MRI protocol (diffusion-weighted imaging (DWI), OE and dynamic contrast-enhanced (DCE)-MRI) at days 0, 3, 6 and 10 in all groups and then at day 13 (control), day 18 and 25 (radiotherapy) and day 18 (chemoradiotherapy). Pathology was obtained at cull in imaged mice and in a separate Calu6 cohort treated with a single 10Gy radiotherapy fraction (*n*=6) or control (*n*=9) at day 10. In the clinical study, twenty three stage I-IV NSCLC patients underwent an identical multi-parametric MRI for protocol development (*n*=6), twice prior to radiotherapy (*n*=10) and after 14±4 radiotherapy fractions (*n*=12). In all tumours we quantified the validated MRI hypoxia biomarker *perfused oxygen-refractory (Oxy-R)*, which identifies absence of OE-MRI signal change in perfused tumour. **Result:** By day 10, *perfused Oxy-R* (hypoxic) volume decreased relative to control in xenografts treated with either radiotherapy (p=0.029) or fractionated chemoradiotherapy (p=0.047). Hypoxia modification persisted in chemoradiotherapy treated tumors to day 16 and in radiotherapy treated tumors to day 22 (both p<0.001). Pimonidazole immunohistochemistry at day 10 showed lower hypoxic fraction in tumors treated with radiotherapy (p=0.026), relative to time matched controls. In addition, imaged xenografts also showed lower hypoxic fractions in radiotherapy (p=0.042) and chemoradiotherapy (p=0.041) treated tumors, relative to size matched control at cull. In the clinical study, OE-MRI was safe, feasible and well-tolerated. *Perfused Oxy-R* (hypoxic) volume demonstrated excellent repeatability with interclass correlation coefficient of 0.961 (95% CI 0.858-0.990). Visual inspection revealed that MRI hypoxia maps were spatially repeatable across a range of tumour and hypoxic volumes. In the absence of volumetric tumour change, *perfused Oxy-R* (hypoxic) volume decreased at mid-treatment (3.23 cm^3 (95% CI 0-9.41 cm^3)), compared to baseline (4.16 cm^3 (95% CI 0-10.6 cm^3)); p=0.0150. **Conclusion:** Our findings support using OE-MRI to detect and monitor hypoxia in clinical trials of hypoxia-modifying therapies or radiotherapy dose painting studies in patients with NSCLC.

Keywords: NSCLC, Hypoxia, MRI

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-36 RANDOMIZED PHASE 2 TRIAL OF SERIBANTUMAB IN COMBINATION WITH ERLOTINIB IN PATIENTS WITH EGFR WILD-TYPE NON-SMALL CELL LUNG CANCER

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Background: Seribantumab (MM-121) is a fully human IgG2 monoclonal antibody that binds to human epidermal growth factor receptor 3 (HER3/ErbB3), to block heregulin (HRG/NRG)-mediated ErbB3 signaling and induce receptor downregulation. This open-label, randomized Phase 1/2 study evaluated safety and efficacy of seribantumab in combination with erlotinib in advanced NSCLC. Here, we report the activity of seribantumab in combination with erlotinib, versus erlotinib alone, in patients with *EGFR* wild-type tumors and describe the potential predictive power of HRG. **Method:** Patients with EGFR wild-type NSCLC were assigned randomly to receive seribantumab plus erlotinib or erlotinib alone. Patients underwent pre-treatment core needle biopsy, and archived tumor samples were collected to support pre-specified biomarker analyses. **Result:** One hundred twenty-nine patients received seribantumab/erlotinib (n=85) or erlotinib alone (n=44). Median estimated PFS in the unselected ITT population was 8.1 and 7.7 weeks in the experimental and control arm, respectively (HR=0.822; 95% CI, 0.37 to 1.828; *P*=0.63). In patients whose tumors had detectable HRG mRNA expression, treatment benefit was observed in the seribantumab/erlotinib combination (HR=0.35; 95% CI, 0.16 to 0.76; *P*=0.008). In contrast, in patients whose tumors were HRG negative, the HR was 2.15 (95% CI, 0.97 to 4.76; *P* = 0.059). **Conclusion:** The addition of seribantumab to erlotinib did not result in improved PFS in unselected patients. However, pre-defined retrospective exploratory analyses suggest that detectable HRG mRNA levels identified patients who might benefit from seribantumab. An ongoing clinical trial is validating this finding in patients with advanced NSCLC and high HRG mRNA expression (NCT02387216).

Keywords: biomarker, Seribantumab, Heregulin

P1.13-37 CLINICAL EVALUATION OF PLASMA-BASED (CFDNA) GENOMIC PROFILING IN OVER 1,000 PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Tumor genomic information from a simple blood collection revealing actionable mutation can improve clinical outcome without the need for an invasive tissue biopsy. We report on the clinical utility of a cell-free DNA (cfDNA) next generation sequencing (NGS) blood test in our patients with non-small cell lung cancers (NSCLC) and the outcome of treatments with targeted therapies based on the reported mutations. **Method:** From May 2015 to February 2017, 1078 blood samples from 1011 consecutive patients with a diagnosis of NSCLC were collected and analyzed using next-generation sequencing of cfDNA with a panel of up to 70 cancer-related genes at a CLIA-certified lab (Guardant360, Guardant Health, Redwood City, CA) with reported sensitivity of 0.02% mutant allele fraction with high specificity (> 99.9999%) (CCR 2018 (17):3831). Patients in this retrospective study received targeted therapy as indicated by cfDNA molecular profiling. Tumor response was evaluated by RECIST V1.1 and standard clinical evaluation. **Result:** From 1011 patients, 1078 cfDNA tests sent (additional follow-up tests: 1 in 64 patients and 2 in 3 patients). In 223/1011 (22%) patients had cfDNA report with at least 1 targetable mutations; with 48/223 (22%) patients meeting criteria for this retrospective review. Study population were 31 female:17 male, median age of 63 years (ranged:31-94). The rationale for the blood test included: insufficient tissue or not available (32%), addition to tissue molecular analysis (17%), alternative to tissue biopsy(10%), on-going treatment evaluation/resistance (41%). Mutations included:EGFR T790M (15), EGFR exon 19del (12), EGFR L858R (9), EGFR exon 20 insertion (4), EGFR others (1), ALK gene fusions (5) and MET exon 14 skipping (2). The median line of therapy was 2(ranged:1-7) with 28 patients receiving TKI as 1st line of therapy based on cfDNA mutations. With targeted treatments based on ctDNA results, the responses (RECIST V1.1) were: CR(3), PR(26), SD(14) and PD(4); median PFS was 8.5 months (ranged:1-26mos) for the overall population with 4 patients still receiving targeted therapy. Median PFS was 9.5 months (ranged:1-20 months) for those receiving TKI as 1st line. **Conclusion:** This is the largest analysis of response rates with cfDNA directed therapy in advanced NSCLC and demonstrates positive clinical outcomes in patients treated with targeted therapy based on plasma identified biomarkers.

Keywords: cfDNA, NSCLC, targeted therapy

P1.13-38 INTER-ORGAN HETEROGENEITY ON MECHANISMS OF TARGETED DRUG RESISTANCE -CENTRAL NERVOUS SYSTEM (CNS) VS EXTRA CNS-

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Background: Molecular-targeted drugs are generally effective against tumors containing driver oncogenes, such as *EGFR*, *ALK*, and *NTRK1*. However, patients harboring these oncogenes frequently experience a progression of central nervous system (CNS) metastasis, such as brain metastasis and leptomeningeal carcinomatosis (LMC), during treatment. While secondary mutations including *EGFR*-T790M, *ALK*-L1196M, and *NTRK1*-G595R, are known to induce highly resistance to corresponding targeted drugs, involvement of these highly resistance mutations in CNS metastasis resistance is largely unknown. **Method:** We developed various *in vivo* imaging models for brain metastasis and LMC with human cancer cell lines, including the *EGFR*-exon 19 deletion-positive PC-9 lung adenocarcinoma cells, the *EML4-ALK*-positive A925L lung adenocarcinoma cells, and *TPM3-NTRK1*-positive KM12SM colon cancer cells. Using these CNS metastasis models, we examined the inter-organ heterogeneity on mechanisms of resistance to targeted drugs. **Result:** While PC-9 cells inoculated in subcutaneous space acquired EGFR tyrosine kinase inhibitor (EGFR-TKI) resistance by *EGFR*-T790M mutation, they inoculated in leptomeningeal space became resistance by *MET* copy number gain. Unlike *EGFR*-T790M mutation, *MET* copy number gain could cause intermediate resistance to EGFR-TKI *in vitro*. Similarly, A925L cells inoculated in leptomeningeal space acquired ALK-TKI resistance by EGFR ligand overexpression. Moreover, KM12SM cells inoculated in the brain acquired entrectinib resistance by *NTRK1*-G667C mutation. Since both EGFR ligand overexpression and *NTRK1*-G667C mutation caused intermediate resistance to targeted drugs *in vitro*, mechanisms which cause intermediate resistance may be sufficient to develop resistant tumors in CNS presumably due to limited drug distribution to CNS. **Conclusion:** These observations indicate inter-organ heterogeneity on mechanisms of targeted drug resistance. Therefore, careful diagnosis of resistance mechanism in CNS metastasis may be necessary when treat the patients who develop CNS metastasis with targeted drug resistance.

Keywords: leptomeningial carcinomatosis, Brain metastasis, Resistance

P1.13-39 EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION AMONG NON-SMALL CELL LUNG CANCER PATIENTS IN TRINIDAD AND TOBAGO: FREQUENCY AND TRENDS

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Background: Almost 70% of non-small cell lung cancer (NSCLC) patients present with unresectable disease and may benefit from chemotherapy or biologic therapy. Mutation testing now plays a vital role in their diagnostic work-up to determine which patients are more likely to receive benefit from biologic therapies. The rate of epidermal growth factor receptor (EGFR) mutations varies significantly across geographic regions and ethnicities, ranging from 13% to 64% in some areas. Several subgroups such as females, East Asians, never-smokers and those with adenocarcinoma histology have the highest reported rates of EGFR mutations. Regionally, the French West Indies reports an EGFR mutation rate of 36%. The frequency of the EGFR mutation among NSCLC patients in Trinidad and Tobago has not been previously reported in the literature. **Method:** An observational, retrospective study was done using data obtained from the Lung Malignancy Unit (LMU) based at the Eric Williams Medical Sciences Complex (EWMSC). The EWMSC is the sole referral centre in Trinidad and Tobago for lung cancer and the LMU is responsible for co-ordinating clinical and educational services regarding lung cancer nationwide.The study population was limited to primary NSCLC patients presenting to the EWMSC from January 2014 to June 2017 whose biopsy samples were sent for EGFR testing and received either a positive or negative result. Patients' clinical data was entered onto a spreadsheet and analysed using Microsoft Excel. **Result:** The data for 94 patients with NSCLC were analysed. 68 of these patients were male, while 58 admitted to a history of smoking. EGFR mutations were present in 39.4% of this study population. Females demonstrated a significantly higher EGFR mutation rate than males (73.1% vs 26.5%, $p < 0.0001$). Smoking status was found to be significantly associated with differences in EGFR mutation status ($p < 0.01$). The mean age of presentation was similar despite of EGFR mutation status. Although a larger number of EGFR positive patients compared to EGFR negative patients had adenocarcinoma histology (97.3% vs. 89.5%), this was not found to be statistically significant ($p = 0.29$). **Conclusion:** The frequency of EGFR mutations in this study population (39.4%) was higher than most regions of the world but similar to that reported in the French Antilles. Sex and smoking status were significantly associated with differences in EGFR mutation status.

Keywords: Trinidad and Tobago, non-small cell lung cancer, Epidermal growth factor receptor

P1.13-40 RAPID, ROBUST AND DURABLE RESPONSES TO LAROTRECTINIB IN PATIENTS WITH TRK FUSION NON-SMALL CELL LUNG CANCER

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Background: Neurotrophic tyrosine receptor kinase (*NTRK)* gene fusions are oncogenic independent of tumor lineage and are widely distributed across cancers. *NTRK* gene fusions were first reported in lung cancer in 2013 (Vaishnavi et al Nat Med 2013). Larotrectinib is a potent and highly selective oral tropomyosin receptor kinase (TRK) inhibitor in clinical development. Initial data of treatment of 55 patients with TRK fusion cancer resulted in an investigator-assessed objective response rate of 80%, and 71% of patients still in response at one year (Drilon et al., NEJM 2018). We report here on the safety and efficacy of larotrectinib in 4 patients with NSCLC from the 55 patient dataset. **Method:** Patients with previously treated lung adenocarcinoma were treated under clinical trial and enrolled based on a molecular report of NTRK gene fusion from a CLIA-certified lab. Larotrectinib was administered at 100 mg BID until disease progression or lack of clinical benefit. Tumors were assessed by investigators every 8 weeks using RECIST v1.1 criteria. **Result:** As of July 17, 2017, four patients with adenocarcinoma of the lung who had progressed after 1 or more lines of platinum-based chemotherapy for advanced disease were enrolled. Three patients harbored an *NTRK1* fusion and one an *NTRK3* fusion. Three of 4 patients had a partial response or complete response confirmed on a subsequent scan. One patient with a possible brain metastasis demonstrated regression of mass on MRI. Responses were rapid and robust, with a time to response ranging between 49 and 56 days. At the time of analysis, 3 patients continued to have an ongoing response ranging between 5.7 and 12 months. The other patient had stable disease and progressed outside of the CNS after 300 days of treatment and continued on larotrectinib for clinical benefit. Larotrectinib was well tolerated, with 3 of 4 patients having grade 1 events only. **Conclusion:** Larotrectinib treatment resulted in rapid and durable responses and had a well tolerated adverse event profile with no CNS progressive events in patients with previously treated lung cancer harboring *NTRK* gene fusions. These results strongly support the inclusion of *NTRK* gene fusions as part of routine testing for patients with lung cancer.

P1.13-41 IN VITRO EVALUATION FOR OPTIMAL MET-TKI SELECTION IN LUNG CANCERS WITH MET MUTATIONS INCLUDING EXON 14 SKIPPING

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Background: MET exon 14 skipping mutation present in 3-5% of adenocarcinoma of the lung is an emerging driver gene alteration. Clinical responses of these tumors to MET-TKI have been reported. However, response rates are not very satisfactory compared with EGFR/ALK/ROS1 TKI. Therefore, it is necessary to create in vitro model system to understand sensitivity/resistance mechanism for various types of MET-TKI, to establish optimal treatment strategy. **Method:** We introduced MET exon 14 skipping mutation as well as Y1003F, D1010Y which had been also reported to be present in lung cancer, to mouse pro-B cell line, Ba/F3. Since Ba/F3 requires interleukin 3 (IL-3) for its growth, IL-3 independent growth of Ba/F3 indicates that transduced mutation is oncogenic. The growth inhibitory assays were then performed using 9 MET-TKIs that include all classes of MET-TKIs ; Type Ia (crizotinib), Type Ib (capmatinib, tepotinib, savolitinib and AMG337) , Type II (cabozantinib, merestinib and glesatinib) and Type III (tivantinib). **Result:** Ba/F3 transfected with wild-type MET did not grow in the absence of IL-3, while all transfected with any of three mutated MET did so. In general, all type Ia/b / type II inhibitors were active for any of 3 MET mutations. Interestingly MET point mutations (Y1003F/D1010Y) were more sensitive to type Ib inhibitors except AMG337 than type II, while exon 14 skipping was likely to be more sensitive to type II inhibitors than type Ib compared with point mutations. IC50 / Cmax of cabozontinib was least for exon 14 skipping while that of capmatinib was least for Y1003F and D1010Y, suggesting most promising activity of these drugs (Table).

Table. Summary of IC50s for 9 MET-TKIs in Ba/F3 cells transfected with MET mutation.

Class		Type Ia	Type Ib				Type II			Type III
Compound		Crizotinib	Capmatinib	Tepotinib	Savolitinib	AMG337	Cabozantinib	Glesatinib	Merestinib	Tivantinib
IC50 (nM)	Exon14 skip	41.4	3.0	41.7	23.5	2.1	0.7	1.3	6.7	607.5
	Y1003F	19.5	0.6	3.6	2.5	9.5	16.1	6.9	25.6	633.4
	D1010Y	18.7	0.3	1.4	2.0	5.4	7.5	5.7	14.0	591.2
Cmax (nM)		1123	16075	2621	N/A	8797	4426	906	539	7465
Trough (nM)		540	N/A	N/A	N/A	N/A	2751	322	N/A	N/A

N/A: Data not available

Conclusion: We found that the MET exon 14 skipping, Y1003F, and D1010Y mutations were all oncogenic in Ba/F3 system. Several type I/II inhibitors especially cabozantinib and capmatinib are expected to be active for treating lung cancer patients with MET mutations.

Keywords: MET Exon14, MET TKI, Met mutation

P1.13-42 ACTIVITY OF NOVEL HER2 INHIBITOR, POZIOTINIB, FOR HER2 EXON 20 MUTATIONS IN LUNG CANCER AND MECHANISM OF ACQUIRED RESISTANCE

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Background: Oncogenic HER2 mutations are present in 2-4% of adenocarcinoma of the lung. However, clinical trials of HER2 inhibitors such as afatinib or neratinib has been unsatisfactory. Recently, a novel HER2 inhibitor, poziotinib has been developed and clinical trial results are being expected. Here, we evaluated poziotinib in comparison with pre-existing TKIs using Ba/F3 system. We also derived resistant clones against poziotinib and investigated their resistant mechanism. **Method:** We introduced three common HER2 mutations into Ba/F3 cells (i.e. G776delinsVC (VC), A775_G776insYVMA (YVMA) and P780_Y781insGSP (GSP)) which account for 13, 72, 9% of HER2 mutations in human lung cancer, respectively. We defined sensitivity index (SI) as an IC_{90}divided by trough concentration of a given drug at the recommended dose for humans in the literature, as a surrogate for drug activity in humans. Poziotinib activity was compared with 8 TKIs (afatinib, osimertinib, erlotinib, neratinib, lapatinib, dacomitinib, irbinitinib, and AZ5104). In addition, we created resistant clones by exposing poziotinib in the presence of N-ethyl-N-nitrosourea (ENU) and HER2 secondary mutations were searched. **Result:** All drugs but lapatinib showed the highest activity against VC (Table). In contrast, YVMA was most resistant in all but neratinib and poziotinib. For most common YVMA, poziotinib was the only drug that had SI of less than 10 (Table). Furthermore, poziotinib was most potent for VC and GSP except dacomitinib for GSP (Table). We established 19 poziotinib-resistant clones, all of which harbored C805S secondary mutation of the HER2 gene homologous to C797S of the EGFR gene.

	C_{trough} [nM]	YVMA	VC	GSP
Afatinib	69	28	5.4	12
Dacomitinib	166	20	4.4	6.6
Erlotinib	2969	337	22	98
Osimertinib	400	40	4.5	30
Neratinib	100	11	11	28
Lapatinib	516	133	117	91
Poziotinib	20	6.0	2.7	10
Irbinitinib	520	34	33	16
AZ5104	50	60	8.0	48

Conclusion: Poziotinib showed the most potent activity against HER2 exon 20 mutations. We also found that secondary C805S HER2 mutation was the common mechanism of acquired resistance, which most likely inhibit covalent binding of poziotinib with HER2.

Keywords: NSCLC, HER2, Poziotinib

P1.13-43 MOLECULAR AND IMAGING PREDICTORS OF RESPONSE TO ADO-TRASTUZUMAB EMTANSINE IN PATIENTS WITH HER2 MUTANT LUNG CANCERS: AN EXPLORATORY PHASE 2 TRIAL

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Background: Ado-trastuzumab emtansine is a HER2 targeted antibody drug conjugate (ADC) that has demonstrated clinical activity in patients with *HER2* mutant lung cancers, independent of HER2 protein expression. We hypothesize that the degree of HER2 homo- and/or heterodimerization may lead to preferential trastuzumab binding and internalization, and may serve as a predictor of response to HER2 ADC. **Method:** Patients with metastatic *HER2* mutant lung cancers were enrolled in a phase 2 trial of ado-trastuzumab emtansine, treated at 3.6mg/kg IV every 3 weeks. The primary endpoint was overall response rate (ORR) using RECIST v1.1. An expansion cohort included patients assessed using PERCIST, with pre-treatment 89Zr-trastuzumab PET/CT as correlative HER2-targeted imaging. *HER2* mutation was identified by next generation sequencing (NGS), and tumors with adequate tissue were subsequently tested by fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), quantitative protein mass spectrometry, as well as quantitative HER2-HER3 heterodimerization by fluorescence lifetime imaging microscopy - Förster resonance energy transfer (FLIM-FRET). **Result:** A total of 35 patients with *HER2* mutant lung cancers were treated across 2 cohorts. ORR was 44% (8/18, 95% CI 22-69%) for RECIST cohort, and 46% (6/13, 95% CI 19-75%) for PERCIST cohort with 4 patients awaiting response assessment. Responders were seen across mutation subtypes (A775_G776insYVMA, G776delinsVC, V659E, S310F, L755P). Concurrent *HER2* amplification was observed in 6 of 35 (17%) patients by either NGS or FISH. IHC ranged from 0 to 3+ and did not predict response. HER2 protein expression was low or absent in 15/18 cases tested by mass spectrometry. HER3 overexpression was seen in 7/18 cases tested and among them 5/6 evaluable patients had a partial response. FLIM-FRET efficiency was tested positive for HER2-HER3 heterodimer, which has been shown to be affected by the symmetrical heterodimer interface mutations (Claus et al, 2018), in 3 patients thus far and 1 of them had a partial response. Pre-treatment 89Zr-trastuzumab PET/CT showed increased uptake in 3/8 patients tested to date, and all 3 patients subsequently had partial metabolic response.

Conclusion: This study confirmed the efficacy of ado-trastuzumab emtansine in patients with *HER2* mutant lung cancers. HER2-containing dimers as indicated by HER3 overexpression or FLIM-FRET efficiency, and HER2-targeted imaging with 89Zr-trastuzumab PET/CT, may predict response to HER2 ADCs.

Keywords: HER2 mutant lung cancers, antibody drug conjugate, HER2 targeted imaging

P1.13-44 SAFETY, PK, AND PRELIMINARY ANTITUMOR ACTIVITY OF THE ORAL EGFR/HER2 EXON 20 INHIBITOR TAK-788 IN NSCLC

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Background: TAK-788 (AP32788) is an investigational tyrosine kinase inhibitor (TKI) with potent, selective preclinical activity against activating EGFR and HER2 mutations, including exon 20 insertions. We report early results of a phase 1/2 first-in-human, open-label, multicenter study of TAK-788 (NCT02716116). **Method:** Patients with advanced non-small cell lung cancer (NSCLC) refractory to standard therapy received daily oral doses (5–120 mg) of TAK-788 in the ongoing dose-escalation phase (3+3 design). Preliminary antitumor activity (by RECIST v1.1), safety, and PK are reported for patients who received ≥1 dose. **Result:** As of 8-Sep-2017, 34 patients (median age, 60 y; female, 65%; ≥2 prior anticancer therapies, 88%; Table) were treated with TAK-788; 10 remain on treatment at data cutoff. $AUC_{024,ss}$ increased in a dose-proportional manner over the dose range evaluated; the effective $t_{1/2}$ was ~16 (range 6–28) h. The most common treatment-emergent AEs (TEAEs; ≥20%) were diarrhea (47%), nausea (26%), and fatigue (21%). Grade ≥3 TEAEs in ≥2 patients (excluding disease progression) were dyspnea (n=3, 9%) and anemia, asthenia, dehydration, lung infection, pleural effusion, pneumonia, and pneumonitis (n=2 each, 6%). Two DLTs, both pneumonitis, were reported (80 mg, grade 3; 120 mg, grade 5). Of 14 evaluable patients, 3 had PR (80 mg, n=2, both confirmed; 120 mg, single PR awaiting confirmation), 6 had SD (40 mg, n=3; 80 mg, n=2; 120 mg, n=1), and 5 had PD as best response (40 mg, n=3; 80 mg, n=1; 120 mg, n=1). All patients with PR had EGFR exon 20 insertions. **Conclusion:** TAK-788 exhibits antitumor activity in patients with EGFR exon 20 insertions with an AE profile consistent with other EGFR TKIs. Phase 2 will begin after determination of the RP2D, with 4 molecularly defined cohorts in NSCLC. Updated data will be presented, including the recommended phase 2 dose (RP2D).

(See next page)

Baseline Characteristics							
	5 mg (n=4)	10 mg (n=5)	20 mg (n=5)	40 mg (n=6)	80 mg (n=7)	120 mg (n=7)	Total (n=34)
Mutation type,[a] %							
Common EGFR mutations (exon 19 deletion / L8585R)	25	20	0	0	0	0	6
EGFR-T790M+	0	0	0	0	14	0	3
EGFR exon 20 insertion	50	40	60	83	71	57	62
HER2	0	20	40	17	14	29	21
[a] One patient (20 mg) had both EGFR and HER2 mutations; 1 patient (80 mg) had EGFR exon 20 insertion + T790M.							

Keywords: EGFR exon 20 mutation, EGFR tyrosine kinase inhibitor, HER2 mutation

P1.13 TARGETED THERAPY
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.13-45 COEXISTENCE OF ACTIVATING BRAF AND KRAS MUTATIONS IN LUNG CANCER PATIENTS

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Background: Activating mutations in both KRAS and BRAF gene can stimulate mitogen-activated protein kinase (MAPK) signaling. So BRAF and KRAS mutations are generally mutually exclusive from each other, acting as an alternative oncogenic driver in NSCLC. There was occasionally case reports of coexistence of BRAF and KRAS mutations in colorectal cancer, lung squamous cell carcinoma. However, to our knowledge, there was no systemic studies in this area **Method:** We retrospectively analyzed mutation profiling of 2000 consecutive lung cancer samples in our institute. Mutation profiles were analyzed using hybridization capture based next-generation sequencing (NGS), which enables the simultaneous detection of single-nucleotide variants, insertions/deletions, rearrangements, and copy-number alterations of at least 59 genes (range 59 – 1021 genes). **Result:** Sixty-three patients with activating BRAF mutation was analyzed in the study, including 48 lung adenocarcinoma, 3 squamous cell lung cancer, 1 lung adenosquamous cell carcinoma, 1 lung large cell carcinoma and 10 lung cancer patients with unspecified pathology. The most common BRAF mutation, BRAF V600E, was identified in 33 patients. BRAF Non-V600E mutation was identified in 30 patients, including G469A/V/R (7), D594G/N (6), K601E/N (6), G464V (3), G466A/V (3), G596R (2), K483E (1), N486_P490del (1) and N581S (1) mutations. Among the 63 patients, 8 (12.7%) had coexistence of activating KRAS mutation. Concurrence of activating KRAS mutation (G12A/D/S, G13D) was identified in 3 of the 30 patients with BRAF V600E mutations, with 2 of the 3 patients had previous EGFR-TKI treatment. The patient with KRAS G12S, G13D, and BRAF V600E mutation but without EGFR sensitive mutation had poor response to chemotherapy. On the contrary, activating KRAS mutation (G12D/V, G13D, A146V) was identified in 5 of the 33 patients with BRAF non-V600E mutation, with only one patient had EGFR-TKI sensitive mutation and previous EGFR-TKI treatment. **Conclusion:** Coexistence of activating KRAS mutation is not uncommon in NSCLC patients with BRAF mutations, especially in patients with non-V600E mutations. Therefore, therapeutic choice for patients with BRAF non-V600E mutation need comprehensive consideration of companion mutations. Moreover, previous EGFR-TKI may increase the incidence of concurrence of generally mutually exclusive mutations.

Keywords: BRAF, coexistence, KRAS

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.14-01 CURRENT PRACTICES IN THE MANAGEMENT OF MALIGNANT PERICARDIAL EFFUSIONS: A SURVEY AMONGST MEMBERS OF THE EUROPEAN SOCIETY OF THORACIC SURGEONS.

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Background: Malignant pericardial effusion (MPE) is a rare presentation, is associated with a high morbidity and mortality, and may be challenging to manage. We sought to determine the current practice in the management of MPE among members of the European Society of Thoracic Surgeons (ESTS). **Method:** A cross-sectional survey examining the case volume, initial workup, urgent and non-urgent management of MPE was developed by the authors, following a review of the literature. The survey was circulated to ESTS membership in an internet-based survey format, between February and April 2016. **Result:** 136 consultant thoracic surgical colleagues responded; representing 43 countries across 5 continents, and with an average (mean±SD) of 14±9 years' independent practice. Annual volume of MPE referral was 9±12 cases (median, range = 5, 0 to 80). Echocardiography (88%), computed tomography (85%) and pericardial fluid cytology (54%) are the preferred initial investigations. In clinically stable patients, pericardiocentesis is the preferred (60%) intervention in first-presentations; with 80% of patients with recurrent effusions being offered pleuro-pericardial fenestration (66% thoracoscopically, 14% thoracotomy). 43 to 50% of respondents would use an intrapericardial sclerosant as part of their management of recurrent MPEs, depending on primary pathology. The preferred approach options in patients with cardiac tamponade are ultrasound-guided pericardiocentesis (56%), subxiphoid pericardiotomy (26%) and landmark pericardiocentesis (11%). Only 24% of respondents felt that their practice was informed by published clinical guidelines, with 53% expressing a need for updating of current guidance. **Conclusion:** There is much variation, and reported uncertainty, in the management of MPEs in clinical practice. There is, additionally, lack of engagement with currently-available clinical guidance.

Keywords: Pericardial Effusion, Complications

P1.14-02 PREDICTING STENT FAILURE IN MALIGNANT ESOPHAGEAL OBSTRUCTION

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Background: Esophageal malignant obstruction is commonly caused by esophageal cancer and seldom caused by malignant disease not originating from the esophagus. Malnutrition and feedin intolerance are commonly present. Palliation is commonly achieved with insertion of an esophageal stent, which has been deemed safe and effective in previous trials. Our objective was to assess the factors predicting the failure of stent treatment in malignant obstruction of the esophagus. **Method:** This was a retrospective cohort study with primary end point of stent failure. Stent failure is defined here as any major complication caused by the stent (perforation, fistula, etc.), migration of the stent the stomach or any need for non-planned urgent removal of the stent. Patient demographic details, stent insertion details (indication, date, location, size, type of stent), complications related to stent-insertion, operations associated with stent insertion, and possible time of death were collected. **Result:** Between March 2005 and December 2013 there were 410 esophageal stents placed for treatment of malignant obstruction. The most common pathology was esophageal cancer (N = 333, 81.2%), lung cancer was the cause in 44 (10.7%) and mesothelioma and breast cancer were found were both found in 5 patients (1.2%), the remaining 23 patients had cancers of various histologies. Median OS was 149 days from stent insertion (IQR: 63-297 days). Stent failure rate in the first 6 months was 27.3% (N = 112) with median time to failure being 46 days (IQR: 9-105). Cox multivariate regression analysis was done by backwards elimination method with a p-value limit of 0.2, the results are shown in Table 1.

Table 1 Multivariate Cox regression analysis of factors affecting stent failure

	HR	95% CI	p
Age	0.96	0.97-1.00	0.112
Proximal stent location*	1.68	1.15-2.44	0.00714

*Top edge under 25 cm from incisors

Conclusion: In the setting of malignant obstruction of the esophagus, stent failure rate is related to the location of the inserted stent. More proximal stents have a higher rate of failure in multivariate analysis (HR =1.68, p = 0.00714).

Keywords: thoracic malignancy, Esophageal obstruction, Esophageal stents

P1.14-03 PHASE II TRIAL OF AMRUBICIN AND CISPLATIN CHEMOTHERAPY FOR INVASIVE THYMOMA: WJOG5509L

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Background: Platinum and anthracycline combination chemotherapy has been considered as the standard treatment for invasive thymoma for a long time. The clinical activity of amrubicin (AMR)—an anthracycline agent—has been previously reported in the treatment of small cell lung cancer (SCLC). The aim of this study was to evaluate the efficacy and safety of the combination of AMR and cisplatin (CDDP) in patients with advanced or recurrent invasive thymoma. **Method:** s: Patients were eligible for inclusion in the study if they met the following criteria: were chemo-naive; not amenable to curative surgery or radiotherapy; and presented with histologically confirmed invasive thymoma in each site. The patients received AMR (35 mg/m^2, on days 1–3) and CDDP (60 mg/m^2, on day 1) every 3 weeks, for up to 4 cycles. The primary endpoint was the objective response rate (ORR) assessed by an independent review, and the secondary endpoints were overall survival (OS) and toxicity profile of the patients. Based on the SWOG 2-stage design, the planned sample size of 40 patients was determined to reject the ORR of 60% under the expectation of 80% with a power of 0.85 and a type I error of 0.05. This trial is registered with the UMIN Clinical Trials Registry, number UMIN000003933. **Result:** s: From August 2010 to November 2014, a total of 26 patients were enrolled at 14 institutions in Japan. During the planned interim analysis in April 2014, the ORR of the 20 patients who had been enrolled so far, was assessed via independent review and found to be 55.6% (11/20), resulting in the early termination of this study because of its futility. In the final assessment, the ORR was 54.2% (95% confidence interval, 32.8–74.4) and the disease control rate was 95.8%. The OS did not reach the median value. The major grade 3 or 4 toxicities noted were neutropenia (96.2%), anemia (26.9%), anorexia (11.5%) and febrile neutropenia (26.9%), albeit these were transient and manageable. There was one treatment-related death. **Conclusion:** s: The combination of AMR with CDDP had minimal activity on invasive thymoma. Thus, we do not recommend further study of this regimen.

Keywords: Thymoma, chemptherapy, amurubicin

P1.14-04 STEREOTACTIC BODY RADIATION THERAPY FOR PLEURAL RECURRENCES OF THYMOMA

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Background: Pleural recurrences are not uncommon as a result of thymoma evolution; yet there is no therapeutic standard for their treatment. The purpose of this study was to evaluate the efficacy and tolerability of stereotactic body radiation therapy (SBRT) for the treatment of pleural metastasis. **Method:** A single institution retrospective study of the patients treated with SBRT using Novalis and VMAT, with doses of 30Gy in 5 fractions or 40Gy in 10 fractions. Treatment responses were evaluated using TDM and/or TEP TDM **Result:** In the period 2014-2017, 10 patients (6 women, 4 men) with a median age of 51 and a total of 21 pleural recurrences were treated with SBRT. Initial Masaoka-Koga stages were: 1 I, 3 IIb, 3 III, 2 IVa and 1 unknown. Nine of them had previously been treated for other pleural recurrences (7 had surgery, 2 conformational RT and 3 chemotherapy). All patients were treated for one to three recurrence locations, either successively or at the same time. At the time of last follow-up, only one patient had died following the metastatic evolution of their thymoma. With a median follow-up for the lesions of 20 months, local control was very good, since all lesions were reduced to a smaller, non-progressive mass or in complete metabolic response. No patient developed Grade 3 or higher acute or late toxicity. **Conclusion:** Treatment of pleural recurrences of thymoma using SBRT with moderate doses allowed for good local control without increased toxicity, constituting a good alternative to surgery. This treatment could furthermore delay the use of chemotherapy.

Keywords: pleural metastasis, Thymoma, SBRT

P1.14-05 THE ASSOCIATION OF PULMONARY FUNCTION WITH SURVIVAL AFTER TREATMENT IN PATIENTS WITH ESOPHAGEAL CANCER

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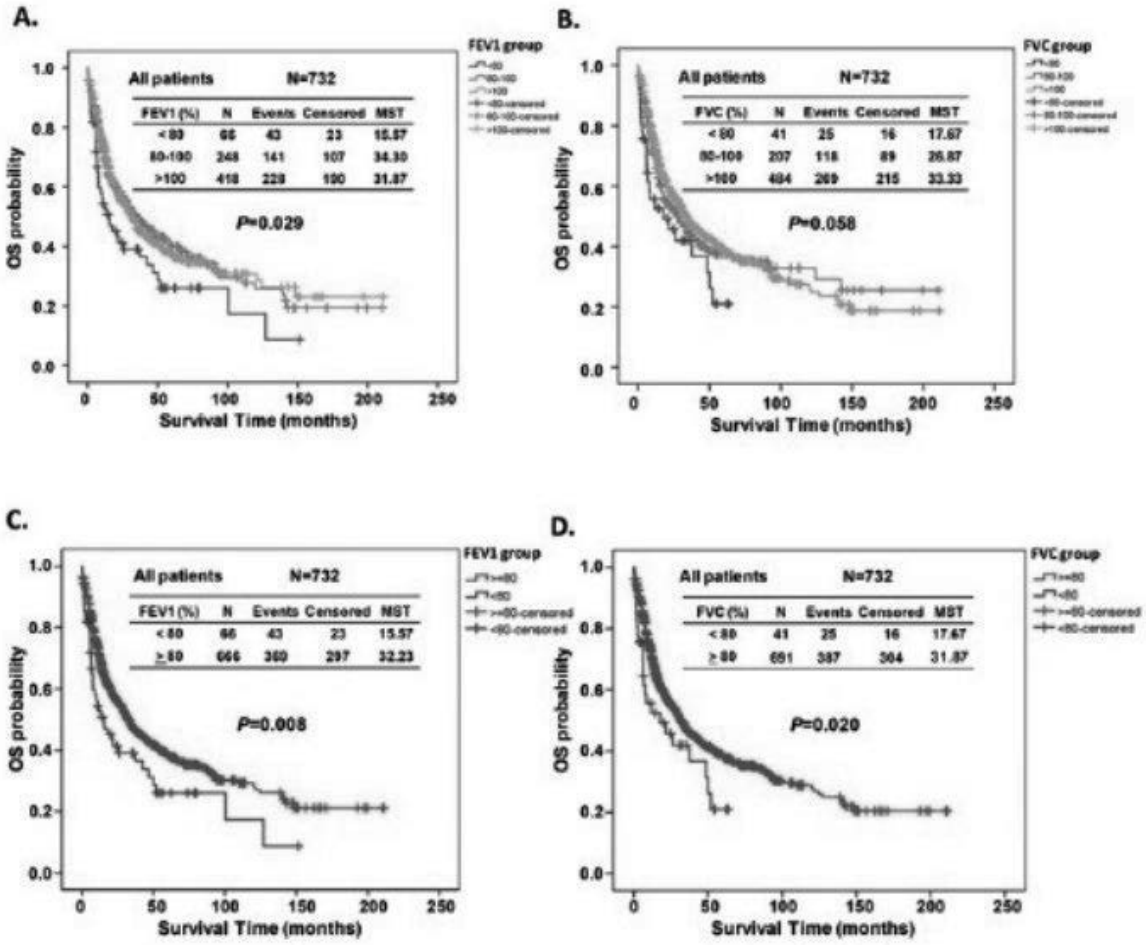
Background: Previously studies have found that inadequate pulmonary function of the patients with esophageal cancer can associate with higher risk of postoperative pulmonary complications which can lead to a higher risk of mortality in the perioperative period or long term follow-up. In this study, we investigate the prognostic effect of pulmonary function for the patients of esophageal cancer after treatment. **Method:** From 2004~2016, 732 esophageal cancer patients underwent surgical treatment were enrolled. They received pulmonary function before treatment, and 542 (74.04%) underwent pre-operative concurrent chemoradiotherapy (CCRT) before surgery. Patients were divided into three groups by pulmonary function level (FEV<80%, inadequate pulmonary function; 80% < FEV1 < 100%, adequate pulmonary function; FEV1 > 100%, well pulmonary function). We use multivariate analysis including all of the possible factors to evaluate overall survival and progression-free survival after surgery. **Result:** As the result, we found that cancer staging, neo-adjuvant CCRT, operation method and pre-operative FEV1 were found statistically significant for survival after treatment. As compared to patients with FEV1 less than 80% of prediction, patients with EFV1 more than 80% had an around thirty percent of decreasing mortality rate after surgery (p = 0.034). The cox-regression with survival analysis also revealed that patients with better lung function, had significantly better progression-free survival (P<0.05, respectively) than those with poor lung function. Besides, the grouping by CCRT-pCR (pathologic complete response) also had similar results. It maybe due to pulmonary function is a important immunological factor in those esophageal cancer patients.

Conclusion: Although the patient selection, surgical technique, and other postoperative management have been markedly improved in recent years, the morbidity rate after esophagectomy for esophageal cancer remains high. Recent studies lead us pay attention to the perioperative and postoperative care, but they may ignored the pulmonary function disturbance is one of the major contributing factor for long-term and progression-free survival.

Keywords: esophageal cancer, Pulmonary Function, survival



P1.14-06 TREATMENT OUTCOMES OF PATIENTS WITH THYMIC CARCINOMA: A MONOCENTRIC EXPERIENCE OF SEQUENTIAL REGIMENS MODALITY

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Background: Thymic carcinoma (TC) compared with thymoma has a lower incidence rate and is more likely to be diagnosed in advanced-stage disease, with a worst prognosis. Platinum combination regimen is widely recognized as the best treatment in the first line setting, followed by other systemic therapies, such as cytotoxic drugs and target agents, with the aim of achieving control disease and prolonging survival. Since there is limited information about the optimal treatment modality in TC, this study aims to identify the most promising therapeutic sequence in terms of efficacy and toxicity profile. **Method:** We conducted a monocentric retrospective analysis of patients (pts) with un-resectable-metastatic TC, referred to our Rare Tumors Reference Center over a 15-year period. All pts with confirmed histological diagnosis, treated with at least three lines of therapy were included in the analysis. For each identified sequence treatment, progression free survival (PFS) and overall survival (OS), according to RECIST 1.1 and toxicity profile according to CTCAE v 4.0, were determined. **Result:** Among 52 patients with advanced TC, 17 of them (32.6%) treated with at least three lines of chemotherapies and target agents (imatinib, sunitinib, everolimus) were included in the study. Three main therapeutic sequences were identified: 1) platinum-based therapy - platinum-based therapy – target agent (7 pts); 2) platinum-based therapy – capecitabine and gemcitabine combination-therapy – target agent (5 pts); 3) platinum- based therapy – target agent – no platinum-based chemo (5 pts). The median OS from the start of first-line chemotherapy was 67 months with no significant difference among sequences, with an OS respectively of 83, 67 and 106 months (p< 0.99). Also for PFS, with a median value of 33 months, there was registered no significant difference, with respectively 33, 38 and 32 months (p< 0.99). A different toxicity profile was instead revealed, with no adverse events more than grade 2 for the second and third sequence, and, conversely, toxicity of grade 3 registered in more than 50% of the pts in first sequence. Asthenia, emesis and pancytopenia which required hospitalization in 3 pts, were the most frequent. **Conclusion:** To our knowledge, this is the first data analysis of sequential regimens modality in patients with advanced TC. Since the efficacy of each treatment sequence did not vary significantly, we suggest to administer the therapy sequence with the better toxicity profile. Moreover, considering the median survival outcome reached, we support the need to refer these patients to reference center with high expertise.

Keywords: Thymic carcinoma, treatment sequence modality, platinum-based chemotherapy

P1.14-07 INTRAOPERATIVE DETECTION OF CIRCULATING TUMOR CELLS IN PULMONARY VENOUS BLOOD DURING METASTASECTOMY FOR COLORECTAL LUNG METASTASES

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Background: Circulating tumor cells (CTC) have been studied extensively in various tumor types and are a well-established prognosticator in colorectal cancer (CRC). This is the first study to isolate CTC directly from the tumor outflow in secondary lung tumors. **Method:** From 24 patients with CRC who underwent pulmonary metastasectomy in curative intent blood was drawn intraoperatively from the pulmonary vein (tumor outflow). In 22 samples CTC-enumeration was performed using CellSieve™-microfilters and immunohistochemical- and Giemsa-staining. Additionally 10 blood samples were analyzed using the CellSearch®-System. **Result:** We could isolate more CTC in pulmonary venous blood (total 41, range 0-15) than in samples taken from the periphery at the same time (total 6, range 0-5, p=0.09). Tumor positive lymph nodes correlated with presence of CTC in pulmonary venous blood as in all cases CTC were present (p=0.006). **Conclusion:** Our findings suggest a tumor cell release from pulmonary metastases in CRC and a correlation of CTC isolated from the tumor outflow with established negative prognostic markers in metastasized CRC. The presented data warrant further investigations regarding the significance of local tumor compartments when analyzing circulating markers and the possibility of tumor cell shedding from secondary lung tumors.

Keywords: Circulating tumor cells, Secondary Lung Tumors

P1.14-08 THE USEFULNESS OF THE HEMICLAMSHELL THORACOTOMY IN THORACIC SURGERY

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Background: The antero-lateral approach provides good exposure of the cervicothoracic region and enables removal of lesions that develop in this complex anatomic area. **Method:** We retrospectively evaluated the indications and outcomes of the hemiclamshell approach in patients undergoing tumor resection in thoracic surgery. Eleven lung cancer patients and one non seminomotous germ cell tumor of the mediastinum who underwent tumor resection via hemiclamshell approach in our department, between 2007 and 2018 were studied retrospectively, analyzing the indications, morbidity and outcome. **Result:** The indications were apical tumors with vascular invasion in four, giant mass (10, 17, 21cm in tumor diameter) with superior or inferior vena cava invasion in three, aortic arch invasion in one, sternal invasion in one, mediastinal lymph node metastasis in the left upper lung cancer in one, and pulmonary artery aneurysm after left upper lobectomy in one. In eleven lung cancer patients, combined resection of the neighboring organ was performed in nine organs among eight patients: subclavian artery in two, carotid artery in one, aorta in one, superior vena cava in one, chest wall in two, phrenic nerve in one, and pericardium in one. One-month mortality was 0%. Operative morbidity was observed in four patients (33%): two patients suffered from deep wound infection, one from a chylothorax, and one from pleural effusion. R0 resection was achieved in eleven patients. **Conclusion:** The hemiclamshell approach was associated with relative high morbidity rate but no mortality. Hemiclamshell is suitable for tumours of the cervicothoracic junction with vascular invasion and giant tumors, providing good access for control of the large vessels including pulmonary artery and vein.

Keywords: Hemiclamshell approach, the cervicothoracic junction

P1.14-09 OUTCOME AFTER LUNG RESECTION FOR PRIMARY LUNG CARCINOMAS/METASTASIS IN PATIENTS WITH PERFORMED TOTAL LARYNGECTOMY FOR LARYNGEAL CARCINOMA

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Background: Total laryngectomy remains the treatment of choice for recurrent / persistent laryngeal carcinoma after radiotherapy or chemoradiotherapy. These patients with laryngeal carcinoma are at risk for developing both pulmonary metastasis and second primary lung cancer. Because of the persistent tracheostomy, postoperative management after lung resection is usually a difficult process. Ineffective evaluation of preoperative pulmonary functions, failure of single lung ventilation due to short trachea, inadequate respiratory physiotherapy are frequently encountered problems. The purpose of this study is to evaluate the outcomes of lung resection in patients with persistent tracheostomy due to laryngeal carcinoma. **Method:** Between Jan 2006-Jan 2016, the data of 9247 patients who underwent lung resection at three different centers were retrospectively examined. The study group consisted of 68 patients (62 male, mean age 59.49 ± 11.4 (31-82)) who had persistent tracheostomy due to laryngeal carcinoma. Patient preoperative evaluation parameters, operation techniques, postoperative complications and survival were analyzed. Result: The mean time between the two operations was 55.68 ± 64.8 (3-312) months. Pulmonary tumors were located in the upper lobe in 53 patients (77.9%), in the lower lobe in 11 patients (16.1%), in the middle lobe in 2 patients (3%) and bilaterally in 2 patients (3%). Lung resection was performed with thoracotomy in 53 patients (78%) and videothoracoscopy in 15 patients

(22%). Extent of lung resection was sublobar resection in 28 patients (41.2%), lobectomy in 37 patients (54.4%) and pneumonectomy in 3 patients (4.4%). Histopathological examination revealed squamous cell carcinoma in 53 (78%) patients and other non-small cell lung carcinomas in 15 (22%) patients. Postoperative complications were present in 24 patients (35.3%). The most common complications observed were prolonged air leak in 7 patients (10,3%), space in 6 patients (8.8%) and pneumonia in 5 patients (7.3%). Mortality was seen due to respiratory insufficiency in 2 (2.9%) patients who underwent right lower bilobectomy and right pneumonectomy. The 5-year survival rate after lung resection was 31.6% and the median follow-up time was 32 months ± 8.45. **Conclusion:** This study shows that the presence of a tracheostomy should not be considered a risk factor for pulmonary resection if there is close cooperation between pulmonary medicine, anesthesia and thoracic surgery clinics. In these patients, besides other lung resections, videothoracoscopic lung resections can be performed safely and good oncologic results can be obtained.

Keywords: Lung Resection, Pulmonary Metastasis, Laryngeal Carcinoma

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
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P1.14-10 SURGICAL TREATMENT OF A RARE CASE OF CLEAR CELL CARCINOMATOUS TRANSFORMATION OF A DIAPHRAGMATIC ENDOMETRIOSIS FOCUS

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Background: Thoracic endometriosis is an ectopic, unusual localization of endometrial tissue in endothoracic organs. The development of thoracic endometriosis can be determined by the embolization of endometriotic foci to the lung by lymphatic, hematic or trans-diaphragmatic way. We report a rare case of carcinomatous transformation of a diaphragmatic endometriosis focus, successfully treated with surgery. **Method:** A 46-year old woman, with a history of previous operation for bilateral endometriotic pelvic cyst, presented to our institution with dyspnoea and massive right pleural effusion, which was treated with chest drainage. After drainage, chest and abdomen computerized tomography (CT) and magnetic resonance imaging (MRI) showed a large (7 x 6 cm), roundish, inhomogeneous, capsulated mass of the right hemidiaphragm, causing compression of the adjacent lung and liver. Fiberbronchoscopy showed an extrinsic compression of subsegmental bronchi of the basal pyramid of the right lung. After cardio-respiratory function evaluation, the patient underwent videothoracoscopic pleural biopsies with frozen section negative for malignancy, therefore we converted in antero-lateral thoracotomy and a radical surgical resection of the diaphragmatic mass, en-bloc with the adherent and apparently infiltrated lung and hepatic parenchyma, was performed. **Result:** Postoperative course was uneventful. Histopathology revealed a clear cell carcinoma deriving from a malignant transformation of an ectopic diaphragmatic endometriosis focus; Ki67 was > 50%; PI3KCA and BRAF genes were not mutated. Total body 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT showed bilateral increased ovarian uptake, thus the patient underwent radical abdominal hysterectomy, with diagnosis of endometriosis, and subsequent adjuvant chemotherapy for the diaphragmatic clear cell carcinoma. Total body CT scan at 7 months from surgery shows neither local recurrence, nor distant metastases. **Conclusion:** Thoracic endometriosis requires a multidiciplinary approach and management. In our experience, surgery represented the treatment of choice, in order to ensure oncological radicality, in a young patient with a rare condition of carcinomatous transformation of a diaphragmatic endometriosis focus, which should be considered among the possible evolutions of endometriosis. To the best of our knowledge, this is the first reported case of radical surgical treatment of a clear cell carcinomatous transformation of a diaphragmatic endometriosis focus.

Keywords: Diaphragm, clear cell carcinoma, thoracic endometriosis

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
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P1.14-11 THE EXPRESSION PATTERN OF PROGRAMMED DEATH-LIGAND 1 ACCORDING TO THE PATHOLOGICAL TYPE OF MALIGNANT THYMIC EPITHELIAL TUMORS

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Background: Malignant thymic epithelial tumors (TETs) have pathological types ranging from low-grade to high-grade malignancy, while the pattern of PD-L1 expression remains unclear. We investigated PD-L1 expression in TETs and verified the pattern of expression associated with the pathological type. **Method:** We examined 66 malignant TETs. Immunohistochemical evaluation of PD-L1 expression was performed using anti-PD-L1 antibody (SP263). We calculated the tumor cell positive rate (Total Proportion Score: TPS) of PD-L1 expression. The discrimination of the tumor region was confirmed by immunostaining with anti-pan-cytokeratin antibody (AE1AE3). PD-L1 expression was examined for each type of histological classification of TETs. We classified a High TPS group (H group) and Low TPS group (L group) using a TPS cut-off value of 25% and examined the correlation with clinical background and prognosis. We classified Type B2, B3, and thymic carcinomas into a high-malignancy group. PD-L1 expression was also digitally analyzed based on Whole Slides Imagings (WSI) for objective analysis as Digital TPS. **Result:** We identified WHO histological types (Type A/AB/B1/B2/B3/metaplastic tumor/thymic carcinomas = 8/19/5/15/6/2/11). In Type A, PD-L1 expression was low in most cases and the median of TPS was 22%. In Type AB, Type A and B regions showed low and high TPS, respectively, and the median was 23%. In Type B1, TPS was low in most cases and the median was 26%. In Type B2, TPS was higher than that in Type B1, and the median was 69%. In Type B3, TPS was high (>50%) in all cases and the median was 86%. The PD-L1 expression of thymic carcinomas ranged from low to high and the median was 28%. Metaplastic tumors showed scanty PD-L1 expression. The High PD-L1 group showed more advanced disease stages according to the Masaoka stage and TMN classification, and the TPS of Type B2 and B3 was significantly higher than that of Type A, AB and B1. The disease-free survival rate was significantly lower in the H group than that in the L group. When we examined the prognosis in high-malignancy group, there were no significant differences in the disease-freel and overall survival rates by TPS. Based on measurements using WSI, Digital TPS correlated with visual TPS (correlation coefficient=0.85,*p*value<0.001). **Conclusion:** TETs had the characteristic features of the PD-L1 expression according to histological types. Type B2 and B3 thymomas was higher PD-L1 expression than the other types of TETs.

Keywords: PD-L1, TETs, Malignant thymic epithelial tumors

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
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P1.14-12 GTF2I MUTATION IN THYMOMAS: INDIAN AND GERMAN STUDY

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Background: Point mutation (L404H) of GTF2I gene on chromosome 7 has been identified in thymic epithelial tumors; most predominantly in A and AB histotypes and associated with good prognosis. The objective of this retrospective analysis was to assess the frequency of GTF2I mutation in Indian and German thymomas and correlate with WHO histotypes. **Method:** A cohort of Indian and German thymomas of different histotypes was retrieved from the archives. Clinicopathological details were obtained from case files. Hematoxylin-eosin stained slides were reviewed and histopathological subtypes along with Masaoka-Koga staging were determined. The available blocks were selected for DNA extraction. Tumors rich in cancer cells (>50%) were evaluated for *GTF2I* mutation using Sanger sequencing. Primer for Exon 15 of GTF2I gene was designed using NCBI and Primer 3 (v.0.4.0) software. Results were compiled and analysed. **Result:** A total of 126 resection specimens were retrieved comprising 23 (18.2%) Type A, 30 (23.8%) Type AB 16 atypical A/AB (12.6%) and 30 (23.8%) Type B thymomas. Remaining 27 cases belonged to 18 thymic carcinomas, 2 sclerosing mediastinitis, 2 metaplastic thymomas, 1 thymolipoma, and 4 non-thymomatous lesions. Out of a total of 69 A/AB thymomas, 53 (76.8%) were positive including 88% (22/25) Indian and 65.9 % (29/44) German cases. 26% (18/69) A/

AB were negative. All Indian B histotypes (n=9) were negative, whereas 4 German B thymomas (4/21; 19%) were positive for GTF2I mutation. No mutations were found in non-thymomatous pathologies. Among 34 Indian cases, there was equal gender distribution, median age was 48 years and 31 were in lower stage groups (Stage I and II). Clinical details and follow up available in 17 of 34 cases had a median follow up of 14 months and revealed presence of myasthenia gravis in 76.5% cases. Recurrence seen in 3 cases revealed high risk morphology (2 Type B histotypes and 1 atypical A) and one death of Type A was due to myasthenic crisis. **Conclusion:** The similarity of Indian and German (and previously published American) cohorts of A/B and type B thymomas in term of GTF2I mutation frequencies suggests a thymus-specific microenvironmental mutagenic mechanism and argues against a relevant impact of environmental or ethnic (germ line) factors. The unusually high prevalence of Myasthenia gravis among the Indian thymomas warrants further analysis to exclude referral bias.

Keywords: thymoma, GTF2I, Indo-German

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
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P1.14-13 PD-L1 IMMUNO-EXPRESSION ASSAY IN THYMOMAS: A STUDY FROM INDIA

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Background: Programmed death ligand 1 (PD-L1), an immune check point inhibitor, is known to be expressed in several malignancies and is being considered as a prognostic factor and a potential immunotherapeutic target. Recent development of anti-PD-1/L1 antibodies has demonstrated anticancer activity of these agents in various neoplasms. The aim of this study was to characterize PD-L1 expression in thymomas and to determine whether PD-L1 represents a therapeutic target in unresectable thymomas. A correlation with clinicopathological features and previously published studies in the literature was established. **Method:** Tissue microarrays were prepared from selected blocks of thymomas and immunohistochemistry (IHC) using SP263 clone of PD-L1 was performed. Cases were considered as PD-L1 positive or negative based on percentage of stained thymic epithelial cells; if these were <25 or >25 percent. Results were compared clinically and with previously published studies using *Google* and *Pubmed* search engines. **Result:** Of 84 cases of thymoma, 69 (82.1%) revealed PD-L1 positivity in more than 25% cells. 94.23% of type B thymoma subtypes (B1/B2/B3) were PD-L1 positive (*P*<.001). There was no correlation of PD-L1 with age, gender, myasthenia gravis, the tumor size or stage of disease. So far, 9 studies of PD-L1 expression in thymic epithelial tumors are available in the literature; most of which showed PD-L1 expression in higher stage and B histotype however percentage positivity varied from 53.7% to over 90%. **Conclusion:** PD-L1 expression is frequent in type B (B1/B2/B3) thymomas. It can be easily evaluated by IHC even on small biopsies in unresectable cases. PD-L1 immunoassay will serve as a potential indicator for benefit from anti-PD-L1 antibody immunotherapy in thymomas thereby enabling improved clinical evaluation as well as prognostic stratification of patients.

Keywords: Thymoma, PD-L1 expression, Immunohistochemistry

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
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P1.14-14 HISTOTYPING OF INDIAN THYMOMAS: A COMPREHENSIVE CLINICOPATHOLOGIC STUDY

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Background: Thymomas are rare, but most common anterior mediastinal lesions. The WHO 2015 classification has defined criteria of classifying these into various subtypes. The histomorphologic spectrum of thymic epithelial tumors (TET) in Indian population has not been explored. We aimed to study the histomorphology of TETs in the Indian patients with clinico-pathological correlation. **Method:** It was a retrospective, tertiary referral centre, study. All cases of morphologically confirmed, surgically resected specimens and small biopsies diagnosed as TETs since 2009 were included. Clinical details and histology slides were reviewed using the Modified Masaoka-Koga staging system and WHO 2015 classification. Clinico-pathological correlation and survival analysis was done. Comparative review from other published Indian studies was performed. **Result:** We identified 219 cases of TETs (138 resections and 81 biopsies). Most common histo-morphologic type was B2 and most frequent stage was I. Clinically, higher stage tumors were found mostly in men (P=.008) and these were type B thymomas (P=.01). Association of myasthenia gravis was prevalent in women (P=.02) and in lower stages (P=.04). Survival analysis revealed significant association between recurrence and tumor stage. Although thymic carcinoma was diagnosed on biopsy, no resectable case was identified. **Conclusion:** Literature lacks detailed histotyping of TETs from India. Indian thymomas are most commonly stage I tumors of B2 and AB histotypes. Resected thymic carcinomas are conspicuously absent in Indian cohort. We hope that broadening the spectrum of recognized pathologic manifestations of Indian thymomas will help global database for future studies.

Keywords: histotyping, Thymoma, India

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
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P1.14-15 PREVALENCE OF MEDIASTINAL TUMORS USING LOW-DOSE SPIRAL COMPUTED TOMOGRAPHY IN HEALTHY POPULATION

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Background: Compared with lung tumors, mediastinal tumors occur less frequently, but the precise incidence of mediastinal tumors in healthy populations is still unknown. Chest radiographic screening is a commonly used conventional method for the detection of thoracic tumors. However, early phase detection of mediastinal tumors is difficult due to the location of these tumors. Using low-dose spiral computed tomography (LDCT), this study aimed to investigate the precise incidence of mediastinal tumors, including that of small early phase masses that cannot be detected by radiography. **Method:** s: Among people who underwent medical check-ups consecutively for 8 years (from April 2010 to March 2018) at our institution, those who also underwent LDCT were enrolled in this study. In total, this study included 3,414 individuals. The presence of mediastinal tumor in these individuals was investigated. **Result:** s: Thirty-two cases of mediastinal tumor (0.9%) were detected using LDCT, of which 20, 5, 4, and 3 were anterior, superior, middle, and posterior mediastinum tumors, respectively; this was a higher prevalence than that reported in our country (0.1%-0.8%). Of the 32 cases, 17 were further examined, and finally, in some of these cases, the tumors were successfully surgically resected. The remaining 15 cases were followed-up periodically owing to the presence of small benign nodular lesions. Among the 32 cases, tumors of only 3 cases were detected using chest radiography. **Conclusion:** The prevalence of mediastinal tumor is higher than that previously reported in our country. Compared with chest radiography, LDCT contributes to the early phase detection of mediastinal tumors.

Keywords: mediastinal tumors, computed tomography, prevalence

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
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P1.14-16 DNA METHYLATION OF GNG4, GHSR, HOXD9 AND SALL3 GENES PREDICT MALIGNANT BEHAVIOR OF THYMIC EPITHELIAL TUMORS

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Background: Our previous studies showed that DNA methylation of cancer-related genes-DAP-K, p-16, MGMT, HPP1 genes in thymic carcinoma (TC) was higher than that in thymoma (Lung Cancer 64:155-, 2009, 83:279-, 2013). Genome-wide screening for aberrantly methylated CpG islands was performed in 7 TC samples and 8 type-B3 thymoma samples using HumanMethylation 450 K BeadChip (Illumina, Santa Clara,

CA, USA) analysis. We identified 22 genes as commonly hypermethylated in TC comparing with B3 thymoma. We picked up 4 cancer-related genes; GNG4, GHSR, HOXD9 and SALL3 from those genes as the most significant hypermethylated gene. **Method:** In total, 47 thymic tumour samples (thymoma; 31, carcinoma; 16) and 18 paired normal tissues were obtained from patients with histologically proven thymic epithelial tumor (TET), who underwent surgery at the Tokushima University Hospital (Tokushima, Japan) between 1990 and 2016. The methylation status of TET samples was validated by pyrosequencing. **Result:** DNA methylation of GNG4 gene in TC was significantly higher than that in thymoma (34.6% versus 8.9%). In other 4 genes, DNA methylation in TC was significantly higher than that in thymoma (GHSR; 59.3% vs 34.2%, HOXD9; 37.3% vs 12.3%, SALL3; 33.5% vs 7.2%). In GHSR and HOXD9 genes, DNA methylation in thymoma was significantly higher than that in normal thymus. And in GNG4 and SALL3, DNA methylation in thymoma was similar to that in normal thymus. **Conclusion:** DNA methylation of several cancer-related genes in TC was significantly higher than that in thymoma or normal thymus. Epigenetic alteration may be related to progression or malignancy in TET.

Keywords: DNA methylation, Thymoma, Thymic carcinoma

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
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P1.14-17 IDENTIFICATION OF MOLECULAR SUBTYPES OF THYMIC EPITHELIAL TUMORS AND NOVEL TREATMENTS USING A COMPUTATIONAL BIOLOGICAL MODEL

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Background: The histologic classification of thymic epithelial tumors (TETs) is based on the description of both epithelial cell morphology and relative abundance of lymphocytes. Here, we used a computational biological model (CBM) approach on The Cancer Genome Atlas (TCGA) dataset to identify molecular subtypes of TETs and associated predicted therapeutic options. **Method:** Whole exome sequencing and gene expression data from the TCGA TET dataset (n = 102) along with the IUTAB-1 cell line was input into CBM software (Cellworks Group, San Jose, CA) to build an unsupervised classification model beyond molecular subtypes previously reported (Loehrer PJ ASCO 2017). The CBM generated a disease specific protein network map using PubMed and other online resources. Using computer simulation, disease biomarkers unique to each tumor were identified within the protein network maps. Among the tumors simulated, 6 molecular clusters were identified (TH1-TH6). The CBM digital drug library was tested against these molecular subtypes and the cell growth score (i.e. cell proliferation, viability, and apoptosis) was analyzed. **Result:** The CBM identified 6 molecular subtypes among 102 TET patients. Among subtypes with a *GTF2I* mutation, TH1, TH4, and TH6 also had chromosomal aberrations in chromosome 22 and 9. Deletion of chromosome 22 was present in TH1, deletion of chromosome 9 in TH4 and TH6, and also amplification of chromosome 22q in TH4. Among *GTF2I* wild type subtypes, chromosome 22q deletion and complex cytogenetics were present in TH2, trisomy of chromosome 1 in TH3, and *HRAS* mutations and chromosome 2 amplification in TH5. The IUTAB-1 cell line had a *GTF2I* mutation and mapped to the TH4 molecular subtype. The CBM predictions of sensitivity of TH4 subtype to Nelfinavir (AKT inhibitor) and Panobinostat (histone deacetylase inhibitor) along with resistance to Everolimus (MTOR inhibitor) were validated *in vitro*. There were two molecular subtypes for which Everolimus was predicted to be sensitive, TH1 and TH6. **Conclusion:** We present an updated classification of TETs based on a CBM approach and associated potential novel therapeutic options that could be further validated in clinical trials.

Keywords: thymic epithelial tumor, The Cancer Genome Atlas, computational biological model

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
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P1.14-18 THE PROMISING ROLE OF SUNITINIB RECHALLENGE IN HEAVILY PRE-TREATED THYMIC CARCINOMA: A CASE REPORT

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Background: The clinical management of thymic carcinomas (TC), remains very challenging, however thanks to the optimization of therapeutic strategy, the 50% of patients is still alive at 5 years. The promising role of sunitinib, a multi tyrosine kinase inhibitor (TKI), has been recently confirmed in several prospective trials, but no data about the rechallenge modality administration are already available. In the case here reported, we illustrate an impressive response disease in a very heavily pre-treated TC after sunitinib rechallenge. **Method:** In August 2013, a 45-year-old caucasian male was referred to our Institution, for a diagnosis of un-resectable/metastatic TC. A systemic therapy strategy was planned. **Result:** Anthracycline-platinum-based chemotherapy was delivered as first, for total 6 cycles, obtained a partial response (PR) with more than 60% of disease reduction (DR). After a brief drug holiday, because of lung progression, the patient underwent capecitabine-gemcitabine combination-chemotherapy. In August 2014, he progressed after 6 cycles and was candidate to start sunitinib at standard dose of 50 mg daily/4 weeks on/2weeks off, in off-label modality. A dose reduction at 50 mg/daily/1 week on/1 week off was made due to persistent diarrhea G2, thrombocytopenia G2 and asthenia G3. Surprisingly, with no more toxicities, he achieved an important partial response with more than 70% of DR, maintained for total 26 months. Unfortunately, a new lung disease progression was registered and oral etoposide at dosage of 50 mg/die 3 weeks on/1 week off was started, without any results. Considering the great response obtained in the first line chemotherapy and envisioning the opportunity to revert target therapy resistance, as already demonstrated for other solid malignancies, 3 cycles of carboplatinum-paclitaxel were delivered, obtained stable disease. Analysis with NGS and microsatellities instability, were performed, with no results useful for the therapeutic decision process. In October 2017, because of the brilliant response achieved with sunitinib and considering the free interval of 12 months, a sunitinib rechallenge was established at 50 mg/daily 1 week on/1 week off. An impressive disease reduction, which is still ongoing, was revealed, no side effects were reported. **Conclusion:** This reported experience, shows sunitinib rechallenge effectiveness for prolonged control disease in thymic carcinoma, despite the number of previous treatments administered before the first and the second drug delivery. A personalized dose reduction can be used for treating heavily pre-treated thymic malignancies to better manage the toxicity profile. Rechallenge with TKI in previous responder patient, should be included routinely in the strategy for the treatment of refractory disease.

Keywords: Thymic carcinoma, sunitinib rechallenge, personalized treatment schedule

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P1.14-19 HEMAGGLUTINATING VIRUS OF JAPAN ENVELOPE (HVJ-E: INACTIVATED VIRAL NANOPARTICLES) AGAINST CHEMOTHERAPY-RESISTANT PLEURAL MESOTHELIOMA

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Background: Hemagglutinating virus of Japan envelope (HVJ-E) derived from inactivated replication-defective Sendai virus possess the various antitumor activities. HVJ-E enhances multiple antitumor immunities such as activation of dendritic cells, induction of natural killer cells and CTL, and suppression of regulatory T cells, and it induces direct tumor-

killing by the induction of cell death through the RIG-I/MAVS pathway by direct administration into the tumor. We performed the phase I dose escalation safety/tolerability and preliminary efficacy study of intra-tumoral and subcutaneous administration of HVJ-E in patients suffering from chemotherapy-resistant malignant pleural mesothelioma. **Method:** We performed the dose upward titration clinical study for checking the safety, drug tolerance, and preliminary efficacy of the intra-tumoral and subsequent subcutaneous administration of HVJ-E. We administrated HVJ-E to the patients 4 times per 2 weeks (the first was intra-tumoral, and residual 3 times were subcutaneous injection), and then washed out the drug from the body for 2 weeks. This cycle was repeated 2 times. We observed the patients for 8 weeks, and evaluated them by CTCAE, modified RECIST, and PERCIST. **Result:** Three patients were enrolled as a low-dose group, and three patients were enrolled as a high-dose group. There was no discontinuation of the administration due to the severe adverse events. Results; The mean disease duration from confirmed diagnosis to this trial was 2.27 years (0.6-4.5 years). We defined the primary endpoint as an assessment of dose limiting toxicity related with HVJ-E. Neither serious adverse events (SAE) nor DLT were observed during the observation period. The following symptoms were observed. Fever (83.3%), and the local symptoms at injection site, for example, rubor, swelling, or induration (100%) were observed, but the local relapse of mesothelioma at the injection site was not observed. It was confirmed that the intra-tumoral and subcutaneous administration of HVJ-E was safe for chemotherapy-resistant pleural mesothelioma patients, because these AEs were transient and slight. The efficacy as a secondary endpoint was evaluated with modified RECIST, and PERCIST. DCR of low dose level cohort was 0% (0/3), because of PD, meanwhile, high dose level cohort indicated 100% (3/3). Consequently, the DCR of all cases who had treated with HVJ-E was 50% (3/6) by mRECIST, meanwhile, the DCR evaluated by PERCIST was 100%. **Conclusion:** It was suggested that HVJ-E was useful for disease control of advanced pleural mesothelioma patients without severe adverse events. Now we do the next step trial for malignant pleural mesothelioma and melanoma with high dose of HVJ-E.

Keywords: Novel Therapy, malignant pleural mesothelioma, Hemagglutinating virus of Japan envelope

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
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P1.14-20 THE EXPRESSION OF DNA METHYLATION OF GAD1 GENE IS AN INDICATOR OF MALIGNANT BEHAVIOR IN THYMIC EPITHELIAL TUMOR.

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Background: Genome-wide screening for aberrantly methylated CpG islands was performed in 7 thymic carcinoma (TC) samples and 8 type-B3 thymoma samples using HumanMethylation450 K BeadChip (Illumina, Santa Clara, CA, USA) analysis. We identified 22 genes as commonly hypermethylated in TC comparing with B3 thymoma. GAD1 (glutamic acid decarboxylase 1) was one of the most significant hypermethylated genes in TC. GAD1 is the enzyme that synthesizes GABA. Recent some reports showed that it is significantly increased in neoplastic tissues. However, the mechanism underlying this increase remains elusive. In this study, we examine mRNA and protein expressions and DNA methylation of GAD1 in thymic epithelial tumors (TETs). **Method:** In total, 49 thymic tumour samples (A; 5, AB; 2, B1; 4, B2; 11, B3; 9, carcinoma; 18) and 20 paired normal tissues were obtained from patients with histologically proven TET, who underwent surgery at the Tokushima University Hospital (Tokushima, Japan) between 1990 and 2016. The methylation status of thymic epithelial tumor samples was validated by pyrosequencing in a larger cohort. The expression status was analysed by quantitative polymerase chain reaction (PCR) and immunohistochemistry (IHC). **Result:** The previous study (Oncogene 2015, 1–14) showed that the key locus responsible for GAD1 reactivation was mapped to a DNA methylation-sensitive CTCF-binding site (CTCF-BS3) within the third intron of GAD1. We targeted this region for pyrosequencing. Pyrosequencing confirmed that DNA methylation of GAD1 gene of TC was significantly higher than that of thymoma (36.5% versus 7.3%, p<0.001), and that DNA methylation of GAD1 gene of thymoma was similar to that of normal thymus (7.3% vs 8.6%). Quantitative PCR and IHC staining revealed that GAD1 mRNA and protein expression levels of TC were higher than those of thymoma (RT-PCR; 8.84 vs 0.72). There were not differences of DNA methylation and expression of GAD1 among subtype of thymoma according to WHO histologic classification. There was a tendency of hypermethylated GAD1 gene in Stage IV comparing with other Stage (Masaoka's clinical staging). **Conclusion:** TC frequently had DNA methylation of CTCF-binding site 3 in GAD1 gene, and high levels of mRNA and protein of GAD1. GAD1 may represent an epigenetic therapeutic target in TC.

Keywords: DNA methylation, GAD1, Thymic carcinoma

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P1.14-21 CIRCULATING BIOMARKERS IN THYMIC EPITHELIAL TUMORS

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Background: Thymic epithelial tumors are the most common mediastinal tumors. Surgery is the mainstay of treatment and complete resection provides the best survival rate. Nevertheless, advanced tumors may require multimodal therapy and additional prognostic factors beyond tumor stage and histological classification might help to risk-stratify patients and personalize the treatment course. **Method:** Between 1999 and 2017 202 patients with thymic epithelial tumors were operated in our center. The preoperative C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels as well as clinical follow-up were retrospectively collected and the association of circulating biomarkers with clinicopathological parameters and their impact on overall survival was analyzed. **Result:** 115 male and 87 female patients were included in the study with 59.5 (±13.1) years mean age at the time of operation. 30 patients (including 12 male patients) suffered from myasthenia gravis. Thymic carcinoma was associated with high CRP (> 1mg/dl) when compared to thymoma cases (34% vs 12%, p=0.001). While LDH levels did not show such association, there was a strong tendency for increased mean LDH levels in Masaoka 4 patients (252.5±18.9 vs 220.5±6.1, p=0.063). Overall survival was analyzed in the thymic carcinoma subcohort. 90% of the patients were treated in a multimodal approach and received chemo- and/or radiotherapy in adjuvant or neoadjuvant setting. Median overall survival was 11.3 years. The Masaoka stage (1-3 versus 4) was a significant prognostic factor (HR 0.23, 95%CI 0.07 to 0.77, p=0.017). Elevated CRP (> 1mg/dl) did not show prognostic power for overall survival (HR 0.82, 95%CI 0.77 to 1.33, p=0.76). In contrast increased preoperative LDH level (>200 U/L) resulted in poorer outcome (HR 0.32, 95%CI 0.09 to 1.13, p=0.076). **Conclusion:** Circulating biomarkers show association with advanced disease stage in thymic epithelial tumors. Importantly, preoperative LDH levels carry prognostic information in thymic carcinoma and could be used to risk stratify surgically treated patients in multimodal treatment settings.

Keywords: LDH, Thymic carcinoma, Thymoma

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P1.14-22 THE PROGNOSTIC ROLE OF THE SUPPRESSOR OF CYTOKINE SIGNALING-5 (SOCS5) IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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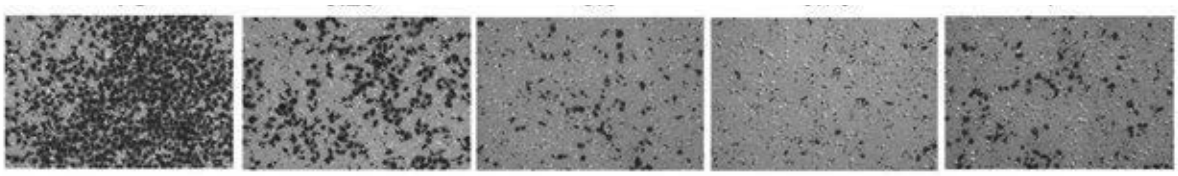
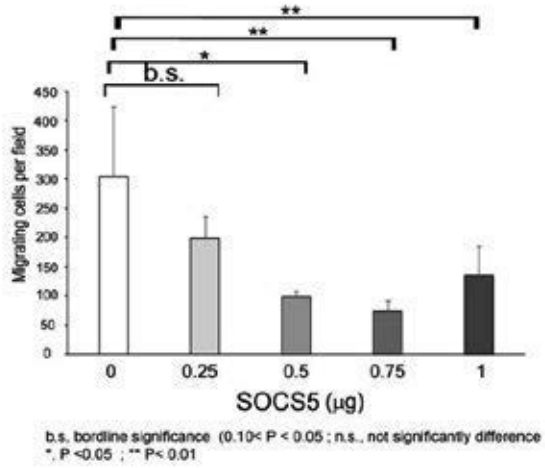
Background: Expression of cytokines and growth factors have been shown to be highly correlated with the prognosis in esophageal squamous cell carcinoma (ESCC), a dead disease with poor prognosis. The suppressor of cytokine signaling (SOCS) family of proteins are key factors in the feedback system that regulates the expression of cytokines and growth factors in cells. Yet the role of the SOCS family of proteins in ESCC is hardly known. **Method:** We analyzed the prognostic effects of 16 single nucleotide polymorphisms (SNPs) within the SOCS family of genes in 632 ESCC patients using MassARRAY system. The underlying mechanisms of SOCS SNPs effect on prognosis was analyzed using luciferase assay. The possible functions of SOCS5 in ESCC cells were analyzed by transiently over-expression. **Result:** We repeatedly observed that the 3 SNPs in SOCS5, SOCS5:rs3814039, SOCS5:rs3738890, and SOCS5: rs3768720, were significantly correlated with both overall (OS) and progression-free survival (PFS) of ESCC patients (rs3814039, p=0.032 for OS and p=0.009 for PFS; rs3738890, p=0.016 for OS, and p=0.008 for PFS; rs3768720, p=0.005 for OS and p=0.002 for PFS). SOCS5: rs3768720 was also significantly associated with distant metastasis (Ptrend=0.028). The

luciferase assay revealed that SOCS5:rs3814039 and SOCS5: rs3738890 might influence the prognosis by regulating SOCS5 expression. Functional analysis demonstrated SOCS5 was able to regulate epidermal growth factor receptor (EGFR) expression and migration activity of ESCC cells. **Conclusion:** Our study demonstrates the roles of SOCS5 in ESCC prognosis. The genetic polymorphisms of SOCS5 could serve as a novel therapeutic biomarker for improving the prognosis of ESCC.





Keywords: EGFR, SOCS5, esophageal cancer

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
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P1.14-23 THYMOMA: AN EPIDEMIOLOGICAL AND CLINICO-PATHOLOGICAL PROFILE IN NEPALESE POPULATION.

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Background: Thymomas and thymic carcinomas are most common tumor of anterior mediastinum representing 0.5 % to 1.5% of all the malignancies. Surgery is the main stay of treatment with adjuvant radiation recommended for the invasive thymomas. It accounts for 0.1% of all the malignancies as per National Cancer Registry Nepal. Because of the rarity of the tumor we aim to review the profile of patient with thymic tumor in our patient population. **Method:** All the patient with diagnosis of thymoma attending the Department of Clinical oncology, National Academy of Medical Sciences (NAMS), Bir Hospital, Nepal during 2009 -2015 was evaluated. We reviewed the record of all registered, histologically diagnosed thymoma and thymic carcinomas and are presented in this study. **Result:** Total of 51 record with thymoma and thymic carcinomas were reviewed out of which 71% (36) patient were male. The mean age was 46.99 years with youngest being 18 years and the eldest 70 years of age. Most common presenting symptom was shortness of breath (37%), followed by cough (23%0, generalized weakness (14%), dysphagia (14%) and drooping of eyelid (12%). About 29.41% of patient was diagnosed with myasthenia gravis. 14% of patients were diagnosed on stage II, 57% on stage III and 29% with stage IV (modified Masaoka clinical stage). WHO pathological stage B 39%(20) [(B1-12%(6), B2-18%(9), B3-10%(5)] was most common, with A 24%(12), AB 20%(10), and C 18%(9). 11% of patient underwent upfront surgery. Neoadjuvant therapy was offered for 63%(32) with 68.75%(22) resectability rate. 27% were eligible only for palliative treatment. About 95% patient received chemotherapy and 90.19% patient received radiation therapy either curative or palliative. 62.74% received curative radiation. 62.74% (32) patients are still on regular follow up with no signs of relapse. **Conclusion:** Multimodality therapy remains the main stay of treatment for thymomas rendering the disease curative. Significant number of patient received neoadjuvant chemotherapy therapy followed by surgery and adjuvant radiation therapy. WHO Type B seems to be more frequent type. Thymoma is quite often associated with myasthenia gravis without adverse effect on prognosis. However, in view of limited study due to rarity of the disease various aspects yet to be explored.

Keywords: Multimodality treatment, thymic carcinoma, thymoma

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P1.14-24 EXTERNAL RADIOTHERAPY CONCURRENT WITH CISPLATIN PLUS 5- FLUROURACIL IN LOCALLY ADVANCED CARCINOMA OF ESOPHAGUS

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Background: Esophageal cancer is the eighth most common cancer in the world with the high rates of local recurrence and metastasis. As per the data of National Cancer Registry Nepal it ranks among the top ten cancers with 2.6% prevalence. Definitive concurrent chemo radiotherapy (CCRT) is the standard for the non surgery patients, and the use of Cisplatin with 5-Flurouracil is the common chemotherapy regimen. **Method:** A prospective and comparative study was undertaken from 2014-2015 to evaluate the effect of CCRT in patients with locally advanced carcinoma of esophagus in our patient population.The eligibilty criteria included locally advanced, ECOG score of <2. Patients received chemo radiotherapy (50Gy / 25fractions) and Cisplatin 75mg/m2 on Day 1 and 5-Flurouracil 1000mg/m2 on Day 1- Day 4 every 4 weeks apart on weeks 1 and 5. Radiation only group received 64 Gy/33 fractions. **Result:**

40 patients were enrolled in the study. Among these patients 65.0% were male and the disease was prevalent at 55-64 years age group. 72.5% of the patients were smokers, 55.0% were alcohol consumers and 20.0% were Tobacco chewers. The most common site of the primary tumor was the mid thoracic region of the esophgus consisting of 62.5%. The combined modality of treatment was toxic but managable with supportive care. Thre were 4 drop outs, 1 from CCRT group and 3 from Radiation (RT) alone group due to the progression of the disease. 65.0% attained partial response and 25.0% achieved complete response in the CCRT group which was in favor of CCRT in comarison to the RTalone group. **Conclusion:** Concurrent chemoradiotherapy yields high locoregional control, in comparison to radiotherapy alone in patients with locally advanced esophgeal carcinoma. Definitive chemoradiotherapy has shown promising results and appears to be superior to RT alone as the sole modality of treatment. Cisplatin and 5-Flurouracil concurrently with radiation therapy is economical alternative with tolerable toxicity profile in resource constraint settings like ours.

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P1.14-25 PULMONARY METASTASIS FROM ORAL CANCER – WHO SURVIVE WITHOUT RECURRENCE AFTER PULMONARY METASECTOMY?

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Background: Oral cancer often performs local recurrence or a neck lymph node metastasis, so pulmonary metastasis from oral cancer is very rare and there have been few reports.. The aim of this study was to evaluate the efficacy of surgical resection of oral cancer pulmonary metastases. **Method:** Between April 2006 and December 2017, 14 patients with oral cancer pulmonary metastases underwent thoracic operations. We considered their clinicopathological features and prognosis. **Result:** There were ten men and four women with median age of 66.5 years (range, 27-76). All tumors were squamous cell carcinoma. Primary sites were tongue (seven patients), gum (three patients), and the mouth bottom (two patients). Five patients had partial resection and nine patients underwent lobectomy or larger operation. Eight of the nine patients who had lobectomy also had systematic lymph node dissection. Overall survival rate after metastasectomy was 46.9% at five years. Overall survival rate at five years by lobectomy with systematic lymph node dissection tended to have a better prognosis than by partial resection or lobectomy without lymph node dissection(p=0.08). Among the patients who had systematic lymph node dissection, lymph node metastasis were found in five patients. However, three of the five got long-term survival (more than two years) in spite of the metastasis. **Conclusion:** For patients with oral cancer pulmonary metastasis, surgical resection especially lobectomy with lymph node desection is recommended.

Keywords: metastatic lung cancer, oral cancer

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P1.14-26 LONG TERM OUTCOME AND CLINICOPATHOLOGICAL FEATURES OF THYMIC CARCINOMA - A RETROSPECTIVE STUDY OF 25 CASES AT A SINGLE INSTITUTION

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Background: Thymic carcinoma is a rare and invasive mediastinal tumor and the optimal treatment is not well defined currently. According to the Clinical report from Japanese Association for Research on the Thymus in 2015, surgical resection is the mainstream of treatment, and the 5-year overall survival was 61%. The patient with complete resection with a 5-year survival of 89%, 68%, 60% for stages I, II & III and IV, respectively. In order to clarify the long-term outcome and prognostic indicators in our facilities, we reviewed our institutional experience with cases of surgical resection for thymic carcinoma. **Method:** A single-institution retrospective study of patients operated for thymic carcinoma. Between 1998 and 2017, 25 patients with thymic carcinoma underwent surgical resection, and their clinical and pathological data were retrospectively reviewed. Overall survival (OS) rates were compared using a log- rank test and Survival curves were plotted using the Kaplan–Meier method. **Result:** Twenty-five patients underwent surgery for thymic carcinoma. The IASLC/ITMIG thymic epithelial tumors Stage according to the 8thedition of the TNM classification was I in 9 patients, II in 6, III in 5, IV in 5. A complete resection was achieved in ten patients (40%) that were no recurrence and death in the follow-up period. There was no fetal complication and no postoperative mortality. Adjuvant radiotherapy and/or chemotherapy was offered to 22 patients. The median follow-up period was 37 months. The 5-year overall survival rate for all the patients were 78.2%. Patients who underwent an incomplete resection had a significantly worse survival as compared to those with complete resection in univariate analyses ($p < 0.01$). **Conclusion:** Our result indicated that complete resection could impact the overall survival of patients with thymic carcinoma after surgical resection.

Keywords: Thymic carcinoma, thymic epithelial tumor

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P1.14-27 DIFFERENTIATION BETWEEN EACH THYMIC EPITHELIAL TUMOR ACCORDING TO WHO CLASSIFICATION SCHEME BY USING MDCT FINDINGS

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Background: Thymic epithelial tumors are the uncommon mediastinal tumors but are the most common primary tumors of the anterior mediastinum. Computed tomography (CT) is the imaging modality of choice for assessment in patients suspected thymic epithelial tumor. The objectives of this study were to assess the CT features of various types of thymic epithelial tumors on the basis of the 2004 WHO classification and to identify the specific CT findings for differentiation between each thymic epithelial tumor. **Method:** A retrospective study reviewed CT findings of 35 patients with thymic epithelial tumors, who underwent surgical resection from January 2010 to April 2017 and had available pre-operative chest CT study. The tumors were reclassified into six types of thymic epithelial tumors (A, AB, B1, B2, B3 and thymic carcinoma) on the basis of the 2004 WHO classification system. The CT findings including the size (longest diameter), margin, shape, presence of focal area of low attenuation of necrosis or cystic change, mediastinal fat invasion, great vessels invasion, degree and pattern of tumor enhancement, presence of tumor calcification and presence of mediastinal lymphadenopathy (short axis diameter more than 10 mm), the presences of pleural effusion, pleural mass, pulmonary nodule, pericardial effusion and extrathoracic metastasis were evaluated. **Result:** Our study consisted of 20 (57.14%) men and 15 (42.86%) women, age 15-78 years (mean 51.25 years). Pathological proven into 30 thymomas (85.71%) and 5 cases (14.29%) of thymic carcinomas. The 30 thymomas were classified according to WHO classification; type A in 5 (14.29%), type AB in 4 (11.43%), type B1 in 5 (14.29%), type B2 in 9 (25.71%), and type B3 in 7 (20%) patients. The tumor sizes of type A, AB, B1, B2 & B3 thymomas and thymic carcinoma were 6.2±1.97, 8.1±2.17, 4.9±2.47, 6.8±3.04, 4.7±1.87, and 9.6±2.78 cm, respectively. No definite CT manifestation that distinguishes between each different WHO pathological type of thymoma with statistical significance. The tumor dimension > 8 cm, irregular margin, mediastinal fat invasion, great vessel invasion, lymphadenopathy, pericardial effusion and extrathoracic metastasis could differentiate between thymoma and thymic carcinoma (P-value <0.05). Great vessel invasion and extrathoracic metastasis had high sensitivity (80%), specificity (100%), PPV (100%) and NPV (96.77%) for diagnosis thymic carcinoma. **Conclusion:** No definite CT manifestation that distinguishes between each different WHO pathological types of thymomas. Tumor size more than 8 cm, irregular margin, presence of mediastinal fat invasion, great vessel invasion, mediastinal lymphadenopathy or extrathoracic metastasis favors the diagnosis of thymic carcinoma.

Keywords: MDCT Findings, thymic epithelial tumor, WHO Classification

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P1.14-28 FREQUENT GENETIC ALTERATIONS AND THEIR CLINICAL SIGNIFICANCE IN PATIENTS WITH THYMIC EPITHELIAL TUMORS

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Background: Thymic epithelial tumors (TETs) are relatively rare neoplasms originating from the epithelial cells of the thymus. Due to the variety of different histology and low incidence, the current knowledge about the genetic alterations and prognostic factors of these tumors is still limited. **Method:** Twenty-four specimens from Chinese patients with resected TETs were collected and sequenced by next-generation technology with 56 cancer-related hotspot genes. The somatic mutation data of TETs was also retrieved from TCGA database (The Cancer Genome Atlas) (n=123). Overall survival was evaluated using Kaplan-Meier methods and compared with log-rank tests. **Result:** We analyzed 12 thymoma (type A, n =3; type AB, n=2; type B1/B2, n = 4; type B3, n = 3) and 12 thymic carcinoma in this study. At least one gene mutation was detected in 15 cases out of total 24 tumors. Half of thymoma and seventy-five percent of thymic carcinoma exhibited genetic alterations, respectively. Twenty-seven gene mutations were detected in total 24 tumors. The most frequent gene mutation of thymoma is BRCA1(25.0%, 3/12), while TP53 mutation is the most commen in thmic carcinoma (25.0%, 3/12). CDKN2A mutaion was exclusively observed in thymic carcinoma (16.7%, 2/12). Our and TCGA cohorts both demonstrated that TETs who presented TP53 mutation had a worse disease free survival and overall survival. **Conclusion:** Comprehensive genomic analysis suggests that the molecular phenotype of thymoma and thymic carcinoma has a distinct difference. TP53 and CDKN2A mutations might play an essential role in the pathogenesis in thymic carcinoma. Lastly, TP53 is the potential biomarker of poor prognosis in TETs.

Keywords: Thymic epithelial tumors, survival, genetic alterations

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P1.14-29 SURGICAL TREATMENT FOR METASTATIC LUNG TUMORS FROM VARIOUS SARCOMAS

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Background: Sarcomas are known to be one of the aggressive malignant tumors. They often develop multiple pulmonary metastasis, and thus systemic therapy is a treatment of choice for metastatic lung tumors. However, effective chemotherapeutic treatments have not yet been established. Surgical resection for metastatic lung tumors is a therapeutic option to control the disease, although it is not a curative therapy. **Method:** Between January 2006 and April 2018, 396 pulmonary resections were performed for 219 sarcoma patients with metastatic lung tumors in Okayama University Hospital. Among them, 129 sarcoma patients who underwent pulmonary metastasectomy between January 2006 and December 2014 were retrospectively reviewed. In total, 229 pulmonary resections were performed. We analyzed the following factors: age, sex, site of primary lesion, histology, operative procedures, size of the largest lesions resected, maximum number of the resected tumors, postoperative complications, and survival rate. **Result:** In total, 939 metastatic nodules were resected. Average number of tumors per intervention was 4.1 (range 1-19). These sarcoma patients consisted of 31 males and 98 females, and their average age was 53.6 years (range 14-80 years). Leiomyosarcoma was the most common histological subtype (n = 72, 55.8%) and uterus was the most common location of the primary disease (n = 55, 42.6%). Operative procedures were composed of 173 partial resections, 31 segmentectomies with or without partial resections, 24 lobectomies with or without partial resections, and 1 basal segmental auto-transplantation after pneumonectomy. The postoperative complications were limited, showing that pulmonary metastasectomies for sarcomas are acceptable. Overall 3-year survival after the first pulmonary metastasectomy was 49.5%, and multivariate analysis revealed that the survival was significantly better for the group with disease-free interval of more than 2 years or the size of the largest resected lesion less than 30 mm. **Conclusion:** Surgical resections for metastatic lung tumors from various sarcomas were performed without major complications, indicating the acceptable feasibility. If disease-free interval is more than 2 years and the size of the largest resected lesion is less than 30 mm, patients may maximally benefit from surgical resection.

Keywords: sarcoma, Surgical resection, metastatic lung tumors

P1.14 THYMOMA/OTHER THORACIC MALIGNANCIES
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P1.14-30 PROGNOSTIC FACTORS FOR SARCOMA PATIENTS WITH LUNG METASTASIS WHO UNDERWENT EXTENDED PULMONARY RESECTION

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Background: Since the effects of chemotherapy and molecular targeting agents for sarcoma with lung metastasis are limited, pulmonary metastasectomy can become one of the treatment options for the control of disease. Partial resection is the first choice of surgical procedure for lung metastasis to preserve pulmonary function. As for the tumors which occur at hilum or are too large for partial resection, the extended resection such as segmentectomy or lobectomy is occasionally required while the clinical impact of these procedures is unknown. In this study, we examined preoperative prognostic factors of sarcoma patients who underwent segmentectomy or lobectomy for lung metastasis. **Method:** During January 2006 to December 2014, a total of 129 patients underwent pulmonary resection for lung metastasis of sarcoma at Okayama University Hospital. Among them, 40 patients (31%) underwent segmentectomy or lobectomy. The 3-year survival rate was evaluated by univariate (KaplanMeier method) and multivariate (Cox proportional hazard model) analyses with log-rank test. **Result:** Among 40 patients, the median age was 55 years old (range, 17 to 76). Thirty-five patients (88%) were female. Thirty patients (75%) harbored two or more distant metastatic lesions at initial diagnosis and 21 patients (52.5%) suffered from bilateral lung metastasis at the first lung metastasectomy. Median maximum diameter of the maximum lung tumor and median number of the lung metastasis was 30 mm (range, 8 to 110) and 3 (range, 1 to 19), respectively. Eight patients (20%) had two years or more disease-free interval at the first lung resection. The 3-year survival rate was 36.8% in the entire cohort. The univariate analyses revealed that the 3-year survival rate was significantly better in the patients with smaller size of lung metastasis (50.5% in the tumors with maximum diameter $\leq$ 30mm vs 20.7% in those > 30mm, $P < 0.01$), unilateral lung metastasis (45.6% vs 29.5% for bilateral, $P < 0.05$), and the absence of metastatic lesion at initial diagnosis (50.9% vs 28.1% for the presence, $P < 0.05$). Smaller numbers of lung metastasis and longer disease-free interval showed favorable prognosis with marginal significance ($P < 0.1$). The multivariate analysis with the above five factors revealed that unilateral lung metastasis at the first pulmonary metasetasectomy was an independent favorable prognostic factor (HR 2.41, 95%CI 1.09 to 5.32, $P < 0.05$). **Conclusion:** Extended pulmonary resection such as segmentectomy or lobectomy may be considered for the patients with sarcoma lung metastasis especially when the tumors are unilateral.

Keywords: sarcoma, Lung metastasis, extended pulmonary resection

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-01 RADIOTHERAPY (RT) AND NIVOLUMAB IN NON-SMALL-CELL LUNG CANCER (NSCLC): A MULTICENTER REAL-LIFE EXPERIENCE

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Background: The combination of RT and programmed death 1 (PD-1) inhibitors seems augment antitumor immune responses. The aim of this study was to assess the outcome of patients (pts) with NSCLC previously

undergone to RT before receiving nivolumab, a PD-1 inhibitor **Method:** We conducted an observational, retrospective analysis of 95 consecutive pts with advanced NSCLC who received any RT within 10 months prior nivolumab, as clinically indicated, at seven Italian institutions. Tumor response to treatment was defined according to RECIST criteria version 1.1. Median overall survival (OS) and the 95% confidence interval (CI) were estimated with the Kaplan -Meier method. **Result:** 95 pts (median age 66 years [range 41-82]; male:63.2%) with advanced NSCLC (adenocarcinoma [adc]:66.3%; squamous cells [sqc]:33.7%) were treated with nivolumab after RT. Median OS was 11.9 months (mo) [95% CI, 6.6-17.2 (adc: 13.0 mo [95% CI,6.7-19.3], sqc 10.5 mo [95%CI,3.9-17.1]). Median progression free survival (PFS) was 6.3mo [95% CI,4.6-8.0] (adc: 6.4 mo[95% CI,4.5-8.3]; sqc: 3.7 mo [95% CI,0.0-8.3]). A better performance status (PS) according to ECOG scale was associated with an improved OS (PS 0[38 pts]: 17.9 mo [95% CI,12.3-23.5; p<0.0001]; PS1[50pts]: 6.9 mo [95%CI,3.2-10.6]; PS2[7pts]: 4.4 mo [95% CI,3.9-4.9]). Median OS in 70 pts who received ≤ 1 previous systemic therapy was 13.0 mo [95% CI, 10.4-15.6] and in 25 pts who received ≥2 prior lines was 7.4 mo [95% CI, 1.8-12.9]. Median OS in 69 pts (72.6%) receiving extracranical RT was 12.0 mo [95%CI,6.6-17.4] and in 26 (27.4%) pts with cranial RT was 11.7 mo [95%CI,NE]; p=0.31. Median OS was shorter in 36 pts receiving bone-RT [7.3 mo; 95% CI, (0-15.3)] when compared with 59 pts receiving extra-bone RT [14.4 mo; 95% CI, (10.3-18.5); p=0.007]. Median OS in 68 pts aged < 70 years was 11.9 mo [95% CI,6.5-17.3] and in 27 elderly (≥ 70 years) was 12.0 mo [95% CI, 3.8-20.1]. 1 (1.0%) complete response, 25(26.3%) partial response, 28(29.5%) stable disease and 41 (43.2%) progressive disease have been observed. **Conclusion:** This study shows that combining irradiation with nivolumab for the treatment of advanced NSCLC leads to improve OS and promote tumor control both locally and distantly.This potentially synergistic effect was comparable among pts regardless previous lines of therapy, histology, type of RT and age.

Keywords: Radiotherapy, NSCLC, Nivolumab

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-02 MIGRATION DIFFERENCES IN SMALL CELL VS NON-SMALL CELL LUNG CANCER

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Background: Every year there is a population diagnosed with lung cancer (LC) that does not receive initial treatment upon diagnosis and then "migrates" to other hospital systems before ultimately getting treatment. We aimed to compare migration rates between non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) and potential factors associated with migration. **Method:** As part of the Kentucky Lung Cancer Education Awareness Detection Survival (LEADS) Collaborative, 29 of 32 Kentucky hospital registries contacted provided LC data of 7660 patients from 2012-2014. Data collected included age at diagnosis, stage, overall survival (OS), sex, race, insurance and treatment history. Treatment included any combination of surgery, radiation, or chemotherapy. Hospital records were matched to Kentucky Cancer Registry records to determine the number of hospitals visited for treatment. Patient treatment and migration patterns were analyzed with a logistic regression model along with additional post-hoc analysis. Difference in rates was calculated by chi-square test. **Result:** Among the 7660 LC patients, 81% were NSCLC and 19% were SCLC. Most patients were treated at their initial hospital - NSCLC (73%) and SCLC (82%) (p value<0.01). However, among the untreated patients, 616 (36%) of NSCLC patients migrated to a different hospital compared to only 23 (8%) of SCLC patients (p value<0.01). Migration of NSCLC patients to another hospital was associated with Stage I-III disease, younger age (66.4 vs 72.2 years), with initial hospitals missing treatment modalities and patients having private insurance. In NSCLC, compared to patients treated initially, patients treated after migration lived longer (591 vs 505 days) and particularly had longer survival with stage III (563 vs 495 days) and IV disease (379 vs 300 days). Too few patients with SCLC migrate to assess association with OS and other patient characteristics. **Conclusion:** There is a significant difference in rates of initial treatment between NSCLC and SCLC that could be due to perceived urgency to treat SCLC. This analysis shows highly significant 4-fold increase in migration rate of NSCLC as compared to SCLC. This could be explained by newer and better treatment options available at referral centers for NSCLC and a lack of these options for SCLC. Increasing research and new innovations in NSCLC will likely drive more patients to migrate in future.

Keywords: Migration, lung cancer

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-03 CLINICAL CHARACTERISTICS OF LONG-TERM SURVIVORS WITH NIVOLUMAB IN PRETREATED ADVANCED NSCLC

from Real-World Data (RWD)

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Background: We have previously analyzed real-world data (RWD) from patients with metastatic NSCLC that progressed to chemotherapy and were subsequently treated with immune-checkpoint inhibitors (ICI). This included patients with performance status of 2, brain metastases, concomitant use of steroids, unknown PD-L1 status, systemic antibiotics during the previous month, and without restriction in the number of previous lines received. Now, with a longer follow-up, we aimed to analyze the baseline clinical characteristics in long-term survivor patients. **Method:** We performed a retrospective study of previously treated advanced NSCLC patients that received nivolumab at 3 mg/kg every 2 weeks outside clinical trials from our institution in Madrid (Spain) between January 2015 and April 2018. We used RWD to analyze the clinical characteristics of patients who were alive 2 years after the start of ICI. **Result:** A total of 38 pts fulfilled inclusion criteria. 7 pts (18%) where alive 2 years after the first dose of nivolumab. Median age at diagnosis was 63 years (53-72 years). 6 pts (86%) had history of tobacco smoking, and 6 pts (86%) had non-squamous histology. 3 pt had ECOG 0 (43%), 3 pts had ECOG 1 (43%) and one pt had ECOG 2 (14%). Median number of previous lines was 3; 3 pts received nivolumab in second line, 3 pts in fourth line and one pt in fifth line. All pts were diagnosed with primary advanced disease. 2 of the pts (29%) had brain metastases and 1 pt (14 %) had ≥ 4 metastatic locations. 2 pts had use antibiotics in the month before and 1 pt used steroids. Best response to nivolumab per RECIST 1.1 criteria included 3 partial responses (43%), and 2 each (29%) had stable and progressive disease. Only 2 pts had no evidence of disease progression during > 2 years at last follow-up when the database was lock (April 2018). Five pts discontinued treatment due to disease progression. After progression, 1 pt continued treatment with nivolumab, 1 pt started osimertinib (EGFR mutant previously treated with TKI and chemotherapy, and confirmed T790M+), and 3 pts started chemotherapy followed by retreatment with ICI. No patients discontinued due to adverse events. **Conclusion:** In our RWD experience, nivolumab resulted in a 2-years survival rate of 18% in previously treated advanced NSCLC patients. Clinical characteristics from real world patients do not predict for long term benefit of nivolumab. Immunological biomarkers are necessary to better select pts who will derive long-term benefit from immunotherapy.

Keywords: advanced non-small cell lung cancer, nivolumab, immunotherapy

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-04 PRACTICE PATTERNS REGARDING MULTIDISCIPLINARY CANCER MANAGEMENT FOR NSCLC AND IMPLEMETANTION: RESULTS OF NATIONAL SURVEY IN MÉXICO

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Background: To manage patients with advanced lung cancer in the most effective way, experts from different disciplines need to be engaged. This has resulted in introduction of the multidisciplinary team (MDT) approach. Because of these advantages, current clinical guidelines recommend discussing the diagnostic and therapeutic plan with an MDT for localized or locally advanced Non-Small Cell Lung Cancer (NSCLC). However, studies suggest despite the advantages of multidisciplinary care, the proportion of new lung cancer diagnoses that are formally discussed in Lung Cancer MDM are disappointing low, in the order of 28–29%. An Australian survey suggests that only one third of hospitals have a multidisciplinary team. **Method:** However, it is unclear how specialists view current evidence about multidisciplinary team (MDT) approach and how they would incorporate into practice. We sought to understand specialist opinions about evidence regarding treatment of NSCLC and how this translates into clinical practice implementation.This study was conducted to explore specialist opinions about multidisciplinary team approach of NSCLC, how this translates into practice and the implementation in Mexico. **Result:** We collected a total of 60 completed responses (50%), 77% were medical oncologist, 7% surgical oncologist

and 17% radiation oncologists. Of these 34% mainly worked in private and 66% in public healthcare Systems. Seventy two percent of all physicians were < 40 years, 25% between 40 and 50 years of age and 22% were 50 years of age or older. Young doctors (up to 5 years of service) accounted for 45 %, with a median length of practice of 12 years. More than two-thirds of physicians were male. Approximately 58% of respondents stated that exist a MDTs for NSLC in their institutions. The Core members of the multidisciplinary cancer team usually include an oncologist (medical, surgical, radiation), pathologist and radiologist in the 65% of the teams. Approximately 55% of respondents stated that MDTs met regularly. Forty two of survey responders do not have a MDT but can discusses new cases directly with surgical oncologist o radiologist. **Conclusion:** While multidisciplinary care has emerged as the standard of care for lung cancer management. The challenge for the future is how to more fully integrate multidisciplinary care into the management of all patients with lung cancer in México.

Keywords: lung cancer, Multidisciplinary team, implementation

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-05 THE FREQUENCY AND SPECTRUM OF EGFR EXON 20 INSERTIONS IN NSCLC: A GLOBAL LITERATURE REVIEW

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Background: There are limited epidemiological data on non-small cell lung cancer (NSCLC) patients with non-classical (uncommon) epidermal growth factor receptor (EGFR) mutations. In light of ongoing development of TAK-788, we describe the global frequency and spectrum of EGFR exon 20 insertions in NSCLC based on a comprehensive literature review as well as highlight possible regional variations. **Method:** A literature search was conducted to identify publications reporting the frequency of EGFR exon 20 insertions in unselected NSCLC patients. PubMed and ASCO, ESMO, and IASLC meeting abstracts were searched up to April 2018 using the following keywords: non-small cell lung cancer, epidermal growth factor receptor, exon 20, insertions and uncommon mutations. Only publications in English were included. The pooled frequency of EGFR exon 20 insertions for each country were determined, and insertion variants (where available) were described at the global level. **Result:** A total of 26 studies from 25 countries were included, reporting on 569 patients with EGFR exon 20 insertions among 41,321 NSCLC patients. The highest mutation frequency was seen in China (2.9%) and the lowest in Indonesia (0.1%). When pooled by country, exon 20 insertions were found in 0.1–2.1% of all NSCLC. Over 50 insertion variants were reported, covering amino acids 761–774. The most commonly detected mutations included D770_N771insSVD, V769_D770InsASV, H773_V774InsH, H773_V774insNPH, and A763_Y763insFQEA.

Country / Region	No. of studies	No. of patients (% total)	Exon 20 insertion frequency, n (%)	Exon 20 insertion frequency, range %)
USA	5	8,189 (19.5%)	172 (2.1)	1.6-2.5%
China	3	7,146 (17.0%)	100 (1.4)	0.3-2.9%
Taiwan	3	4,896 (11.6%)	99 (2.0)	2.0%
Japan	2	599 (1.4%)	11 (1.8)	1.4-2.2%
India	1	580 (1.4%)	9 (1.6)	-
Lebanon	1	201 (0.5%)	1 (0.5)	-
Denmark	1	462 (1.1%)	3 (0.6)	-
Greece	1	956 (2.3%)	12 (1.3)	-
France	1	10,117 (24.1%)	41 (0.4)	-
Indonesia	1	1779 (4.2%)	1 (0.1)	-
Pakistan	1	94 (0.2%)	1 (1.1)	-
Argentina	1	113 (0.3%)	2 (1.8)	-
Central and South America[a]	1	4,500 (10.7%)	88 (2.0)	-
Russia	1	189 (0.4%)	1 (0.5)	-
Asia Pacific[b]	1	1,309 (3.1%)	27 (2.1)	-
Brunei	1	191 (0.5%)	1 (0.5)	-
Philippines	1	710 (1.7%)	17 (2.4)	-
Total	**26**	**41,321 (100)**	**569 (1.4)**	-

[a]Argentina, Columbia, Costa Rica, Ecuador and Panama; results not split by country. [b]China, South Korea, Taiwan, Australia, Indonesia, Malaysia, Singapore, and Thailand; results not split by country.

Conclusion: The frequency of EGFR exon 20 insertions was 0.1–2.1% of NSCLC patients, with a high variability in both length and position of insertions within exon 20. Currently, available data are sparse and come primarily from studies based on single-center experiences, with data gaps across several large geographic regions and populations. Results also indicate a need to further explore underlying geographic variations in epidemiology. Larger, multi-center global studies will further help to refine the frequency of exon 20 insertions and other uncommon mutations in NSCLC.

Keywords: non-small cell lung cancer, EGFR mutation, Exon 20 Insertion

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-06 INTEGRATIVE QUALITY IMPROVEMENT FOR MANAGEMENT OF LUNG CANCER IN UGANDA

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Background: Uganda is currently engaged in quality improvement initiatives for cancer patients. One of them is the creation of an integrative quality system, consisting of guideline development, quality indicators definition and feedback to hospitals. This approach has already been successfully implemented for five types of cancers: rectum (in collaboration with development partners), breast, testis, oesophagus and stomach. Building on previous experience, the study presents the development of a set of quality indicators (QIs) for the management of lung cancer. **Method:** We followed the standardized MOH methodology to identify, select, test and measure the indicators. Because patients may be in contact with different hospitals (for instance, be diagnosed in one hospital but receive treatment – surgery or radiotherapy – in another), we developed a specific algorithm to attribute each patient to the centre where he/she was diagnosed or received treatment (surgical centre or centre of radiotherapy). The method to test the feasibility of identifying comorbidities of patients based on their pharmaceutical billing data during the year before the cancer diagnosis is also described. **Result:** The results of this project made clear that we need more complete and accurate reporting of data to allow more precise and correct evaluation of the quality of care for lung cancer patients in Uganda. Quick and fluent data collection would make it possible to provide comprehensive feedback to care providers on a regular and timely basis. To make this happen, investments in data registration and analysis will be necessary. **Conclusion:** When benchmarking results between hospitals, cautious interpretation is warranted. The use of funnel plots avoids spurious ranking of hospitals and outlier dots can reliably designate either good or bad performers. Statistical modeling can often only partially account for differences in case-mix and other biases. Judging quality of care delivered by a hospital is further hindered by the often small number of patients treated per hospital. Hence, from a sheer statistical point of view, small volumes of activity make it impossible to offer an acceptable level of assurance about the quality delivered to the patient.

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-07 GERIATRIC ONCOLOGY - LUNG CANCER IN ELDERLY PATIENTS AND PALLIATIVE TREATMENT: PROSPECTIVE ANALYSIS OF A. C. CAMARGO CANCER CENTER

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Background: Special attention is required by elderly population, due to chemotherapy (ch) risks and comorbidities, which may limit the capacity to deliver optimal cancer care. We aimed to describe the clinical features and survival outcomes of elderly patients (pts) with lung adenocarcinoma (ADC) treated with non-curative intent at A. C. Camargo Cancer Center. **Method:** We evaluated all pts aged 70+ with lung ADC treated with ch or target therapy in 1st or 2nd-line from 2007 to 2015 who underwent a comprehensive geriatric assessment (CGA), in a convenient prospective series. We used summary statistics to describe the population. Overall survival (OS) was calculated according to Kaplan-Meier method, from CGA date to last follow-up or death. We performed univariate and multivariate analysis in order to look for potential prognostic factors for OS. **Result:** CGA was done in 55 pts aged ≥70y with lung ADC. The median age was 76y and 22% had ECOG ≥ 2. Half of pts were male. 51% had polypharmacy (≥5 drugs). Pts were functionally classified according to activities of daily living (ADL): 76% as Katz A and 50% as Lawton ≤27. 68.5% were at risk for malnutrition or malnourished. The median age-adjusted Charlson Comorbidity score was 10 – remembering that 4+ is considered clinically significant. 61% had ≥2 comorbidities and 26 pts had at least 2 metastatic sites. CNS was affected in 7.5% of the cases and liver in 9.2%. 79.6% of the pts underwent ch and the others received target therapy. After follow-up of 29m, median OS was 17.1 months (13.5-27.8m). In univariate analysis, significantly worse survival outcomes were

observed for pts with ECOG 2-4 (HR 10.6; p < 0.001), increasing number of sites of metastases (HR 2.2; p = 0.04) and hepatic metastasis (HR 6.03; p < 0.001). In the multivariate analysis, male gender, ECOG 2-4 and liver metastasis were associated with higher risk of death. **Conclusion:** ADL, an important part of CGA, showed little prognostic value in our small population. Pts with ECOG 2-4 or hepatic metastasis were those that presented the highest risk of death. CGA is a good tool to help in stratifying risk of elderly cancer pts and is mandatory in cost-benefit analysis to identify the best treatment to each individual patient.

Keywords: Geriatric Oncology, lung, elderly

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-08 IMPLEMENTATION AND FEASIBILITY OF THE ASSESSMENT OF EGFR MUTATION IN NSCLC USING LIQUID BIOPSY AT AN ARGENTINEAN UNIVERSITY HOSPITAL

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Background: Molecular characterization of lung cancer is standard of care. Almost 85% of NSCLC patients have advanced disease at diagnosis, being a challenge get enough tissue for diagnosis. That´ s why using less invasive methods as liquid biopsy by determining cftDNA (circulating free tumor DNA) represents a promising tool. The detection of EGFR mutations in plasma by Therascreen (EGFR RGQ Mutation Kit) showed a sensitivity and specificity of 65.4% and 100 % respectively. It is also useful to detect TKI´s resistance previous to clinical progression. The advantages of using PCR, even there are more sensitive methods available, are its simplicity and cost. **Method:** We will prospectively recruit EGFR mutation-positive (n=40) NSCLC patients. Plasma samples are collected: baseline, after three months of treatment, every six months and at the time of progression. We report our first interim analysis. We evaluate the concordance of EGFRm in tissue and plasma with the implementation of the Therascreen test (Qiagen). We test other available plasma EGFRm detection kit (EGFR Plasma Mutation Analysis Kit, Entrogen) (n=10) **Result:** Since February 2017, plasma EGFRm status could be determined in 17 out of 22 NSCLC patients with EGFRm in tissue. L858R was present in 9 (53%), del19 in 7 (42%), del19+T790M in 1 (5%). Baseline plasma analyzed with Therascreen and Entrogen kits showed similar sensitivity of 61.1% and 66% respectively. Only 1/11 pt had discordance between both kits (Therascreen negative , entrogen DEL19+T790M). In 17 analyzed ptes, median age was 59 (51-76) years. Most of the population were women (88%), were never smokers (58%), had stage IV disease (58%). Frequent site of metastasis was bone (n=7). With a median follow up of 18 months (12-23), 7/15 (56%) patients who experienced clinical progression were detected also in plasma. Two patients presented T790M in plasma without evidence of disease progression until last follow-up (July 2018). We also observed two patients with mutations detected out of range to be considered as positive which became positive for these mutations during the follow up. **Conclusion:** This is the first work showing a cohort of EGFRm patients prospectively analyzed by successive liquid biopsies in a public institution in Argentina. We could successfully obtain cftDNA and analyze it by two commercial kits. The sensitivity of both kits was comparable to previous reports. The study is ongoing and more samples will be analized to shed light about the plasma dynamics of EGFRm related to clinical behavior.

Keywords: liquid biopsy EGFR NSCLC

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-09 TRENDS IN LUNG CANCER SURVIVAL IN LITHUANIA

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Background: Lung cancer is the most common cancer-related death worldwide. The prognosis of lung cancer is unfavourable and improvements in survival in recent decades have been minimal. The aim of this study is to describe the most recent survival rates by sex, age group, extent of disease and histology of lung cancer in Lithuania. **Method:** The study is based on the Lithuanian Cancer Registry database covering a population of around 3 million residents according to 2011 census. The analysis included patients with primary invasive lung cancer diagnosed in 1998-2012 who were at least 15 years old at the time of diagnosis. Patients were followed-up with respect to vital status until December 31, 2012. Cases notified by the death certificate only were excluded. Five-year relative survival estimates were calculated using period analysis. Relative survival was calculated as the ratio of the observed survival of cancer patients and the expected survival of the underlying general population. The latter was calculated according to the Ederer II method using national life tables for Lithuanian population stratified by age, gender and calendar year. **Result:** In our study the overall 5-year relative survival was low, but increased slightly from 6,4% in 2003-2008 to 7.9 % 2009-2012. Positive changes in survival were evident in both sexes, in almost all age groups and for all histological groups and disease stages. Adenocarcinoma relative survival increased from 6.7% in 2003-2008 to 12.8% in 2009-2012 and squamous cell carcinoma increased from 7.4% in 2003-2008 to 11.1% in 2009-2012. Patients with small cell carcinoma had the worst survival (2.9% in 2003-2008 and 3.6% in 2009-2012). Only less than 10% of lung cancer cases were diagnosed localised and proportion of those tumours decreased slightly (from 8.5% to 7.6%). In 2009-2012 relative survival of localised stage lung cancer was 43 %, locally advanced – 19,9%, regional disease - 6% and metastatic disease – 0.7%.The highest number of lung cancer was diagnosed with distant metastases and proportion of metastatic tumours increased from 35.1% to 37.8%. 5-year relative survival was higher in women (9.4 % in 2003-2008 and 12.6 % in 2009-2012) than in men (5.8 % in 2003-2008 and 7% in 2009-2012). **Conclusion:** Despite low overall survival, there were positive changes in survival in both sexes, in almost all age groups and for all histological groups and disease stages. The high proportion of metastatic disease at the time of diagnosis was the main factor that influenced low survival rates.

Keywords: lung cancer, survival

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-10 COMPARISON OF SELECTED COLOMBIAN NATIONAL ADMINISTRATIVE CANCER REGISTRY (NACR) DATA IN LUNG CANCER WITH THE U.S.

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Background: Lung cancer (LC) is the seventh leading cause of cancer in Colombia and the leading cause of cancer mortality in the United States. In Colombia, previous estimates of lung cancer have been limited to city specific cancer registry (Cali Cancer Registry) and broad estimates from GLOBOCAN. The Colombian Health Ministry in 2015 created the National Administrative Cancer Registry (NACR) to obtain national cancer data. We investigated selected 2016 NACR data and compared it to data from the U.S. to gauge for areas of improvement in lung cancer delivery. **Method:** We obtained NACR data compiled from the Colombian Department of Health Ministry regarding lung cancer from 2015-2016. We compared this to U.S. data consisting of Surveillance, Epidemiology, and End Results (SEER) and National Cancer Database (NCDB) data from 2003-2015. **Result:** NACR data in 2016 shows incidence of 1.7 cases per 100,000 and mortality of 2.5 cases per 100,000. SEER data from 2015 shows incidence of 47.2 cases per 100,000 and mortality of 40.6 cases per 100,000. NACR data shows average age of 66 (IQR = 65.7-66) while NCDB data shows median age to be in the age 60-69 category. NACR data in 2016 shows that 14.02% of 849 diagnosed LC patients received surgery compared to 24.83% of 168,093 diagnosed non-small cell lung cancer and small cell lung cancer patients in 2015 from the NCDB. NACR data demonstrates that of those receiving chemotherapy with documented regimens (n=275), 52% received carboplatin, 28.3% received pemetrexed, 27.6% received cisplatin, 25.4% received paclitaxel, 10.9% received bevacizumab, and 5.1% received erlotinib. In comparison, SEER data from 2000-2011 show metastatic NSCLC patients receiving antineoplastic agents (n = 2022) with increasing use of pemetrexed (39.2%), erlotinib (20.3%), and bevacizumab (18.9%) and declining use of paclitaxel (38.7%), gemcitabine (17.0%), and vinorelbine (5.7%). NACR data shows median wait time from diagnosis to first treatment of 31 days (IQR=14-62, n=346) compared to NCDB data showing median wait time of 35 days from diagnosis to first treatment. **Conclusion:** Data shows significantly higher incidence and mortality in the U.S.; this is multifactorial due to screening and data reporting. Comparison shows higher rates of surgery and use of biologics in the U.S. There were similar

wait times from diagnosis to first treatment and age of LC patients. Limitations include limited reporting on chemotherapy, radiation, and staging. Future improvements from a Colombian standpoint will include outcomes data collection, increased screening, resources for surgery, and updated access to antineoplastic agents.

Keywords: lung cancer, Colombia, United States

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-11 LUNG CANCER AS ONE OF MULTIPLE CANCERS: A POPULATION-BASED STUDY IN ESTONIA 1995-2015

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Background: Due to recent developments in cancer prevention, early diagnosis and treatment, more cancers are detected at earlier stages and more patients are cured. As a result, the burden of second and further primary malignancies in a growing and ageing population has remarkably increased over the last decades. Lung cancer is one of the most frequent but most deadly types of cancer. Whether this type of malignancy has a considerable role among multiple cancers is not known. Therefore, the aim of the present study was to assess lung cancer cases as one of the multiple cancers in Estonia. **Method:** We used the data from the Estonian Cancer Registry (ECR), a population-based registry with nationwide coverage (total 1.3 million inhabitants). The ECR provided data on all lung cancer cases and associated multiple cancer cases diagnosed in Estonia 1995-2015. **Result:** During the time period of 20 years, 146541 cancer cases (ICD-10 C00-C97 and in situ cancers D00-D09) were recorded. Lung cancer cases (n=16350) comprised 11% of all malignancies. Out of all diagnosed lung cancer cases, 10% of patients had multiple cancers (n=1619). Lung cancer as first multiple cancer was diagnosed in 398 patients (25%; 338 men, 60 women; median age 67 years, range 31-87 years). Lung cancer as second cancer was diagnosed in 1130 patients (70%; 851 men, 279 women; median age 67 years, range 32-91 years). Ninety one patients had lung cancer as their third cancer (5%; 67 men, 24 women; median age 66 years, range 32-79 years). None of the patients had lung cancer as fourth or further multiple cancers. Next to lung cancer, patients had mostly melanoma and other malignant tumors of skin (18%), malignant neoplasms of digestive organs (18%), male genital organs (18%) and urinary tract (13%) as well as respiratory tract cancers including new lung primaries (10%). Other types of cancers represented 23% of malignancies. After first diagnosis of lung cancer, second tumor was diagnosed approximately 5 months (median) later. As second multiple cancer, lung cancer was diagnosed 7 years (median) after the first cancer diagnosis. Lung cancer as third cancer developed approximately 2 years (median) after the second diagnosis of malignant tumor. **Conclusion:** Multiple cancers are common among lung cancer patients in Estonia. Particular attention is needed, when patient with lung cancer develops skin changes, gastrointestinal and genitourinary symptoms or presents with newly developed respiratory tract complaints.

Keywords: Multiple cancers, lung cancer, population-based study

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-12 REAL WORLD APPLICATIONS OF NEXT-GENERATION SEQUENCING OF NON-SMALL CELL LUNG CANCER IN THE VETERAN POPULATION

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Background: Population studies to date have demonstrated decreased rates of driver mutations in non-small cell lung cancer (NSCLC) for veterans with prior tobacco use who receive care at Department of Veterans Affairs (VA) facilities. Causes of this reduced rate have not been identified, but may result in underutilization of broadly based genetic tumor profiling. The VA recently expanded next-generation sequencing (NGS) to include both tissue and liquid biopsies for comprehensive genetic profiling for patients (pts) with advanced malignancy. Herein, we describe clinical utility of NGS from our retrospective cohort of a rural-based NSCLC veteran population. **Method:** We performed a retrospective cohort analysis of 79 veterans with metastatic NSCLC from 07/2015-04/2018. A trainee-initiated quality improvement initiative in 07/2017 disseminated education at the VA facility about the role of NGS testing for non-squamous NSCLC, with support from the University of Wisconsin Precision Medicine and Molecular Tumor Board. Baseline demographics, time to tissue biopsy, and genetic tumor profiling were analyzed; clinical outcome data were collected including overall survivial and progression-free survival. **Result:** As expected, the cohort was predominantly male (91.1%), with tobacco use (median 45 pk-yrs, 95% >5 pk-yrs) and median age 69 yrs. For molecular profiling, 52% had sufficient tissue at metastatic diagnosis, 20% underwent repeat biopsy within 30 days, 17% underwent biopsy after 30 days, and 11% presented with comorbidity resulting in empiric or palliative management. After implementation of the quality improvement project, the frequency of genetic profiling increased compared to pre-expanded NGS availability in the following targets: *EGFR* (59% v. 90%), *ALK* (65% v. 90%), *ROS1* (35% v. 90%), and *BRAF* (8% v. 60%). Actionable targets were identified in *EGFR* 15.4% (5/39 pts), *ALK* (1/41), *ROS1* (1/24), and *BRAF* (1/11); additional mutations in *NTRK1*, *NTRK3*, *ERBB2,* and *FGFR1* were detected. **Conclusion:** Our preliminary results demonstrate that the availability and use of NGS was associated with increased rates of comprehensive genetic profiling in a largely rural veteran population. Ongoing work will expand this retrospective cohort to more thoroughly characterize barriers to diagnosis and target-specific frequency over historical advances in precision oncology. We will review how these genetic profiles may offer both prognostic and predictive value by reporting clinical outcomes between targeted therapy and early applications of immunotherapy within the veteran population.

Keywords: veterans health, next generation sequencing, NSCLC

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-13 WAIT TIMES FOR DIAGNOSIS AND TREATMENT OF LUNG CANCER ACROSS THE PROVINCE OF QUEBEC, CANADA

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Background: Multiple clinical practice guidelines recommend rapid evaluation of patients with suspected lung cancer. Diagnostic pathways and wait times vary considerably from one centre to another. **Method:** We retrospectively reviewed medical records of all patients (n=1217) across the province of Quebec who had a biopsy-proven diagnosis of lung cancer between February 1st and April 30th, 2017. Median wait times for diagnosis and treatment were calculated. **Result:** Patient characteristics are shown in Table 1. Median wait times for investigation and treatment are shown in Table 2. There were variations between centres and regions.

Characteristic	No (%)
Age, years, mean (range)	68.5 (20-94)
Male sex	585 (48)
Smoking status Former or current smoker Never smoker Unknown	1120 (92) 60 (5) 37 (3)
ECOG performance status 0 1 ≥2 Missing	416 (34) 358 (30) 393 (32) 50 (4)
Histology	
Adenocarcinoma	631 (52)
Squamous cell carcinoma	284 (23)
NSCLC NOS	70 (6)
SCLC	178 (15)
Other	54 (4)
TNM stage	
I	213 (18)
II	114 (9)
III	227 (19)
IV	475 (39)
Limited SCLC	40 (3)
Extensive SCLC	138 (11)

Missing	10 (1)
Known positive ***EGFR*** mutation status (n=395 tested) Known positive ***ALK*** translocation status (n=387 tested) PD-L1 TPS (n=386 tested) <1% 1-49% ≥50% Number of investigations per patient, median (IQR)	28 (7) 6 (2) 85 (22) 151 (39) 150 (39) 7 (6, 8)
Tumor board review	194 (16)
Final diagnostic procedure	
Flexible bronchoscopy	338 (28)
EBUS/EUS	223 (18)
Transthoracic needle biopsy	301 (25)
Thoracoscopy	139 (11)
Biopsy of metastatic site	145 (12)
Sputum cytology	1 (0)
Thoracentesis	61 (5)
Mediastinoscopy Missing	2 (0) 7 (1)

ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; NOS = not otherwise specified; SCLC = small cell lung cancer; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; TPS = tumor proportion score; IQR = interquartile range; EBUS = endobronchial ultrasonography; EUS = endoscopic ultrasonography. **Table 2 – Median wait times for investigation and treatment**

Investigation or treatment interval	Pts (n)	Median wait, days (IQR)
Referral to first appointment with specialist	972	2 (0, 7)
First appointment to diagnosis	1152	18 (8, 43)
Diagnosis to first treatment	930	22 (5, 42)
Referral to first treatment	737	58 (28, 89)
Abnormal imaging to first treatment	902	72 (39, 111)
Surgery	268	109 (80, 142)
Radiation	362	59 (28, 98)
Systemic therapy	330	62 (35, 92)

Conclusion: To our knowledge, this is the largest multicentre review of wait times for diagnosis and treatment of lung cancer with detailed characteristics of patients. Data will be completed and updated prior to the meeting, to try to identify specific factors associated with longer wait times.

Keywords: diagnosis, treatment, wait times

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-14 PNEUMONIA IN PATIENTS WITH LUNG CANCER OF SOUTH KOREA: A NATIONWIDE POPULATION BASED STUDY

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Background: We analyzed the prevalence of pneumonia in lung cancer survivors using claims data from the Health Insurance Review and Assessment Service (HIRA) in South Korea. **Method:** We defined pneumonia among a nationwide cohort of 173,390 patients who were diagnosed with lung cancer and underwent surgery from January 1, 2010 to December 31, 2014, based on HIRA claim data. Descriptive statistics were calculated to estimate the frequency of pneumonia using diagnostic code and utilization pattern at medical institutions. **Result:** Thirty two thousand five hundred lung cancer survivors (19.8%) were diagnosed with pneumonia. The overall frequency of influenza increased from February (n=8089) and peaked in May (n=9,654). Over 59.06% (57,979) of claims for pneumonia treatment were in the clinic, whereas general hospitals accounted for 40.94% (40,184). Among 101,351 claims, admission rate increased as patients get older and the average length of hospitalization was 4.8 days. Elderly breast cancer survivors over 70 years old had the longest length of hospitalization at 6.2 days. **Conclusion:** Lung cancer survivors are more susceptible to pneumonia than non-cancer survivors. It is important not only to raise the vaccination rate among young cancer survivors, but also to quickly identify symptoms and begin treatment for pneumonia in elderly cancer survivors.

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P1.15-15 REAL-WORLD EXPERIENCE WITH AFATINIB AFTER FAILURE OF FIRST-GENERATION EPIDERMAL GROWTH FACTOR RECEPTOR-TYROSINE KINASE INHIBITOR

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Background: Afatinib, a second-generation epidermal growth factor receptor (*EGFR*)-tyrosine kinase inhibitor (TKI) is the recommended first-line treatment for patients with advanced non-small cell lung cancer harbouring sensitizing *EGFR* mutations. The role of afatinib after failure of first-generation *EGFR*-TKIs is controversial. **Method:** A retrospective observational study of patients with *EGFR* mutant advanced NSCLC receiving second-line afatinib after failure of first-generation *EGFR*-TKI in University Malaya Medical Center from 1st December 2014 to 30th April 2018. **Result:** The demographic and clinical characteristics of 27 patients treated with afatinib after failure of first-generation *EGFR*-TKI are shown in Table 1. Twenty-three patients received gefitinib and 4 patients received erlotinib as first-line treatment. The mPFS with first-line treatment was 11.9 months. Fifteen patients had progression of disease (PD) following second-line afatinib with mPFS of 4.2 months and median time-to-treatment failure of 5.7 months. The mPFS2 conferred by first-line first-generation *EGFR*-TKI and second-line afatinib was 18.4 months. The overall response rate to second-line afatinib was 18.5% (5/27) while the disease control rate as 70.3% (19/27). Two patients who had PD on first-generation *EGFR*-TKI due to *T790M* mutation received second-line afatinib while waiting for compassionate access to osimertinib. Nine of the 15 patients (69.2%) with PD on afatinib underwent investigations for resistance mechanisms. Three patients had *T790M* mutation, one of whom had concomitant small cell lung cancer transformation. *c-MET* amplification was detected in another 3 patients. One patient each had *EML4-ALK* rearrangement and epithelial mesenchymal transition.

Table 1 Demographic and clinical characteristic of 27 patients on second-line afatinib

Demographic and clinical characteristics		
Age, years	Mean ± SD	63.4 ± 9.6
Gender, No. (%)	Male	15 (55.6)
	Female	12 (44.4)
Smoking status, No. (%)	Never smoker	20 (74.1)
	Ex/current smoker	7 (25.9)
ECOG performance status, No. (%)	0-1	23 (85.2)
	2-4	4 (14.8)
Stage, No. (%)	IIIb	2 (7.5)
	IV	25 (92.5)
Symptomatic brain metastases, No. (%)	No	24 (88.9)
	Yes	3 (11.1)
EGFR mutation subtype, No. (%)	Exon 19 del	13 (48.1)
	Exon 21 L858R	11 (40.7)
	Rare/complex mutation	2 (7.4)
	Not tested*	1 (3.7)

*This was a patient in the IPASS study who was not tested for *EGFR* mutation but who had prolonged partial response to gefitinib with a PFS of 8 years suggesting that her tumor most likely harbored a sensitizing *EGFR* mutation

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Conclusion: Afatinib conferred a modest mPFS benefit after failure of first-generation *EGFR*-TKI. The mPFS of sequential treatment with first-generation *EGFR*-TKI followed by afatinib seems longer than the mPFS of first-line afatinib in phase 3 randomised controlled trials. Apart from *T790M mutation,* the resistance mechanisms to second-line afatinib in our patients are more heterogenous.

Keywords: afatinib, resistance mechanism, second line treatment

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-16 ALKCONNECT: AN ANAPLASTIC LYMPHOMA KINASE POSITIVE (ALK+) NON-SMALL CELL LUNG CANCER (NSCLC) PATIENT INSIGHTS NETWORK

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Background: ALK+ NSCLC is a subset of NSCLC present in ~3-5% of NSCLC patients. Little is known about ALK+ NSCLC patients' unique journeys, their perspectives on the burden of disease, and their 'real-world' treatment experiences. Online patient networks provide opportunities to gain valuable insights into outcomes meaningful to patients, directly from patients. The objective of this study is to develop an ALK+ NSCLC patient network to facilitate patient interaction and to conduct patient-centered research including understanding unmet needs, patient preferences, health-related quality of life (HRQoL), and product differentiation. **Method:** The ALKConnect Patient Insights Network (www.alkconnect.com) will be a patient-focused registry that directly collects information from patients living with ALK+ NSCLC. Patients meeting study criteria will be enrolled in the online survey over a 2-year period. Inclusion criteria are US, adult, English-speaking patients with ALK+ NSCLC providing written, informed consent, internet access, and willing to answer regular e-surveys. Retrospective and cross-sectional 'real-world' data that will be collected include demographics, clinical characteristics including ALK+ NSCLC disease history and status, comorbidities, past and present treatment experiences and outcomes, quality of life, patient preferences, healthcare resource use, and work productivity. Supplementary data may be collected through uploading of electronic medical records. **Result:** The ALKConnect Patient Insights Network will systematically characterize the natural history of ALK+ NSCLC and its treatment and the overall impact on patients. The data collected will be reported descriptively for the population overall and by subgroups of interest (e.g., age, sex) where sample sizes permit. The associations between treatment history/disease status and patient-reported outcomes including symptom severity, HRQoL (e.g., responses to the MD Anderson Symptom Inventory lung cancer module [MDASI-LC]), healthcare resource use, and work productivity will be analyzed. Longitudinal trends will be evaluated to enable a better understanding of the impact of ALK+ NSCLC over time. All de-identified information gathered from ALKConnect will be shared with the ALK+ NSCLC community, including patients, caregivers, healthcare professionals, advocacy organizations, and fellow researchers. **Conclusion:** We present ALKConnect, an online ALK+ NSCLC patient insights network directly from patients. ALKConnect will provide patients with ALK+ NSCLC opportunities to share their treatment experiences, disease burden, HRQoL, and preferences. Through dissemination to scientific and medical communities, researchers will gain first-hand insights into ALK+ NSCLC patients' experiences of care, and into opportunities for addressing patients' unmet needs.

Keywords: Patient-reported outcomes, Real-world treatment, ALKConnect

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P1.15-17 RISK FACTORS OF LOCAL RECURRENCE IN EGFR-MUTANT STAGE III-PN2 ADENOCARCINOMA AFTER COMPLETE RESECTION: A MULTI-CENTER REAL-WORLD COHORT STUDY

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Background: Postoperative radiotherapy (PORT) of complete resected stage IIIA non-small cell lung cancer with N2 nodal involvement remained contentious. Our previous study suggested low locoregional recurrences in epidermal growth factor receptor (EGFR) mutant patients. We sought to launch a multi-center large cohort study to evaluate the risk factors of locoregional recurrence in R0 resected EGFR mutant III-pN2 patients without PORT, producing evidence for the design of adjuvant regimens. **Method:** Three-hundred and fifty-nine consecutive patients with complete resected, pathological approved stage III-pN2 lung adenocarcinoma with sensitive EGFR mutation (exon 19 or exon 21) have been investigated. Patients were excluded if they received induction therapy (7.5%) or PORT (9.6%). Three hundred cases have been analyzed. Clinicopathologic characteristics, pretreatment work-ups, EGFR mutant status and patterns of failure were documented. Patients were sub-staged by the International Association for the Study of Lung Cancer (IASLC)/the Union for International Cancer Control (UICC) 7th classification on N2 disease. Risk factors of locoregional recurrence-free survival (LRFS) were evaluated by univariate and multivariate analyses. **Result:** According to IASLC/UICC 7th classification, there were 198 (66.0%) patients with unforeseen N2 (N2a), 36 (12.0%) with minimal/single station N2 (N2b), 41 (13.7%) with selectively centrally located N2 (N2c) and 25 (8.3%) with bulky and/or multilevel N2 (N2d). After surgery, 70 (23.3%) patients were treated with adjuvant tyrosine-kinase inhibitors (TKIs), while other 230 (76.7%) were free from adjuvant TKIs. With median follow-up of 28.5 (range: 6-133) months, the 2-year LRFS, distant metastasis-free survival (DMFS), disease-free survival (DFS) and overall survival (OS) were 88.3%, 65.3%, 57.7% and 89.7%. Ultimately, 15.7% (47/300) patients developed locoregional recurrences. Distant metastasis was the predominant failure pattern. Multivariate analysis indicated that N2d disease (HR: 2.65, p=0.030) and extranodal extension (HR: 3.48, p<0.001) were risk factors of LRFS. **Conclusion:** R0 resected stage III-pN2 NSCLC patients with sensitive EGFR mutation (exon 19 or exon 21) tended to present limited N2 disease and low locoregional recurrences. Patients without bulky N2, multilevel N2, and extranodal extension might be refrained from PORT. Further studies evaluating the optimal radiotherapy approach for completely resected N2-positive NSCLC are required for validation.

Keywords: lung adenocarcinoma, EGFR mutation, local recurrence

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P1.15-18 THE IMPACT OF PATIENT AGE ON CLINICAL OUTCOMES IN NSCLC: A NATIONAL STUDY

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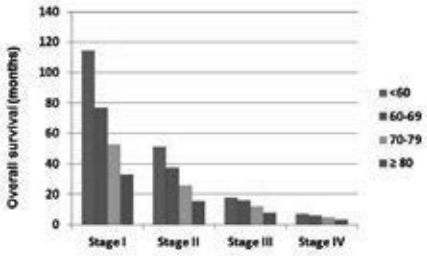
Background: Treatment of NSCLC is rapidly advancing. Clinical outcomes and treatment modalities for patients in each age group remain unknown. This study investigates the treatment modalities in each age group and the impact of patients' age on survival. **Method:** The National Cancer Database with NSCLC between 2004-2014 was used. Overall survival (OS) and treatments were analyzed by age groups, accounting for multivariates. **Result:** A total of 2,327,158 NSCLC patients were included. Median OS is 114.6, 76.7, 52.6 and 33 months for stage I lung cancer patients at age <60, 60-69, 70-79 and ≥ 80 respectively (p<0.0001). Median OS is 7, 5.9, 4.6 and 3.3 months for stage IV patients at age <60, 60-69, 70-79 and ≥ 80 respectively (p<0.0001). The impact of age on survival is cross all stages. Younger patients are associated with larger tumor size and higher percentage of stage V at time of diagnosis. Patients with age ≥ 80 are associated with high income, high education and pacific region. Despite comparable comorbidity, patients with age ≥ 80 are treated differently and received much less aggressive therapy at each stage (p<0.0001). **Conclusion:** The overall survival of NSCLC is significantly impacted by patient's age. Under-treatment in elderly patients might contribute to poor survival. (See next page)



Parameters	60-69 (N=695814)	70-79 (N=762654)	<60 (N=489622)	≥ 80 (N=379068)	p value
Sex					<0.0001
Male	379932 (54.6%)	411040 (53.9%)	257514 (52.6%)	196688 (51.9%)	
Female	315882(45.4%)	351614 (46.1%)	232108 (47.4%)	182380 (48.1%)	
Tumor Size					<0.0001
Mean (SD)	41.8 (40.9)	40.6 (38.7)	44.5 (43.5)	41.8 (37.7)	
Cancer Stage (TNM)					<0.0001
Missing	40248	52354	25832	34986	
Stage I	174144 (26.6%)	218132(30.7%)	86124 (18.6%)	100072 (29.1%)	
Stage II	57080 (8.7%)	64612 (9.1%)	34858 (7.5%)	29960 (8.7%)	
Stage III	157306 (24.0%)	165530 (23.3%)	114526 (24.7%)	79440 (23.1%)	
Stage IV	267036 (40.7%)	262026 (36.9%)	228276 (49.2%)	134610 (39.1%)	
Race					
NH White	591013 (85.6%)	672119 (88.8%)	389166 (80.2%)	341177 (90.7%)	
NH Black	80726 (11.7%)	65181 (8.6%)	79696 (16.4%)	25291 (6.7%)	<0.0001
NH Asian/PI	13737 (2.0%)	15355 (2.0%)	12526 (2.6%)	7895 (2.1%)	
NH NA/AN	1982 (0.3%)	1622 (0.2%)	1523 (0.3%)	524 (0.1%)	
Hispanic	2907 (0.4%)	2712 (0.4%)	2634 (0.5%)	1265 (0.3%)	
Charlson-Deyo Comorbidity Score					
0	401801 (57.7%)	418152 (54.8%)	328625 (67.1%)	221889 (58.5%)	
1	205768 (29.6%)	231339 (30.3%)	120920 (24.7%)	103698 (27.4%)	<0.0001
2	66122 (9.5%)	84488 (11.1%)	28945 (5.9%)	39229 (10.3%)	
≥3	22123 (3.2%)	28675 (3.8%)	11132 (2.3%)	14252(3.8%)	
Median Income Quartiles 2007-2012					
<$38,000	147722 (21.6%)	143545 (19.2%)	116171 (24.2%)	61084 (16.4%)	
$38,000-$47,999	175134 (25.6%)	190505 (25.5%)	124177 (25.8%)	89802(24.1%)	<0.0001
$48,000-$62,999	181326 (26.5%)	203749 (27.2%)	123631 (25.7%)	101514 (27.3%)	
$63,000+	179100 (26.2%)	210665 (28.1%)	116426(24.2%)	119727(32.2%)	
Insurance status					
Not insured	15649 (2.3%)	13558 (1.8%)	13562(3.1%)	5920(1.6%)	<0.0001
Goverment insured	425003 (63.1%)	664635(87.6%)	151930(34.2%)	340084(90.1%)	
Private Insured	232748 (34.6%)	80500 (10.6%)	278239 (62.7%)	31621 (8.4%)	
Geographic region					
East coast	302052(43.4%)	329782(43.2%)	207234 (43.3%)	166388 (43.9%)	
Central	305709 (43.9%)	329451(43.2%)	217588(45.5%)	154059 (40.6%)	<0.0001
Mountain	24295 (3.5%)	28607 (3.8%)	13908 (2.9%)	14106 (3.7%)	
Pacific	63758 (9.2%)	74814 (9.8%)	39403 (8.2%)	44515 (11.7%)	
% No high school degree 2007-2012					<0.0001
>=21	133037 (19.5%)	127906 (17.1%)	104766 (21.8%)	53076(14.3%)	
13-20.9	201001 (29.4%)	207924 (27.8%)	146897 (30.6%)	94391 (25.4%)	
7-12.9	219940 (32.2%)	253111(33.8%)	147928 (30.8%)	130233 (35%)	
<7	129679 (19%)	159885 (21.4%)	81096(16.9%)	94569 (25.4%)	
Treatment modalities					<0.0001
Stage I					<0.0001
Surgery of Primary Site (Yes)	133496 (76.8%)	149086 (68.5%)	71842(83.6%)	45720 (45.8%)	
Radiation (Yes)	33644 (19.5%)	53590 (24.8%)	12698(14.9%)	37748 (38%)	
Chemotherapy (Yes)	27668(16.5%)	25322(12%)	17734 (21.4%)	7209 (7.4%)	
Stage II					<0.0001
Surgery of Primary Site (Yes)	38292 (67.2%)	37642 (58.4%)	25826 (74.3%)	10838 (36.3%)	
Radiation (Yes)	19152(33.9%)	22446 (35.1%)	12080 (35.1%)	12588 (42.4)	
Chemotherapy (Yes)	33880 (61.5%)	29326(47.1%)	23724 (70.7%)	7246 (25.0%)	
Stage III					<0.0001
Surgery of Primary Site (Yes)	32932 (21.0%)	29134 (17.7%)	25744 (22.5%)	7642 (9.6%)	
Radiation (Yes)	98066 (62.8%)	92058 (56%)	76096 (66.9%)	36544 (46.3%)	
Chemotherapy (Yes)	115198 (75.0%)	102280 (63.4%)	90360 (80.8%)	29606 (38.2%)	
Stage IV					<0.0001
Radiation (Yes)	133036 (50.1%)	108824 (41.8%)	130346 (57.4%)	43536 (32.5%)	
Chemotherapy (Yes)	156266 (60.1%)	128636(50.4%)	149640 (67.3%)	41178 (31.4%)	
Palliative therapy (yes)	69794 (26.3%)	64170 (24.6%)	63744 (28.1%)	30418 (22.6%)	
High Volume Center	376773 (54.1%)	401377 (52.6%)	265709 (53.3%)	187425 (49.4%)	<0.0001

Keywords: survival, non small cell lung cancer, age

P1.15-19 TREATMENT OF CHOICE FOR FIRST-LINE THERAPY OF EGFR-MUTATED STAGE IIIB LUNG ADENOCARCINOMA BASED ON THE REAL WORLD DATA

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Background: There is a lack of consensus on the choice of first-line therapy for stage IIIB EGFR-mutated lung adenocarcinoma. **Method:** A prospectively maintained database at the Shanghai Chest Hospital was used to identify patients who received therapy for stage IIIB EGFR-mutated lung adenocarcinoma between 2015 and 2017. Clinicopathological data were extracted from the database and analyzed. Patients were stratified into four groups based on the therapy they received; chemotherapy alone, chemoradiation (concurrent or sequential), first-generation EGFR-TKI, or surgical resection with or without chemoradiation. Log-rank test and Kaplan-Meier method were used to determine significant differences in the progression free survival (PFS) between treatment groups **Result:** Of the 114956 patients treated at the institution during the study period 85 (0.07%) were eligible for the study. 12 patients (14.1%) received chemotherapy, while 19 (22.4%), 30 (35.3%) and 24 (28.2%) received chemoradiation, EGFR-TKI and surgery respectively. The common mutations included Del19 (N=35, 41.18%), L858R (N=42, 49.41%), G719X (N=4, 4.71%) and S768I (N=2, 2.35%). The median PFS was shorter in patients who only received chemotherapy (8.5 months) as compared to those managed with chemoradiation (14.6 months), EGFR-TKI (16.2 months) or resection (18.6 months) (p=0.04,figure 1b). No statistically significant difference was observed in PFS between EGFR-TKI and chemoradiation (p=0.86), or EGFT-TKI and resection (p=0.90). A subgroup analysis of patients with N3 disease resulted in similar findings (figure1c).

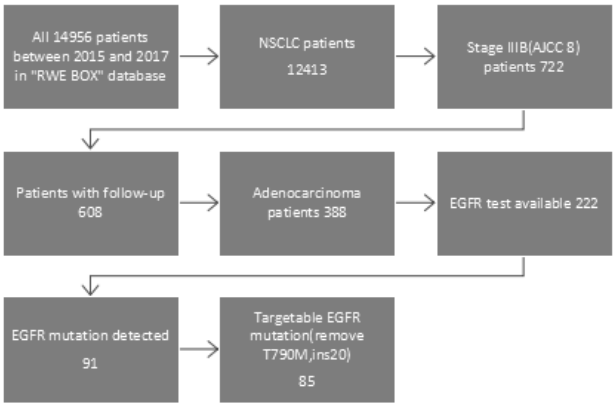

Figure1a

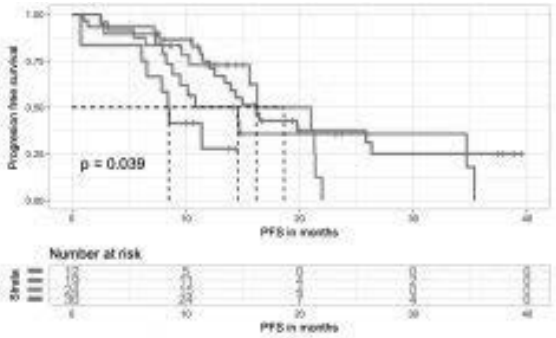

Figure1b

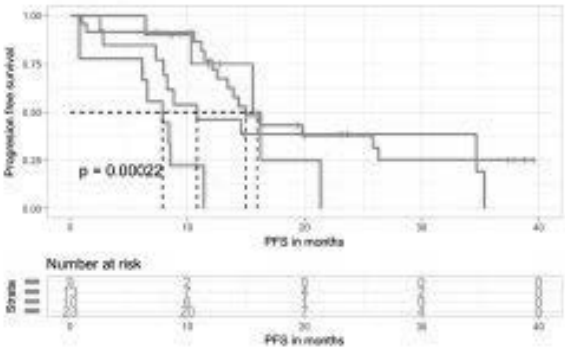

Figure1c

Conclusion: In conclusion, when used as a first-line therapy chemoradiation, EGFR-TKI and resection with or without chemoradiation can achieve similar PFS, which is superior to that of patients receiving chemotherapy alone. Further studies are required to elucidate the efficacy of EGFR-TKI as a first-line or as maintenance therapy for these patients.

Keywords: stage IIIB, EGFR positive, Real world data

P1.15-20 DIAGNOSIS AND TREATMENT DELAY AMONG PATIENTS WITH LUNG CANCER IN MEXICAN POPULATION

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Background: In Mexico, lung cancer is the seventh in incidence and first in mortality. Diagnosis in advanced stages accounts >70% of cases. We analyze factors associated with a late diagnosis and delay in the beginning of treatment. **Method:** Observational, cross-sectional study carried-out from August to October 2017 in the National Cancer Institute of Mexico (INCan). An interview was conducted to identify: 1) onset of symptoms, 2) time elapsed to seek medical attention, 3) number of doctors visited, 4) diagnosis established prior to cancer diagnosis pulmonary, 5) time elapsed from diagnosis of cancer until admission to INCan and 6) Time elapsed from diagnosis to start treatment. **Result:** 414 patients included and main characteristics are included in the next table

Mean age	**64 years (±12.98)**
Genre	**58% females**
Histology	**Adenocarcinoma - 74.6% Epidermoid - 9.7% Other – 15.7%**
Clinical Stage	**I - 5.5% II - 3.7% III - 16.2% IV - 74.6%**
Physicians/Clinical Assessments Before Diagnosis	**1 physician – 25% 2 physicians – 22.9% ≥3 physicians – 33.1%**
Risk factor	**Smoker – 44.7% Wood smoke – 32% Asbestos – 6% Passive smoker – 6%**

Median time from beginning of symptoms to start of oncologic treatment are shown in the next image **Conclusion:** In Mexico, lung cancer is diagnosed in advanced stages due to a lack of clinical suspicion in primary care physicians. Delay from initial medical assessment to specialized center referral is considered an opportunity window. Identification of these factors will lead to establishment of public health policies that ensures improvement of diagnostic approach and the timely reference and initiation of treatment in specialized centers to improve the prognosis.

Keywords: diagnostic delay, real world lung cancer treatment, treatment delay

P1.15-21 CREATING AN OPTIMAL CARE COORDINATION MODEL TO IMPROVE MULTIDISCIPLINARY CARE FOR LUNG CANCER PATIENTS ON MEDICAID

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Background: The Association of Community Cancer Centers (ACCC) created an Optimal Care Coordination Model (OCCM), which provides a comprehensive self-assessment tool designed to orient cancer programs to achieving patient-centered, multidisciplinary care. The OCCM is designed to help cancer programs, regardless of resources, location, or population, improve care for lung cancer patients, especially those on Medicaid. **Method:** Using findings from an environmental scan (April 2016) and visits to 5 US cancer programs to explore current care models (July-October 2016), a Technical Expert Panel developed the OCCM, which has 13 defined Assessment Areas and utilizes an evaluation matrix (Table 1). To validate the OCCM, a competitive application process among ACCC's membership used a comprehensive institutional quantitative and qualitative questionnaire. Applicants completed a self-assessment using the OCCM and then developed quality improvement projects designed to move their OCCM-scored care delivery performance from baseline to a higher level over a 12-month implementation period. Seven US community cancer centers were selected as Testing Sites. Quantifiable outcome measures were identified for each site, standardized across sites, and collected by a centralized data coordinating center.

Table 1

OCCM Assessment Areas

1. Patient Access to Care
2. Prospective Multidisciplinary Case Planning
3. Financial, Transportation, and Housing
4. Management of Comorbid Conditions
5. Care Coordination
6. Treatment Team Integration
7. Electronic Health Records and Patient Access to Information
8. *Survivorship Care*
9. *Supportive Care*
10. *Tobacco Cessation*
11. *Clinical Trials*
12. *Physician Engagement*
13. *Quality Measurement and Improvement*

Level 1: Optimal care coordination for lung cancer care has a low priority as evidenced by fragmented care.

Level 2: Early progress in coordinating care is underway.

Level 3: Reflects average or typical care coordination.

Level 4: Exceeds the average and reflects a cancer program's ongoing commitment to the pursuit of optimal care coordination.

Level 5: Defined by optimal care coordination with a patient-centered focus. Depending on the assessment area, achieving Level 5 performance will require significant time, effort, and resources.

Patient Focus: Optimal care coordination must be patient-centered, which requires understanding of what is important to patients and their caregivers, including their knowledge, goals, needs, desires, social connections, and resources for care. This requires the cancer program to educate and engage patients and caregivers to facilitate shared decision-making and patients' participation in their care.

Quality Measures and Metrics: Each assessment area requires at least one measurable parameter. Optimal care coordination requires analysis and development of an action plan for continuous improvement. These parameters should include both evidence-based and institution-specific benchmarks that address patient outcomes, patient experience, and cost effectiveness. These measures and metrics should be continuously measured and fed back to key institutional stakeholders for ongoing quality improvement.

Result: Table 2 shows Assessment Areas being validated and patient demographics.

Table 2	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	TOTAL
Project # 1 Selected Assessment Area(s)	#2	#7	#10	#2	#1	#5 & #9	#1	
Project # 2 Selected Assessment Area	#8	#11	n/a	#10	n/a	n/a	#2	8 of 13 Assessment Areas being validated
	N=50	N=29	N=77	N=53	N=76	N=101	N=35	N=421
Age								
Median (IQR)	70 (57-76)	74 (63-76)	71 (57-76)	65 (60-71)	68 (61-75)	61 (55-65)	66 (60-73)	68 (61-74)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sex								
Male	29 (58)	14 (48)	40 (52)	27 (51)	49 (64)	48 (48)	18 (51)	225 (53)
Female	21 (42)	15 (52)	37 (48)	26 (49)	27 (36)	52 (51)	17 (49)	195 (46)

Race								
Caucasian	46 (92)	23 (79)	76 (99)	51 (96)	73 (96)	47 (47)	27 (77)	343 (81)
African American	4 (8)	1 (3)		2 (4)		5 (5)	6 (17)	18 (4)
Asian		4 (14)				8 (8)		12 (3)
Other/ Unknown			1(1)		1 (1)	8(8)	2 (6)	12 (3)
Not reported		1 (3)			2 (3)	29 (29)		32 (8)
Insurance								
Commercial	7 (14)	7 (24)	13 (17)	8 (15)	29 (38)	8 (8)	9 (26)	81 (19)
Medicare	38 (76)	20 (69)	55 (71)	37 (70)	40 (53)	28 (28)	21 (60)	239 (57)
Medicaid	4 (8)	2 (7)	6 (8)	8 (15)	6 (8)	63 (62)	4 (11)	93 (22)
None/Self-Pay			2 (3)		1 (1)			3 (1)
Smoking Status								
Active Smoker	14 (28)	10 (34)	27 (35)	17 (32)	38 (50)	34 (34)	11 (31)	151 (36)
Former Smoker	20 (40)	15 (52)	44 (57)	34 (64)	28 (37)	51 (50)	23 (66)	215 (51)
Never Smoker	7 (14)	3 (10)	2 (3)	2 (4)	7 (9)	9 (9)		30 (7)
Not reported					2 (3)	1 (1)		3 (1)
Stage at Diagnosis								
Stage 0			2 (3)					2 (<1)
Stage I	9 (18)	4 (14)	21 (27)	1 (2)	9 (12)	9 (9)	2 (6)	55 (13)
Stage II	1 (2)	2 (7)	10 (13)	5 (9)	3 (4)	7 (7)		28 (7)
Stage III	6 (12)	5 (17)	11 (14)	3 (6)	4 (5)	13 (13)	2 (6)	44 (10)
Stage IV	6 (12)	3 (10)	8 (10)	14 (26)	13 (17)	18 (18)	4 (11)	66 (16)
Not reported/ Missing	28 (56)	15 (52)	25 (32)	30 (57)	47 (62)	54 (53)	27 (77)	226 (54)
*Percentages may not add to 100 due to missing data								

Conclusion: Project implementation and patient accrual are ongoing at all Testing Sites through September 2018.

Keywords: care coordination, multidisciplinary, patient-centered

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.15-23 FACTORS AFFECTING TREATMENT IN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Lung cancer continues to be the leading cause of cancer deaths with Kentucky having the highest incidence of lung cancer. Despite advances in treatment and subsequent survival improvements, a significant number of non-small cell lung cancer (NSCLC) patients remain untreated. Factors such as age, stage at diagnosis and insurance status appear to play an important role in this disparity. **Method:** In the Kentucky LEADS Collaborative, 27 of 31 (81%) Kentucky hospital registries provided all NSCLC data from 2012-2015. Variables collected included hospital accreditation by the Commission on Cancer (CoC), patient age at diagnosis, stage, race, number of comorbidities, insurance status, and overall survival (OS). Treatment included combinations of surgery, radiation, chemotherapy or immunotherapy. Hospital records were matched to the Kentucky Cancer (KCR) records and analyzed with a logistic regression model along with additional post-hoc analysis. **Result:** Of the 13,975 patients diagnosed with NSCLC, 10,367 (74.2%) were treated leaving 3,608 (25.8%) untreated. Overall survival reported as person-days was significantly longer for the treated versus untreated patients (593 days vs 161 days). Neither race nor gender showed statistical significance while age at the time of diagnosis was significant with the untreated patients being diagnosed at a mean age of 72 and the treated patients at a mean age of 66 (p=<0.001). The mean average of comorbidities reported was 4.1 for treated patients and 4.4 for untreated patients though the specific comorbidities were not discernable. Treatment versus lack of treatment was also significantly associated with stage at the time of diagnosis with 87.9% vs 12.1% for stage I, 88.2% vs 11.8% for stage II, 73.9% vs 26.1% for stage III, and 64.2% vs 35.8% in stage IV; untreated patients tended to present at a later stage than those who received treatment with OR 2.91 (95% CI 2.57-3.28) for stage III and OR 4.28 (95% CI 4.29-5.41) for stage IV. Lastly, insurance proved to be an important factor with untreated patients more likely to have Medicaid, Medicare or be uninsured. **Conclusion:** Treatment for lung cancer is correlated with improved outcomes and yet a large number of patients are still untreated. We aimed to assess these barriers to treatment and found untreated patients were more likely to be older, diagnosed at a later stage, and not have private insurance. While therapies are constantly changing and improving, it is important to factor in the many barriers that still exist in preventing patients from being treated.

Keywords: NSCLC, untreated

P1.15-24 SMALL CELL LUNG CANCER: CLINICAL CHARACTERISTICS AND SURVIVAL OF A SPANISH COHORT OF 221 PATIENTS

B. Núñez[1], R. Gómez[1], J. Sánchez[1], B. De La Puente[1], C. Alfaro[1], V. Calvo[1], L. Núñez[2], M. Blanco[1], I. Curto[1], M. Soriano[1], M. Méndez[1], A. Morito[1], F. Franco[1], M. Provencio[1]

[1]*Oncology, Hospital Puerta de Hierro, Madrid/ES,* [2]*Pneumology, Fundacion Jiménez Díaz, Madrid/ES*

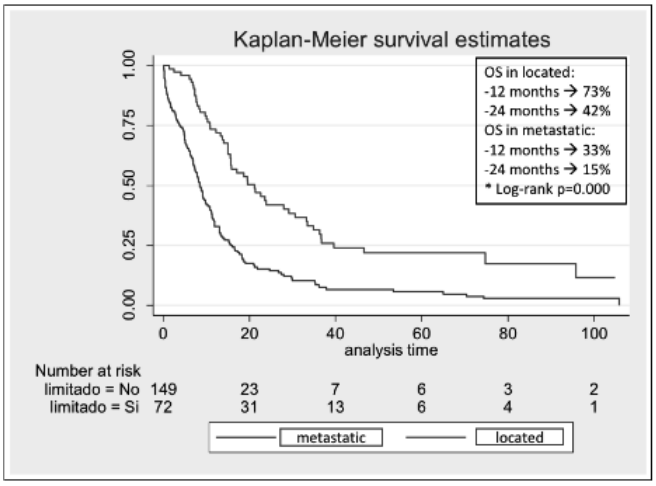
Background: Lung cancer is the leading cause of death from cancer, of which 15% corresponds with small cell lung cancer (SCLC) subtype, directly related with tobacco. SCLC is the most aggressive subtype with an elevated percentage of metastatic patients at diagnosis and a poor prognosis. **Method:** A cohort of 221 patients diagnosed of SCLC were retrospectively analyzed in our center between 2008-2016. Patient data was analyzed for baseline demographics and stage at diagnosis. Progression free survival (PFS) and overall survival (OS) analysis were made comparing SCLC stage at diagnosis. **Result:** The median age at diagnosis was 64 years and 74% were male, of whom 33% were older than 70 years. Only 0.5 % were never smokers and 16% had history of other malignancies, mostly related with tobacco. At diagnosis, 67% were metastatic and 88% symptomatic. Complete baseline characteristics shown at Table 1. PFS was 13.5 versus 6.83 months in located versus metastatic disease (p = 0.000) and median OS was 21.2 versus 8.5 months comparing located and metastatic stage (p = 0.000). Kaplan-Meier curves shown at Image 1.

Table 1. Complete baseline characteristics.

BASELINE CHARACTERISTICS	ALL PATIENTS (n=221)
SEX	164 (74%) male; 57 (26%) female
AGE AT DIAGNOSIS	64 years (IQR 58-71); 65 years (IQR 59-73) male; 61 years (IQR 55-68) female.
PATIENTS OLDER THAN 70 YEARS	72 (33%); 60 males and 12 females
SMOKING HABIT	Smoker --> 137 (61.9%) Former smoker --> (> 365 days without smoking) à 81 (36.65%) Never smoker --> 1 (0.45%) Unknown --> 2 (0.9%)
SMOKING PACK YEAR	58 pack/year; 60 pack/year male and 50 pack/year female
AGE AT THE BEGINNING OF TOBACCO HABIT	16 years
STAGE	Stage I --> 10 (5%) Stage II --> 8 (4%) Stage III --> 53 (24%) Stage IV --> 150 (67%)

Table 1. Complete baseline characteristics.

BASELINE CHARACTERISTICS	ALL PATIENTS (n=221)
ECOG	0-1--> 191 (86.4%) 2--> 23 (10.4%) 3--> 7 (3.2%)
CARDIOPULMONARY DISEASE	COPD 23% HBP 47% DM 25% DL 43% Cardiopathy 19%
HISTORY OF OTHER MALIGNANCIES	16%, most frequent: bladder cancer 7 (20.6%); head and neck cancer 6 (17.7%); lung cancer 4 (11.8%)
FAMILIAR HISTORY OF LUNG CANCER	39%
SYMPTOMS AT DIAGNOSIS	Cough 42%; weight loss 30%; pain 28%; dyspnoea 27%; asthenia 21%
TREATMENT	8.2% palliative treatment 91.8% active treatment (98.8% standard treatment with platinum-based chemotherapy and 1.2% clinical trial)
PROGRESSION FREE SURVIVAL	13.5 (IQR 7.4-40.8) months in located and 6.8 (IQR 4.8-10.2) in metastatic disease compared with (p = 0.000)
OVERALL SURVIVAL	21.2 (IQR 10.8-39.6) months in located and 8.5 (IQR 3.9-15.5) in metastatic disease with (p = 0.000)
12 AND 24-MONTHS OVERALL SURVIVAL	Located: 73% and 42% respectively Metastatic: 33% and 15% respectively



Conclusion: SCLC is mostly diagnosed at metastatic stage, but even in located disease prognosis is poor, so investigation is needed to improve PFS and OS.

Keywords: OS, SCLC, Prognosis

P1.15-25 HAS LUNG CANCER RADIOTHERAPY UTILISATION CHANGED OVER TIME IN NEW SOUTH WALES, AUSTRALIA?

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Background: Evidence based indications suggest that 73% of all Australian lung cancer patients would benefit from radiotherapy at diagnosis. In 2001-2002, the radiotherapy utilisation (RTU) rate in NSW for lung cancer was 39%. Since then a number of new radiation oncology centres have opened and the number of linear accelerators increasing from 29 to 46. There has also been an increase in the number of lung cancer multidisciplinary teams. We aimed to evaluate whether there had been any change in RTU for lung cancer in NSW from 2001-2002 to 2009-2011. **Method:** All patients diagnosed with lung cancer in NSW between 1/1/2009 and 31/12/2011 were identified from the NSW Central

Cancer Registry (NSWCCR). Data linkage with the Admitted Patients Data Collection, Retrospective Radiotherapy Data and Clinical Cancer Registry was performed to ascertain radiotherapy treatment within 1 year of diagnosis. Patients with non-lung cancer pathologies and those who lived closer to interstate radiotherapy centres were excluded. Patients with a clinical diagnosis of lung cancer (no pathological confirmation (NPC)) were included. **Result:** A total of 10,712 patients were identified through NSWCCR of which 947 patients were excluded leaving 9,765 patients for analysis. The median age was 71 years and 60% were males. Histopathology was NSCLC, SCLC and NPC in 76%, 12% and 13% respectively. Stage was I&II in 12%, III in 12%, IV in 28% and unknown in 47%. The overall RTU for lung cancer was 40%. RTU was 43% for NSCLC, 56% for SCLC and 8% for NPC. RTU by stage compared to previous figures is shown in Table 1.

Table-1 Radiotherapy utilisation rate by stage of lung cancer, NSW 2001-2002 and 2009-2011

Histology	Stage	RTU N (%) (2001-2002)	RTU (%) (2009-2011)
NSCLC	I	76(26)	201(27)
	II	35(39)	164(41)
	III	170(55)	753(72)
	IV	258(49)	1,497(66)
	Unknown	17(22)	544(18)
	Total	556(43)	3,159(43)
SCLC	I-III	39(47)	157(80)
	IV	61(32)	280(61)
	Unknown	1(17)	202(41)
	Total	101(36)	639(56)
NPC	I	12(22)	12(43)
	II	4(33)	3(50)
	III	11(35)	17(71)
	IV	20(27)	37(60)
	Unknown	5(8)	25(2)
	Total	52(23)	94(8)
OVERALL	Total	709(39)	3,892(40)

Conclusion: Increased RTU was seen in some groups of patients including Stage III-IV NSCLC, Stage I-IV SCLC and Stage I-IV NPC. Despite an increase in resources, overall RTU for lung cancer has remained unchanged over the last decade.

Keywords: lung cancer, Radiotherapy, utilization

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.15-26 A REVIEW OF COLOMBIAN NATIONAL ADMINISTRATIVE CANCER REGISTRY (NACR) DATA TO EVALUATE HEALTHCARE DELIVERY AND BIOLOGICS USE

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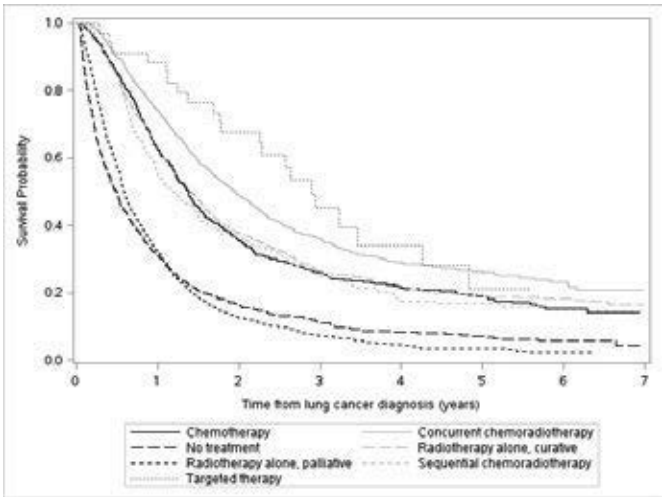
Background: In anticipation of new treatment strategies for unresectable stage III NSCLC, we undertook a retrospective study to determine how these patients have been managed in Ontario, Canada and their survival by treatment approach. **Method:** Individuals diagnosed with stage III NSCLC between April 1, 2010 and March 31, 2015 were identified in the Ontario Cancer Registry (OCR). Patients with stage III disease were considered to be unresectable if no surgery was undertaken within 3 months of diagnosis. Initial treatments included: radiation (classified as curative or palliative based on treatment intent, body region, dose/fraction, number of fractions); chemotherapy categorized as single or doublet IV chemotherapy, single chemo+RT, doublet chemo+RT, oral targeted therapy. Concurrent chemo+RT (cCRT) was defined as an overlap between chemotherapy and RT, while sequential chemo+RT (sCRT) had no overlap and a 30-day window between treatments. Survival was calculated from date of diagnosis to death. **Result:** 24,729 individuals were diagnosed with NSCLC in Ontario during the study period; 5,243 (21.2%) were stage III and 4,542 (18.4%) were stage III unresectable. Mean age of the unresectable group was 69.7±10.3 years; 54.2% were male. 64.2% of patients were treated within 3 months of diagnosis. The frequency of treatment approach was: cCRT (21.6%), palliative RT (21.3%), curative RT (20.2%), no treatment (19.6%), chemotherapy (11.6%), sCRT (4.9%) and targeted therapy (0.7%). Median survival (IQR) was 2.9 yrs (1.7-4.8) for targeted therapy, 2.0 yrs (1.0-5.5) for cCRT, 1.4 yrs (0.7-3.4) for curative RT, 1.4 yrs (0.7-3.1) for chemotherapy, 1.2 yr (0.6-2.9) for sCRT, 0.6 yrs (0.3-1.2) for palliative RT and 0.5 yrs (0.2-1.2) for no treatment (Figure 1). Figure 1. Kaplan-Meier survival curves for stage III unresectable lung cancer patients based on treatment type.



Conclusion: Although cCRT is generally considered standard of care for stage III unresectable NSCLC, patients in Ontario receive various treatment approaches. Survival outcomes vary widely.

Keywords: Real World Evidence, non small cell lung cancer, treatment patterns

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.15-28 REAL WORLD TREATMENT PATTERNS AND SURVIVAL OF STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC) IN ONTARIO, CANADA.

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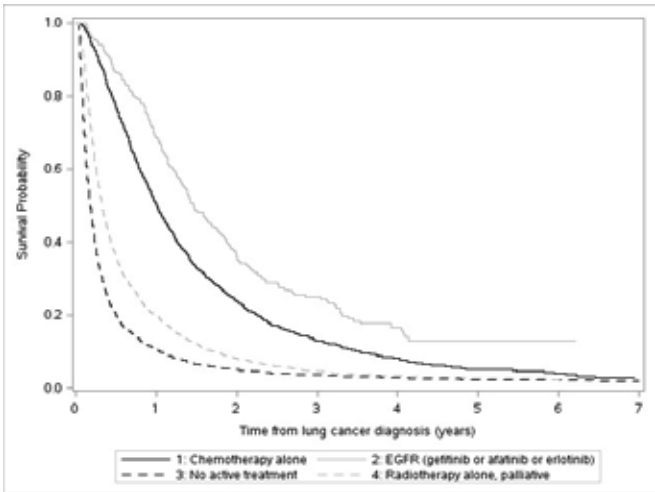
Background: The majority of NSCLC patients are diagnosed with stage IV disease. With the development of targeted therapies for advanced NSCLC, it has become important to understand which patients are being treated with systemic therapies and to what benefit. **Method:** We conducted a longitudinal, population-level study to determine the treatment patterns and survival in patients with stage IV NSCLC in Ontario, Canada between April 1, 2010 and March 31, 2015 from the Ontario Cancer Registry (OCR). Individuals were further identified as having non-squamous disease, and those who received an EGFR-TKI (afatinib, erlotinib, gefitinib) were assumed to be EGFR mutation-positive (EGFR+). Survival was calculated from date of diagnosis to death. **Result:** 24,729 individuals were diagnosed with NSCLC. Approximately half (12,159; 49.2%) had stage IV disease, including 10,103 with non-squamous disease, of whom 508 were categorized as EGFR+. The mean age for the stage IV non-squamous and EGFR+ cohorts were 68.7±11.0 years and 69.1±10.4 years, respectively; 49.3% and 60.8% were female, respectively. The most frequent treatments for stage IV non-squamous patients were palliative radiotherapy (RT) (46.7%) and systemic therapy (14.9%). Patients received no treatment in 26.7% of cases. 75.6% of the EGFR+ cohort received gefitinib, with the majority receiving no subsequent treatment (44.6%). Of EGFR+ patients receiving a second-line treatment, 20.1% received palliative RT and 18.7% received chemotherapy. Mean and median survival times (IQR) for the stage IV non-squamous patients were 0.9±0.0 years and 0.4 (0.2-1.0) years,

respectively. Substantial variation in survival was noted by treatment (Figure 1). Mean and median survival times (IQR) for the EGFR+ cohort were 1.9±0.1 years and 1.5 (0.9-3.0) years, respectively. Figure 1. Kaplan-Meier survival curves for stage IV non-squamous NSCLC patients based on treatment



Conclusion: Relatively few patients with stage IV non-squamous NSCLC receive any systemic therapy. Survival is generally very poor, but best in the subgroup of EGFR+ patients.

Keywords: Real World Evidence, treatment patterns, non small cell lung cancer

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.15-29 IMPACT OF RADIATION THERAPY QUALITY ASSURANCE ON PROGRESSION-FREE AND OVERALL SURVIVAL IN RANDOMIZED TRIALS OF LUNG CANCER

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Background: To evaluate if the estimates of treatment effect differ between randomized trials (RCTs) that reported radiation therapy quality assurance (RTQA) and RCTs, which did not report RTQA, for treatment of lung cancer (LC) [C1] using curative intent thoracic radiation therapy (TRT). **Method:** We searched MEDLINE for eligible meta-analyses (MAs) of RCTs of LC. For each trial in the selected MAs, we reviewed if RTQA was performed and extracted the hazard ratios (HR) with 95% confidence interval (CI) for progression-free (PFS) and overall survival (OS). We quantify the differences in the estimated intervention effect on PFS and OS by a ratio of HRs (rHRs): the HR for trials that performed RTQA to that of trials that did not perform or report RTQA. An rHR more than 1 would indicate a larger HR for trials that performed RTQA compared to trials that did not perform or report. We estimated a combined rHR across MAs using a random effects MA model. We performed a meta-regression analysis to adjust for potential confounders including cancer type, comparisons type, sample size and single-vs-multi center trial . **Result:** We included six MAs that comprised of six comparisons and 50 RCTs (22 reported RTQA; 28 did not). Trials that performed RTQA showed similar intervention effect on PFS (rHR 0.96, 95% CI 0.82 to 1.12, P value (P) = 0.57, I squared (I^2) = 0%) and OS (rHR 1.00, 95% CI 0.88 to 1.15, P = 0.94, I^2 = 0%) compared to trials that did not perform or report RTQA, with low heterogeneity across individual MAs. There was no significant change in the summary rHRs after adjusting for potential confounders. **Conclusion:** The conduct of RTQA did not modify the estimates of intervention effects on progression-free and overall survival in randomized trials of lung cancer treated with curative intent thoracic radiation therapy.

Keywords: radiation therapy, clinical trials, Quality assuarance

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.15-30 SURVIVAL OF PATIENTS WITH ADVANCED NSCLC TREATED WITH FIRST-GENERATION EGFR-TKIS AT A CANCER HOSPITAL IN THAILAND, 2011-2016

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Background: This study was to find the survival in advanced NSCLC patients treated with an EGFR-TKI in a real-life practice. **Method:** The researcher conducted this retrospective study by review medical records in stage IIIB-IV NSCLC patients treated with first-generation EGFR-TKIs at Chonburi Cancer Hospital from January, 2011 to December, 2016 and follow up until December, 2017. **Result:** This study enrolled 50 patients with median follow up time 16.78 months. The median age of patients was 58.5. There were female (46%), non-smoking (62%) and adenocarcinoma (90%). The patients received an EGFR-TKI by purchase by themselves (52%), reimbursement system (32%) and compassionate use (14%), additionally Eastern Cooperative Oncologic Group (ECOG) performance statuses were 0-1 (54%), 2-4 (28%) and non-available (NA) (18%).Treatment responses stratified by line of therapy and EGFR status were shown (table)

EGFR-TKIs treatment	EGFR mutation status	Response to an EGFR-TKI				Total (N)
		PR	SD	PD	NA	
First-line (1L)+ maintenace (MN) (n=16+2)	Sensitive	3	1	0	0	4
	Wild-type	0	2	0	0	2
	Unknown	4	4	2	2	12
Second-line (2L) (n=18)	Sensitive	1	3	0	0	4
	Wild-type	0	0	1	1	2
	Unknown	5	2	4	1	12
Third-ine or more (>/=3L) (n=14)	Sensitive	2	1	0	0	3
	Wild-type	0	0	1	1	2
	Unknown	1	1	5	2	9
Total (N)		16	14	13	7	50

The overall survivals (OS) of the patient receiving an EGFR-TKI as 1L or MN (n=18), 2L (n=18) and >/=3L (n=14) were 15.86 (95%CI, 10.26-21.46), 10.87 (95%CI, 0.00-28.29) and 20.23 (95%CI, 6.26-34.21) months (p=0.392), respectively. Regarding EGFR status, the OS of patients with EGFR sensitive mutation (n=11), wild-type (n=6) and unknown (n=33) were 30.75 (95% CI, 13.76-47.74), 7.91 (95% CI, 0.00-20.45) and 13.99 (95%CI, 9.17-18.82) months (p=0.086), respectively. Multivariate analysis indicated that age >/=70 years old (p=0.047) ,current or former smoking (p=0.012), ECOG performance status 2-4 or NA (p<0.001), received EGFR-TKIs by payment (p=0.033) or compassionate use (p<0.001) were the unfavorable prognostic factors for the OS. **Conclusion:** The OS of the patients harboring EGFR sensitive mutation at our hospital was comparable to those of other pivotal studies. Clearly, patients harboring EGFR wild-type had the OS much shorter than those of the sensitive mutation group. In real practice at that time, two-third of patients still have not been proved their EGFR statuses before starting an EGFR-TKI and often received it as second-line or more.

Keywords: Real-world practice, first generation EGFR-TKIs, advanced NSCLC

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.15-31 SURVIVAL AND PATTERNS OF CARE COMPARING BLACK AND WHITE PATIENTS WITH ALL STAGES OF NSCLC: AN NCDB ANALYSIS

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Background: Race and other socioeconomic factors continue to influence survival in patients with non-small cell lung cancer (NSCLC). Recent population-based studies have paradoxically shown a survival advantage

in the black population compared to white patients with stage III NSCLC. To further investigate this, we analyzed stage-wise overall survival (OS) and patterns of care in black patients as compared to white patients with NSCLC using the National Cancer Database (NCDB). **Method:** All black and white patients within the NCDB with biopsy-proven, stages I-IV NSCLC from 2004-2013 were analyzed. Associations between demographics was assessed using c^2-tests. Guideline concordant care (GCC) and non-guideline concordant care (NGCC) were defined for each stage as per NCCN guidelines. OS between the races were analyzed using the log-rank test and the multivariable Cox proportional hazards regression. **Result:** When compared to white patients, black patients were younger at presentation (</=60years: 36.2% vs. 22.5%, p<0.001), had a lower household income (<$30,000: 37.9% vs. 11.5%, p<0.001), twice as likely to not have insurance (6.4% vs. 2.9%, p<0.001) and were diagnosed with more advanced disease (stage I: 18% vs. 24.9%, stage II: 6.1% vs. 6.9%, stage III: 25.9% vs. 23.7%, stage IV: 50% vs. 44.5%, p<0.001). White patients were more likely to undergo GCC in stages I-III when compared to black patients (stage I: 77% vs. 69.6%; stage II: 68.5% vs. 65.3%; stage III: 52.8% vs. 51.9%) but had a very similar incidence of GCC in stage IV (stage IV: 66.7% vs. 67.3%, p<0.001). Black race was associated with a 17%, 5%, and 3% increase risk of NGCC in stage I (OR: 0.835, 95% CI: 0.817-0.852, p<0.001), stage II (OR: 0.947, 95% CI: 0.916-0.978, p=0.001) and stage III (OR: 0.970, 95% CI: 0.954-0.985, p<0.001) disease, respectively, when compared to white patients in multivariate analysis (MVA). While in stage IV, being black predicted for a 4% greater receipt of appropriate treatment (OR: 1.041, 95% CI: 1.028-1.054, p<0.001). In the Cox MVA, race was not linked to OS in stage I or II disease, but being black predicted for a 3% lower risk of death in stage III and IV (stage III: HR: 0.973, 95% CI: 0.965-0.982, p<0.001; stage IV: HR: 0.967, 95% CI: 0.961-0.973, p<0.001). **Conclusion:** Black patients with NSCLC had similar or slightly improved OS when compared to white patients after accounting for socioeconomic demographics, staging and patterns of care. To explain this contradictory finding, further research should investigate biological differences between the two races.

Keywords: NSCLC, Disparity, Black

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.15-32 REAL WORLD EGFR MUTATION PROFILE FROM 1699 NON-SMALL CELL LUNG CANCER PATIENTS IN EASTERN CHINA

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Background: The EGFR mutation frequency and mutation types had significant geographic differences. The purpose of this study was to evaluate prevalence, clinical characteristic in eastern China which has not been reported. **Method:** From March 2016 to March 2018 who were newly diagnosed or postoperative recurrence NSCLC received EGFR mutation detect were included analysis. Commercially available ARMS-PCR kits were used to detect EGFR mutations. **Result:** A total of 1699 consecutive NSCLC patients included in our study. The median age was 64 years (range 23-91), with 892 (52.5%) were male and 807 (47.5%) male. There were 852 (50.2%) with EGFR mutations out of 1699 patients in the total population. EGFR mutations were more frequent in female (64.9%) patients than in males (36.8%). Considering the frequency of mutations according to histology, adenocarcinomas (835/1495, 55.9%) show mutations more often than squamous carcinoma (4/142, 2.82%), other NSCLC histology (13/62, 21.0%). The rate of EGFR mutation in total was lower in biopsy specimen (246/613, 40.1%) than in surgical specimen (557/993, 56.1%) or cytology specimen(49/93, 52.69%). A total of 755 (88.6%) harboring a common EGFR mutation were identified: among the 755, the most EGFR mutation type was the point mutation L858R at 21 exon (49.5%), followed by exon 19 deletion (39.1%). Ninety-seven (11.48%) patients harboring uncommon EGFR mutation, the exon 20 INS (34.0%) was the most frequently observed mutation among the uncommon EGFR mutations. The detailed EGFR mutation type were show in table1.

Table1. The detailed EGFR mutation type

	Mutation type	Case number	Percentage of all cases	Percentage of uncommon mutation
common mutation	L858R	422	49.53%	
	19-del	333	39.08%	
uncommon mutation	20-Ins	33	3.87%	34.0%
	L858R/T790M	18	2.11%	18.6%
	G719X	14	1.64%	14.4%
	L861Q	11	1.29%	11.3%
	G719X/S768I	5	0.59%	5.2%
	L858R+-S768I	5	0.59%	5.2%
	S768I	4	0.47%	4.1%
	19-del/T790M	3	0.35%	3.1%
	G719C	1	0.12%	1.0%
	L858R/19-del	1	0.12%	1.0%
	L858R/20-Ins	1	0.12%	1.0%
	T790M	1	0.12%	1.0%

EGFR: Epidermal growth factor receptor.

Conclusion: In our eastern China cohort, the most common EGFR mutation was L858R, differing from previous reported data in Asian population describing 19 deletion was the most common EGFR mutation. The frequency of EGFR mutations in biopsy specimen population was lower than both in surgical specimen and cytology specimen.

Keywords: epidermal growth factor receptor (EGFR), mutation, non-small cell lung cancer (NSCLC)

P1.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.15-33 REAL-WORLD DATA ON PROGNOSTIC FACTORS FOR OVERALL SURVIVAL IN NSCLC PATIENTS TREATED WITH BEVACIZUMAB COMBINATION THERAPY

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Background: Bevacizumab is used as combination with chemotherapy as 1st-line treatment for non-squamous cell carcinoma. In order to understand the influence of bevacizumab on different combination medication response, this study aimed to identify independent prognostic factors for overall survival (OS) of NSCLC patients receiving bevacizumab treatment in real-world practice. **Method:** We performed retrospective collected non-squamous cell carcinoma patients undergoing bevacizumab treatment and analyzed their response and overall survival to bevacizumab. Demographic data, TTF-1 stain status, *EGFR* mutation status, and survival data were collected. Survival data analysis were plotted by the Kaplan–Meier method and compared by the log-rank test. **Result:** From November 2009 to October 2015, 114 non-squamous cell carcinoma patients treated with bevacizumab were enrolled for analysis. The median overall survival was 21.9 months. There were 11 patients who received continuous bevacizumab beyond disease progress of 1st-line treatment and in all treatment courses. They had longer overall survival than those (N = 103) who did not received bevacizumab in all treatment courses (p = 0.003). The patients harboring positive TTF-1 tumor also had a longer overall survival than those harboring negative TTF-1 tumors (p = 0.025). Multivariate analysis revealed that patients harboring tumor with positive staining of TTF-1 (p < 0.001) and those received bevacizumab in all treatment course (p = 0.013) had a longer median OS. **Conclusion:** Non-squamous cell carcinoma patients receiving bevacizumab beyond 1st-line treatment failure, as all treatment course, had a longer median OS than those received bevacizumab in partial course.

Keywords: bevacizumab, lung cancer, overall survival

P1.15-34 TREATMENT PATTERNS AND OUTCOMES OF STAGE III NON-SMALL CELL LUNG CANCER (NSCLC): REAL WORLD EVIDENCE OF HOW OUR PATIENTS FARE

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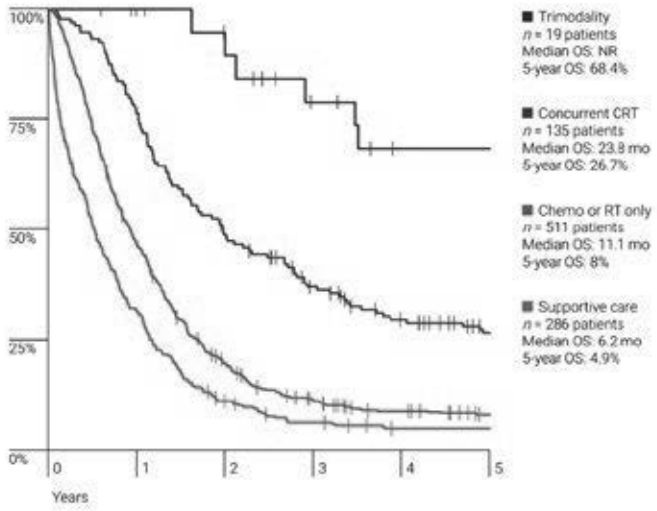
Background: Most patients withstage III non-small cell lung cancer (NSCLC) develop metastases and succumb to their cancer. New treatment strategies, including concurrent chemo–RT (cCRT) followed by adjuvant immunotherapy, are improving outcomes, but need to be contextualized with real world data. In this study, we described population-based treatment patterns and outcomes for stage III NSCLC in a large Canadian province. **Method:** Through the provincial cancer registry, patients diagnosed with stage III NSCLC from April 1st 2010 to March 31st 2015 were identified. Using electronic medical records and administrative claims, stage III patients were merged with treatment and survival information. Patient characteristics, treatment patterns, and outcomes were analyzed. **Result:** 6,438 patients were diagnosed with NSCLC, including 1,151 (17.9%) with stage III disease. Median age at diagnosis was 70 years (22–94); 50.2% were male. The majority were stage IIIA (61.2%); the remainder was stage IIIB (36.4%) or unspecified (2.4%). Most patients received palliative RT (32.8%), supportive care until progression (24.8%), or palliative chemotherapy (14.8%) as initial treatments. Relatively few underwent cCRT (11.7%) or trimodality therapy (1.7%). Resection was performed on 14.8% of patients. Within the resected cohort, the majority (47.6%) did not receive further perioperative treatment, while others had surgery as part of trimodality (11.2%) or alongside perioperative chemotherapy (37.1%). Overall, the median OS (mOS) was 13.3 months (0–NR). Initial treatment strategy predicted outcomes (p< 0.05). Patients who underwent cCRT had mOS of 23.8 months (1.1–not reached [NR]). mOS for patients who initially received palliative chemotherapy or RT was 11.1 months (0.3–NR), and 6.2 (0–NR) with supportive care (Figure 1). **Figure 1: Kaplan–Meier curves for stage III NSCLC stratified by treatment class**



Conclusion: Treatment rates for cCRT and trimodality therapy in our cohort appear lower than expected despite evidence supporting the benefits of these strategies. Use of other treatment options was associated with poorer outcomes.

Keywords: outcomes, Treatments, NSCLC

P1.15-35 REAL WORLD OUTCOME OF DIFFERENT ADMINISTRATIONS ENDOSTAR COMBINED WITH CHEMOTHERAPY IN DRIVER GENE MUTATION NEGATIVE ADVANCED NSCLC

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Background: To compare the efficacy and safety of different administration endostar combined with platinum-based chemotherapy with first-line treatment of driver gene mutation negative advanced NSCLC patients, and provides real-world evidence for optimum administration of endostar. **Method:** From April 2014 to April 2017, 88 driver gene mutation negative patients who received platinum-based chemotherapy alone or combined with endostar were retrospectively enrolled in this project. All the patients were divided to three groups, including platinum-based chemotherapy alone (arm A), combined with 14 days endostar (7.5 mg/m2, d1-14, q21d, arm B) and 7 days endostar (15 mg/m2, d1-7, q21d, arm C). The primary endpoint was median overall survival (OS). The secondary endpoints were median progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). The efficacy and safety was evaluated every 2 cycles. **Result:** Of all the 88 enrolled patients, the median OS was 20 months in endostar groups (arm B and arm C) and 10 months in chemotherapy alone group (arm A, P<0.001). The median PFS was months and 4.5 months respectively (P=0.073). The median OS was 22 months (arm B) and 14 months (arm C, P = 0.01). The median PFS was 6 months in arm B, 6.5 months in arm C, and 4.5 months in arm A. The ORR were 44.4%, 22.2% and 20.6% for arm B (P=0.046), arm C (P=0.877) and arm A respectively. The DCR were 88.9%, 77.8% and 64.7% for arm B (P=0.046), arm C (P=0.266) and arm A respectively. There is no meaningful difference in OS between arm B and arm C (P=0.111), as well as ORR (P=0.074) and DCR (P=0.234), but a meaningful difference in PFS (P=0.044). The incidence of adverse event in the three groups was 22.2%, 3.7%, and 11.6%, respectively. There was no new occurring intolerant adverse event. **Conclusion:** Endostar plus platinum-based doublet chemotherapy can significantly improve short-term and long-term outcomes in driver gene mutation negative advanced NSCLC. The administration of 14 days endostar compared to 7 days has no significant improvement in efficacy, but results in a higher incidence of adverse events.

Keywords: Endostar, driver gene mutation negative advanced NSCLC, Different administrations

P1.15-36 A BETTER REAL WORLD PRACTICE FOR PEMETREXED IN FIRST-LINE TREATMENT OF ADVANCED MON-SQUAMOUS NON-SMALL CELL LUNG CANCER

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Background: To investigate the real world practice of first-line pemetrexed combined with different drugs in patients with advanced Non-squamous non-small cell lung cancer. **Method:** A total number of 164 patients from February 2012 to August 2017 in Hunan Cancer Hospital in the combination of pemetrexed with cisplatin were enrolled in this study. All the patients were divided into 5 groups: PC-P (pemetrexed combined with platinum for 4 cycles and pemetrexed maintenance, arm A), PCA-PA (Pemetrexed plus platinum and bevacizumab 4cycles, pemetrexed combined with bevacizumab maintenance, arm B), PC (pemetrexed combined with platinum chemotherapy 4 cycles, arm C), PCA (pemetrexed with platinum chemotherapy, plus bevacizumab 4 cycles without maintenance, arm D), PC-EGFR TKI (pemetrexed plus platinum chemotherapy 4 cycles, and then EGFR TKI as maintenance treatment, arm E). Efficacy and safety of pemetrexed was performed in each group comparing with each major clinical data. **Result:** According to retrospective study , the median PFS for arm A, B, C, D and E were 13 months, 12 months, 5 months, 5 months, 15.8 months respectively; the median OS was 27 month, 21 months, 15 months, 11 months and 31 months respectively. Arm A and Arm C, Arm B and Arm D achieved statistically different on PFS (p<0.05). And Arm A and Arm C, Arm B and Arm D also achieved statistical differences between OS (p<0.05). In the multivariate regression analysis of all patients, we found that the ECOG PS score may be an independent prognostic factor for death from lung cancer patients. Among all the patients, 35 (21.4%) patients presented with non-hematologic serious adverse event (grade 3 and 4). There

was no new occurring intolerant adverse event comparing with other clinical trials. **Conclusion:** In this real world study, pemetrexed proved to be high efficacy and well tolerant in advanced NSCLC. The efficiency of maintenance pemetrexed treatment group achieved significantly better outcome than the non-maintenance treatment group. In addition, ECOG PS score may be an independent prognostic factor for the death of patients in lung cancer. There was no new occurring intolerant adverse event comparing with previous clinical trials, the main adverse events in this study were also focused on non-hematologic toxicity. This is consistent with clinical trials.

Keywords: pemetrexed, Efficacy and safety, nonsquamous non-small-cell lung cancer

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-01 PROGNOSTIC VARIABLES ASSOCIATED WITH IMPROVED OUTCOMES IN STAGE III NSCLC PATIENTS TREATED WITH CONSOLIDATION PEMBROLIZUMAB

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Background: HCRN LUN 14-179 is a phase II trial of consolidation pembrolizumab following concurrent chemoradiation for the treatment of patients with stage III NSCLC. Time to metastatic disease, PFS, and OS appear superior to historical controls of chemoradiation alone. Unfortunately, not all patients benefit from consolidation immunotherapy. We performed a univariate analysis evaluating variables associated with PFS, metastatic disease, and OS. **Method:** We conducted a retrospective analysis from patients enrolled on HCRN LUN14-179. Data collected included age, sex, stage, smoking status, PD-L1 status, ≥G2 vs ≤G1 adverse event, ≤G2 vs. ≥G3 pneumonitis, duration of pembrolizumab (<4 vs. ≥4 cycles), chemotherapy regimen, PS 0 vs 1, time to start pembrolizumab (<6 vs. ≥6 weeks from radiation), V_{20} (<20% vs. ≥20%), and total radiation dose. Univariate Cox regression was performed to determine the variables associated with 3 endpoints: time to metastatic disease/death; progression free survival; and overall survival. **Result:** From April 2015 to December 2016, 93 patients were enrolled and 92 were included in the efficacy analysis (1 patient was ineligible). For time to metastatic disease or death, improved outcomes may be associated (p<0.1) with stage IIIA, non-squamous cell, >4 cycles of pembrolizumab, and V_{20}< 20%. For PFS, improved outcomes (p<0.1) may be seen for females, stage IIIA, non-squamous histology, PD-L1 [-] tumors, ≥4 cycles of pembrolizumab, and V_{20}< 20%. For OS, improved outcomes (p<0.1) may be seen for non-squamous histology, PD-L1 [-], ≥4 cycles of pembrolizumab, V_{20}< 20%, and ≤G2 pneumonitis. **Conclusion:** Non-squamous NSCLC, PD-L1 [-] tumors, and V_{20} <20% may be associated with prolonged time to metastatic disease or death, PFS, and OS for patients with stage III NSCLC treated with chemoradiation followed by pembrolizumab.

Variable	Alive without metastatic disease	Alive without progression	Alive
IIIA (n=55) IIIB (n=37)	69% p=0.12 51%	56% p=0.21 41%	69% p=0.13 59%
Non-SCCA (n=51) SCCA (n=41)	69% p=0.11 54%	55% p=0.21 44%	75% p=0.16 61%
PD-L1 [-] (n=11) PD-L1 [+] (n=42)	82% p=0.13 57%	64% p=0.19 40%	91% p=0.07 62%
≥ 4 pembro (n=77) < 4 pembro (n=15)	67% p=0.01 33%	55% p=0.04 27%	75% p=0.001 33%
V_{20} < 20% (n=19) V_{20}≥ 20% (n=59)	79% p=0.07 54%	63% p=0.08 39%	79% p=0.15 61%
G ≤ 2 pneumonitis (n=87) G ≥ 3 pneumonitis (n=5)	63% p=0.28 40%	51% p=0.61 40%	70% p=0.16 40%
Female (n=33) Male (n=59)	67% p=0.37 59%	67% p=0.11 59%	73% p=0.51 66%

Keywords: survival, Stage III NSCLC, pembrolizumab

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-02 SUPPORT AND INFORMATION NEEDS FOR PATIENTS WITH NSCLC RECEIVING CONCURRENT CHEMO-RADIOTHERAPY: FINDINGS FROM THE INSIGHT STUDY.

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Background: The curative intent pathway for patients with non-small cell lung cancer (NSCLC) is complex and burdensome. Concurrent chemotherapy and radiotherapy (chemo-radiotherapy) is used as first line treatment for inoperable stage 3 cancer,and requires the patient to attend multiple investigational procedures, separate appointments for chemotherapy and radiotherapy, intensive monitoring during treatment and multiple follow-up visits post treatment for up to 5 years to monitor late-toxicities and disease recurrence.The aims of this study are to identify the information needs of patients and their carers at key points along the treatment pathway and the preferred methods for information provision. A grant was awarded by the NLCFN to fund this patient experience, qualatative research study. **Method:** Semi-structured interviews were conducted with 15 patients, and their carer dyads where appropriate, recruited from a cancer centre in Manchester, U.K. **Result:** Data collection is now complete with 15 patients recruited, of whom 6 were interviewed with a carer dyad. Thematic analysis is on-going and has been employed inductively to identify some of the emerging themes and key issues from the data collected. These include; preferred means of receiving information and level of information given, burden of treatment and earlier access to supportive care, information about life after treatment and the after effects of treatment, and preferred methods to access appropriate support. **Conclusion:** Further research is needed into the on-going needs of this patient cohort and data collection so far highlights areas for consideration when providing information to this patient cohort. Emerging themes highlight that a specific booklet on concurrent chemo/radiotherapy would be preferred, covering all aspects of treatment, including a personalised treatment plan to include, where relevant mask wearing, the impact of side effects of treatment and how assess support. Early indications are that patients prefer a combination of verbal, written and visual information giving. Collaboration work to link these patients on the concurrent treatment pathway in with early supportive care is optimal. Implementation of this service as part of the Concurrent treatment pathway will commence as a pilot study in July 2018, to assess the impact of earlier intervention to manage disease burden and treatment side effects, with an aim to reduce hospital admissions. The evidence suggests further work is needed to improve information giving and support to these patients both pre and post treatment. Additional advice is required to support proactive management, to enhance recovery, whilst addressing the fear and anxiety patients and carers experience due to uncertain outcomes.

Keywords: patient, Experience, treatment

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-03 PROGNOSTIC SIGNIFICANCE OF PD-L1 IN STAGE II/III NON-SMALL CELL LUNG CANCER

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Background: Prognostic significance of PD-1/PD-L1 axis expression in non-small cell lung cancer (NSCLC) remains uncertain despite being a predictive biomarker for novel immunotherapeutics. In this study, we have investigated PD-1/PD-L1 expression and its effect on disease prognosis and overall survival in stage II-III NSCLC patients. **Method:** Clinic and pathologic features of stage II and stage III NSCLC patients were retrospectively analyzed from patients' records in this study. PD-1 and PD-L1 immunohistochemistry staining were carried out to archived tumor specimens of the eligible patients. Percentages of PD-1 positive lymphocytes, PD-L1 positive tumor cells and PD-L1 positive tumor infiltrating immune cells were evaluated and considered as positive if ≥1% of the cells displayed staining. **Result:** Sixty-six male (89,2%) and 8 female (10,8%) of total 74 patients were eligible for the study. Thirty-three (44,6%) patients were diagnosed as stage II disease while 41 patients (55,6%) were diagnosed as stage III. PD-1 expression, PD-L1 expression in tumor cells and PD-L1 expression in tumor infiltrating

immune cells were positive in 83,8% (n = 62), 45,9% (n = 34), 67,6% (n = 50) of total 74 patients, respectively.Three-year overall survival (OS) rate was calculated as 57,7%. Univariate analyses did not reveal any significant difference in 3-years OS between those with PD-1 and PD-L1 expression in tumor infiltrating immune cells and those without expression. (p = 0,413 and p = 0,099; respectively) However, 3-years OS was more favorable in those with PD-L1 expression in tumor cells than in those without PD-L1 expression (76,6% vs %41%, p = 0.031). In multivariate analyses, a positive trend was revealed in 3-years OS between those with PD-L1 expression in tumor cells and those without expression. (HR: 0,405; 95% CI: 0,153, 1,074; p = 0,069) **Conclusion:** In this study, better prognosis was obtained with positivity of PD-L1 in tumor cells. Therefore, it should be taking into consideration while designing adjuvant immunotherapy trials which are generally formed with stage I-III NSCLC patients, that expression of PD-1/PD-L1 pathway may have a positive prognostic effect.

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-04 OUTCOMES OF PATIENTS <70 OR ≥70 YEARS OF AGE IN PACIFIC

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Background: In the Phase 3 PACIFIC study of durvalumab versus placebo in patients with stage III, unresectable NSCLC without progression after concurrent chemoradiotherapy (cCRT), the co-primary endpoint PFS was significantly longer with durvalumab (stratified HR 0.52, 95% CI, 0.42–0.65; P<0.0001). In a prespecified analysis, PFS benefit with durvalumab was observed regardless of a 65-year age cutoff. However, median age at NSCLC diagnosis is 70 (CA Cancer J Clin, 2014). We therefore performed subgroup analyses to explore outcomes using a 70-year age cutoff. **Method:** PACIFIC (NCT02125461) was a Phase 3, randomized, double-blind, all-comers study of patients with WHO PS 0/1 who did not progress following ≥2 cycles of platinum-based cCRT. Patients were stratified by age, sex, and smoking history and randomized (2:1) 1–42 days after cCRT to receive durvalumab 10 mg/kg IV Q2W or placebo up to 12 months. Co-primary endpoints were PFS (BICR, RECIST v1.1) and OS (not available). Secondary endpoints included ORR, time to death/distant metastasis (TTDM), and safety. Between-treatment endpoint comparisons were performed for patients <70 and ≥70 years. **Result:** As of Feb 13, 2017, 713 patients were randomized; 78% and 22% were <70 and ≥70 years, respectively. Baseline patient and tumor characteristics were generally well balanced across subgroups. However, patients ≥70 were more likely to be male, have PS 1, and, within the placebo arm, to be Asian. Older patients more commonly received carboplatin-based CT than younger patients. Durvalumab demonstrated PFS benefit compared with placebo, regardless if patients were <70 years (median 16.9 vs 5.6 months, HR=0.53, 95% CI: 0.42–0.67) or ≥70 years (median 12.3 vs 6.1 months, HR=0.62, 95% CI: 0.41–0.95). Durvalumab improved TTDM (<70 years: HR=0.53, 95% CI: 0.39–0.71; ≥70 years: HR=0.66, 95% CI: 0.39–1.13) and ORR (<70 years: 27.6% vs 15.4%; ≥70 years: 31.9% vs 17.6%) regardless of age. Younger patients on durvalumab received treatment longer (median total duration 45.5 vs 36.0 weeks). Regardless of treatment, older patients discontinued more due to AEs (durvalumab: 22.0% vs 13.7%; placebo: 16.1% vs 7.8%) and had more grade 5 AEs (durvalumab: 10.9% vs 2.7%; placebo: 9.1% vs. 4.5%). Among patients receiving durvalumab, older patients experienced more all-cause SAEs (42.6% vs 24.9%) and grade 3/4 AEs (41.6% vs 29.4%) but fewer AESIs (56.4% vs 67.9%) than younger patients. **Conclusion:** Patients achieved clinical benefit with durvalumab regardless of age. Increased AEs/SAEs observed in older patients across treatments may reflect age/cCRT related morbidity.

Keywords: elderly, PACIFIC, durvalumab

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-05 EFFECT OF INDUCTION CHEMOTHERAPY IN THE PACIFIC STUDY

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Background: The Phase 3 PACIFIC study of patients with stage III, unresectable NSCLC without progression after concurrent chemoradiotherapy (cCRT) demonstrated significantly longer PFS with durvalumab versus placebo (stratified HR 0.52; 95% CI 0.42–0.65; P<0.0001). Overall, 26% and 29% in the durvalumab and placebo groups, respectively, received induction chemotherapy (ICT) before cCRT. Here, we report exploratory analyses of baseline characteristics, disposition, and outcomes from this study based on the presence or absence of prior ICT. **Method:** PACIFIC (NCT02125461) was a Phase 3, randomized, double-blind study of patients with WHO PS 0/1 and any tumor PD-L1 status without progression after ≥2 cycles of platinum-based cCRT. Patients were stratified by age, sex and smoking history and randomized (2:1) to durvalumab 10 mg/kg IV Q2W or placebo up to 12 months. Co-primary endpoints were PFS (blinded independent central review, RECIST v1.1) and overall survival (not available). We investigated associations between the presence/absence of ICT and disposition, baseline characteristics, and efficacy and safety endpoints. **Result:** As of February 13, 2017, 713 patients were randomized; 27% had prior ICT. Baseline characteristics were similar between treatment arms; however, patients with ICT were generally younger, less frequently Asian, had lower incidence of squamous histology, and more often had stage IIIB disease. There were no differences between groups in terms of prior RT dose. PFS benefit with durvalumab was demonstrated irrespective of ICT use (ICT: HR=0.61, 95% CI, 0.41–0.88; no ICT: HR=0.54, 95% CI, 0.42–0.69). Similarly, ORR with durvalumab was numerically higher than with placebo irrespective of ICT use (ICT: 16.1% vs 13.1%; no ICT: 32.9% vs 17.1%). ICT did not affect treatment duration for durvalumab or placebo. Between-treatment safety differences were minimal across subgroups; however, patients with ICT experienced fewer SAEs, treatment-related SAEs and pneumonitis/radiation pneumonitis regardless of treatment arm. **Conclusion:** Durvalumab demonstrated clinical benefit irrespective of ICT. The safety profile of durvalumab was consistent in patients with or without ICT. A lower rate of toxicity was observed in patients with ICT regardless of treatment arm.

Keywords: induction chemotherapy, PACIFIC, durvalumab

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-06 EXPANDED EFFICACY AND SAFETY ANALYSIS OF PACIFIC BASED ON A PD-L1 CUTPOINT OF 25%

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Background: In the Phase 3 PACIFIC study of patients with stage III, unresectable NSCLC without progression after concurrent chemoradiotherapy (cCRT), PFS was significantly longer with durvalumab versus placebo (stratified HR 0.52; 95% CI 0.42–0.65; P<0.0001). We report exploratory analyses of PACIFIC outcomes by PD-L1 expression assessed in tumor samples collected prior to cCRT. **Method:** PACIFIC

(NCT02125461) was a Phase 3, randomized, double-blind study of patients with WHO PS 0/1 without progression after ≥2 cycles of platinum-based cCRT. Eligibility was irrespective of PD-L1 expression; archived samples were optional for testing (VENTANA PD-L1 [SP263] assay). No samples were obtained after cCRT, prior to infusion with durvalumab or placebo. Patients were randomized (2:1) to durvalumab 10 mg/kg IV Q2W or placebo up to 12 months, stratified by age, sex and smoking history. Co-primary endpoints were PFS (blinded independent central review, RECIST v1.1) and OS (not available). Secondary endpoints included ORR and safety. We investigated associations between subgroups of patients with PD-L1 expression on tumor cells (TC) of <25% or ≥25% and efficacy. **Result:** As of February 13, 2017, 713 patients were randomized; 451 (63.3%) had known PD-L1 status (TC<25%, 64.7%; TC≥25%, 35.3%; **Table**). Baseline characteristics and prior therapy (including best response to prior therapy) were generally well balanced between arms across both PD-L1 subgroups. PFS benefit with durvalumab was demonstrated irrespective of PD-L1 status (HR 0.59; 95% CI, 0.43–0.82 for TC<25% and HR 0.41; 95% CI, 0.26–0.65 for TC≥25%) (**Table**). ORR was greater with durvalumab compared to placebo regardless of PD-L1 status (**Table**). The overall safety profile of durvalumab in each PD-L1 subgroup was consistent with the ITT population treated with durvalumab. **Conclusion:** Durvalumab demonstrated clinical benefit and had a well-tolerated, manageable safety profile irrespective of PD-L1 status obtained from archival tumor samples prior to cCRT.

	PD-L1 TC<25%		PD-L1 TC≥25%	
	Durvalumab (n=187)	Placebo (n=105)	Durvalumab (n=115)	Placebo (n=44)
Completed 12 months treatment, n (%)	74 (39.6)	35 (33.3)	55 (47.8)	13 (29.5)
PFS*				
Median (95% CI), months	16.9 (11.0–NR)	6.9 (5.0–11.0)	17.8 (11.1–NR)	3.7 (2.0–13.2)
HR (95% CI)	0.59 (0.43–0.82)		0.41 (0.26–0.65)	
ORR†	n=170	n=96	n=108	n=40
n (%) [95% CI]	50 (29.4) [22.7–36.9]	19 (19.8) [12.36–29.17]	31 (28.7) [20.4–38.2]	6 (15.0) [5.71–29.84]

**In the overall ITT population, median PFS was 16.8 months (95% CI, 13.0–18.1) with durvalumab (n=476) vs. 5.6 months (95% CI, 4.6–7.8) with placebo (n=237), with an HR of 0.52 (95% CI, 0.42–0.65; P<0.001) (stratified log-rank); PD-L1 assessment was not required in the study; in PD-L1 unknown patients, median PFS was 14.0 months (95% CI, 9.2–NR) with durvalumab (n=174) vs. 6.4 months (95% CI, 3.8–9.0) with placebo (n=88), with an HR of 0.59 (95% CI, 0.42–0.83) (unstratified Cox proportional hazards model); †ORR for n evaluable patients included unconfirmed responses. ITT, intention-to-treat; NR, not reached; ORR, objective response rate; PFS, progression-free survival.*

Keywords: durvalumab, PACIFIC, PD-L1

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P1.16-07 COST-EFFECTIVENESS OF PEMBROLIZUMAB AS 1ST LINE TREATMENT FOR METASTATIC NSCLC PATIENTS WITH HIGH PD-L1 EXPRESSION IN SINGAPORE

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Background: Pembrolizumab, an immune checkpoint inhibitor, has been approved as monotherapy for 1st line treatment of metastatic NSCLC with PD-L1 tumor proportion score (TPS) ≥50% based on the pivotal Keynote (KN)-024 study. This study aims to evaluate the cost-effectiveness of pembrolizumab compared with standard-of-care (SoC) platinum-based chemotherapy in patients with TPS≥50% from a societal perspective in Singapore based on results from KN024. **Method:** A known partitioned-survival model was adapted to estimate progression-free survival, overall survival, costs of treatments, adverse events and disease management, and health utilities over a time horizon of 20 years. The maximum treatment duration of 2 years was applied for pembrolizumab. Clinical and resource utilization inputs were based on data from KN024 study and input from local oncologists. Unit costs captured both patients' payments and government subsidies. Utility scores in different health states were based on EQ-5D data from KN024 with weighting indices suggested by a local quality-of-life study. An annual discount rate of 3% was applied and a series of sensitivity and scenario analyses were conducted to address uncertainty. **Result:** For 1st line treatment for NSCLC patients with TPS≥50%, pembrolizumab monotherapy is estimated to result in 0.91 quality-adjusted-life-years (QALY) gained. The projected incremental cost for pembrolizumab is S$141,979 compared to SoC, leading to an incremental cost-effectiveness ratio (ICER) of S$155,630 per QALY gained. A similar ICER of S$156,862 is observed in a scenario analysis whereby all patients are tested for PD-L1 and those with high PD-L1 expression are treated with pembrolizumab. With a Pembrolizumab Patient Access Program (PAP), the ICER is estimated to be S$95,279 per QALY. In another scenario analysis where government subsidies and claim limits of Medishield / Medisave are considered, the estimated ICER is S$46,308 per QALY from the Ministry of Health (MOH) perspective. **Conclusion:** For NSCLC patients with TPS≥50%, the ICER in the base-case for pembrolizumab as 1st-line treatment is $155,630 – which is between 2-3x gross domestic product (GDP) per capita of Singapore (S$73,167) in 2016, whereas the estimated ICER with Pembrolizumab PAP is 1-2x GDP per capita. Depending on threshold boundaries adopted, 1st line pembrolizumab for patients with similar profile (TPS ≥50%) as those in KN024, would be a cost-effective treatment compared to SoC in Singapore.

Keywords: pembrolizumab, NSCLC, Cost-effectiveness

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-08 WEEKLY NAB-PACLITAXEL PLUS CARBOPLATIN AS NEOADJUVANT THERAPY FOR IIIA-N2 LUNG SQUAMOUS CELL CARCINOMA: A PROSPECTIVE PHASE II STUDY

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Background: To evaluate the safety and antitumor activity of weekly nab-paclitaxel combined with carboplatin in patients with advanced stage IIIA-N2 NSCLC patients with squamous histology **Method:** From April 2015 to August 2017, 36 treatment-naive, pathologically diagnosed IIIA-N2 lung squamous cell carcinoma patients were enrolled and given two cycles of weekly nab-paclitaxel (100mg/m^2, day1,8,15 of a 21-day cycle) plus Carboplatin (AUC = 5 at day 1, q3w) as neoadjuvant therapy. Then resectability was assessed and surgery was performed for resectable lesions. Post-operative adjuvant chemotherapy regimens is the combination of Nab-paclitaxel (100mg/m^2, qw x 6) and carboplatin (AUC 5, Q3W x 2) for patients with PD, adjuvant chemotherapy regimen will be changed. The primary objective is the safety and efficacy, and the secondary objectives are quality of life and the role of prognostic biomarker SPARC. **Result:** Of 36 patients, 3 stopped treatment due to patient decision. 33 were finally evaluated and 1 is still on treatment. Significant tumor volume shrinkage was seen in some patients after the neoadjuvant therapy. 66.7% patients achieved partial response (PR), 21.2% patients achieved stable disease (SD). Disease control (PR +SD) rate was 87.9%. Finally, 23 patients underwent surgical resection, the respectability rate was 69.7%. 12.1% occurred disease progress and failed to achieve resection, including 3 with local progress and 1 with pulmonary metastatic nodule; Among 22 PR pts, 4 failed to achieve resection, in which 1 was due to heart function, the other 3 due to personal unwillingness. 2 of 7 with stable disease failed to achieve resection; the pathological improvement in T stage and N stage before and after treatment was 81.8% (18/22) and 50% (11/22) respectively. The major adverse event was neutropenia (grade I and II) and no serious AE was found. **Conclusion:** Nab-paclitaxel in combination with Carboplatin showed promising ORR rate and resection rate in of IIIA-N2 lung squamous cell carcinoma. The regimen could be a new chemo option as the neoadjuvant treatment. PFS and OS data will be reported after follow up completing.

Keywords: nab-paclitaxel, neoadjuvant therapy, Lung Squamous cell carcinoma

P1.16-09 SURGICAL RESULT OF PATHOLOGIC STAGE III A NON SMALL CELL LUNG CANCER: HAVE WE IMPROVED?

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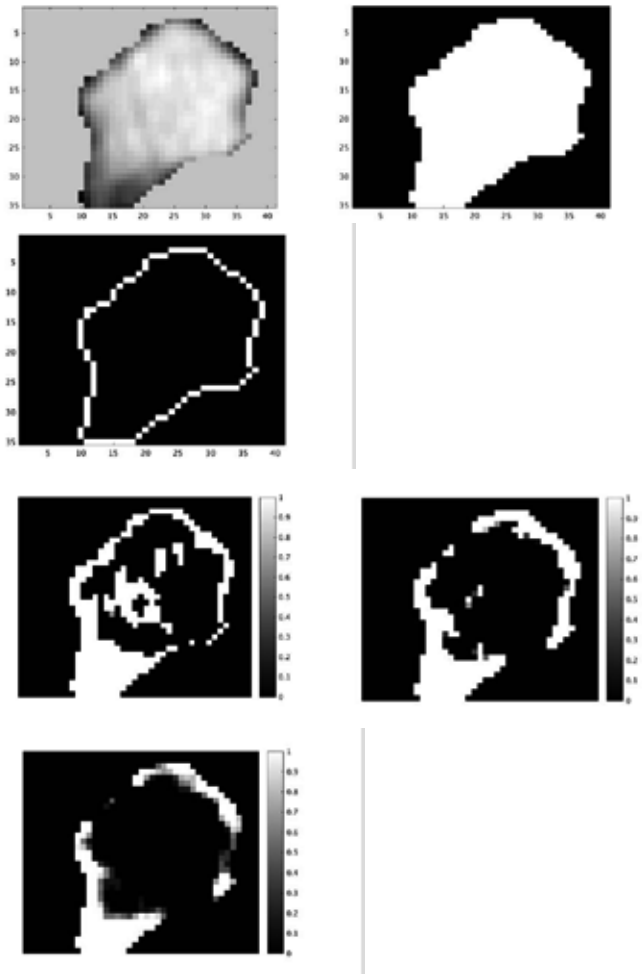
Background: Non small cell lung cancer was the leading cause of cancer death worldwide. five-year survival of pathologic stage IIIa still remain poor and the management remain controversial. Many new medicines and surgical techniques were utilized as treatment for pathologic stage IIIIa patient. The aim of study was tried to analyzed the survival impact of these treatment modalities and the stage migration effect during new TNM staging classification system. **Method:** From Jan 2005 to Jun 2014, there were 166 pathologic stage IIIa patients were enrolled into study. All patients were follow up till 2016/7. Patients were divided into two groups since year 2010 because of difference of surgical technique switch. Medical records were reviewed retrospectively and survival status were analyzed. **Result:** From January 2005 to May 2014, 166 patients who had received tumor resection and were confirmed as pathologic stage IIIa by 7th AJCC stage classification system were included for further analysis. The 5-year disease free and overall survival rates were 24.9% and 38.2%, respectively. Patients who received neoadjuvant therapy showed inferior disease free survival compared with those without neoadjuvant therapy. (p< 0.0001). Patients who presented as adenocarcinoma and received tumor resection showed better overall survival than non-adenocarcinoma patients. (p=0.0011) Because the operation method was shifted to video-assisted thoracoscopic surgery in the year 2010, we analyzed survival status separately before and after 2010. In addition, we found that patients who received tumor resection and were conformed as pathologic stage IIIa adenocarcinoma has had better overall survival than other subgroups. (p =0.0005) 28 patients who were identified stage migration had worse disease-free and overall survival. **Conclusion:** Disease free survival of pathologic stage IIIa patients remain unchanged but overall survival had much improvement. Patients who presented with adenocarcinoma who received tumor resection during 2010 to 2014 has better survival. This may be related to medical improvement but further investigation was warranted. Stage migration and worse disease and overall survival for those presented as 3b in new stage classification were identified. Different treatment strategy was needed for these patients who were identified stage migration.



P1.16-10 MARGINAL FEATURES ANALYSES OF LUNG ADENOCARCINOMA FOR SURVIVAL PREDICTION

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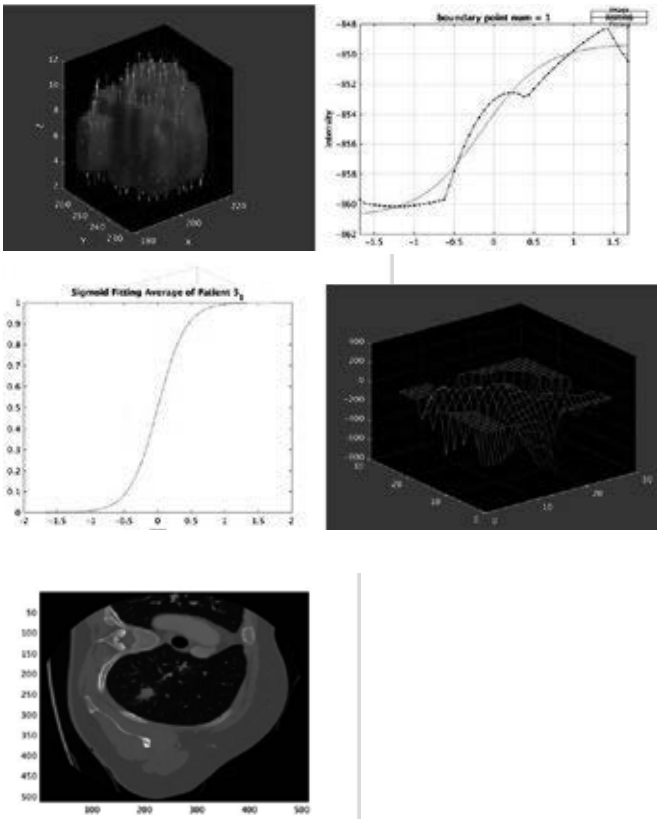
Background: Tumor microenvironment is a complex mixture of assorted cells and extra-cellular components which make up an amazingly dynamic area that includes signaling interactions between cancer cells and their surrounding tissue. Tumor microenvironment makes up the peripheral portion of the tumor and major changes in this area has been reported to be associated with a poor prognosis. However, very few studies have investigated the tumor marginal features quantitatively extracted from CT images using a radiomics approach. We aimed to clarify the relationship between tumor marginal features and the micropapillary pattern and correlated with survival. **Method:** We enrolled 334 patients who underwent complete resection for lung adenocarcinoma. Quantitative histologic subtyping was performed for the whole tumor. Using a radiomics approach, quantitative CT analysis was performed and 82 marginal features were extracted. Clinical variables and marginal features were correlated with survival. Using selected clinical variables and marginal features a prognostic model was calculated with subsequent internal and external validation. **Result:** Among various subtypes, solid predominant adenocarcinomas had the lowest proportion (6.9%) of combined micropapillary pattern. At univariate analysis, patient age, tumor size, and multiple marginal features (convexity, surface area, compactness, maximum 3D diameter, sphericity, surface-to-volume ratio, mean pixel value, median pixel value, entropy, uniformity, skewness, kurtosis, roundness factor, solidity, and lacunarity)were predictive of survival. At multivariate cox proportional analysis, convexity (P=0.017), kurtosis (P<0.001), and patient age (P=0.006) were identified as being predictive of survival. Ten-fold cross-validation tests demonstrated that our prediction model significantly classified patients according to survival (P<0.001). Although lower than internal validation, the prediction model also worked at external validation.



Conclusion: Marginal radiomics features of convexity and kurtosis reflect the tumor microenvironment and were predictive of patient survival in lung adenocarcinomas.

Keywords: Tumor margin, Adenocarcinoma, Radiomics

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-11 MONITORING OF EARLY STAGE LUNG CANCER USING LIQUID BIOPSIES.

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Background: This study aims to validate the use of chromosome rearrangements as tumour-specific biomarkers for the detection of circulating tumour DNA (ctDNA) to enable monitoring of cancer using digital PCR.We consider that rearrangements are the best source of robust disease markers that can be used for every lung cancer patient without a clear truncal mutation. The current high cost of the whole genome sequencing required for identification of chromosome rearrangements is offset by the low cost, high sensitivity and specificity of the subsequent assays. **Method:** s for ctDNA detection using chromosome rearrangements that leverage advances in next generation sequencing (NGS), bioinformatics and droplet digital PCR (ddPCR) have now been developed by our laboratory. **Result:** We are using whole genome sequencing and bioinformatic analysis of lung tumour samples. The genomic sequence was aligned to the human reference genome (hg19). Rearrangements were identified using the GRIDSS algoriths. Large numebers of potential genomic rearrangements ithat could be used as a biomarker to detect ctDNA were identified in each tumour. These were used to design primers which were used to monitor the success of surgical resection and to detect early relapse. **Conclusion:** Patients with early-stage primary tumours are the group in which appropriately timed therapeutic intervention is most likely to make a clinical difference. Our study assesses ctDNA in a large cohort of lung cancer patients with early-stage primary tumours that are being treated with the primary aim of cure. In addtion, whole genome sequencing also identifies genomic information such as rare functional rearrangements and mutational burden which can also be used in patient management.

Keywords: Monitoring, minimal residual disease, liquid biopsy

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-12 IDENTIFICATION OF A BIOMARKER PANEL IN RESECTED NSCLC THAT PREDICTS PATIENT OUTCOMES AND BENEFIT FROM ADJUVANT CHEMOTHERAPY

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Background: Adjuvant chemotherapy for resected NSCLC improves overall survival by approximately 10%. Physicians need tools to predict which patients are most likely to benefit from chemotherapy, sparing those unlikely to benefit. A 15-gene expression profile (GEP) published by Zhu *et al* is both *prognostic* and *predictive* of benefit from adjuvant chemotherapy. The aim of this study is to translate this GEP into a readily applicable immunohistochemistry (IHC) panel. **Method:** We constructed NSCLC tissue microarrays at the Saint John Regional Hospital and semiquantitatively assessed the IHC expression and prognostic significance of proteins encoded by 7 of the genes in the Zhu panel for which commercial antibodies were available. **Result:** In 62 patients with resected stage II-III NSCLC, the prognostic significance of IHC assays for four proteins were concordant with the Zhu GEP results. Low FOSL2 (OS, HR = 2.6; p = 0.0231; PFS, HR = 3.3; p = 0.0052), and low ATP1B1 (PFS, HR = 2.0; p = 0.0338) were adverse prognostic factors. High STMN2 and low TRIM14 expression trended towards worse OS and PFS. Multivariate analysis verified the prognostic impact of the four assays. These markers could also be integrated as a panel with retained prognostic value (OS, HR=2.1, p=0.03). **Conclusion:** An IHC panel with results concordant to the Zhu GEP is prognostic. Ongoing studies will examine the prognostic and predictive impact of this IHC panel in larger, independent datasets. If the panel turns out to be robust and predictive, it will have potential clinical application as a tool to select patients for adjuvant chemotherapy.

Keywords: Immunohistochemistry, biomarker, adjuvant chemotherapy

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-13 PHOTO DYNAMIC THERAPY (PDT) IN OUR HOSPITAL

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Background: Lung cancer is the leading cause of cancer death worldwide. A large part of lung cancer is diagnosed at an advanced stage, but the number of lung cancer diagnosed at an early stage are increasing due to improved diagnostic imaging techniques. In Japan, sputum cytology for mass screening provides chances to detect very early stage centrally located lung cancer which is good adaptation of PDT. Although PDT is less invasive therapy which enable us to treat the patients with poor pulmonary function or poor performance status. It is important to clarify the therapeutic outcome and the morbidity after PDT such as airway narrowing, pneumonia, and sunlight hypersensitivity. **Method:** We analyzed 14 patients who received PDT in Tohoku University Hospital between January 2010 and April 2017 retrospectively and evaluated the therapeutic outcome of PDT. **Result:** 14 cases were all male and the average age was 71. Nine cases were detected in cancer screening examinations and other 5 cases were detected accidentally while observing other diseases. Lung cancer existed in trachea 1, in segmental bronchi 4, in sub segmental bronchi 7, and more peripheral lesion 2. All 14 cases were pathologically squamous cell carcinoma. In 2 cases, we performed PDT twice. In 3 cases, we performed surgical resection after PDT. Within follow-up period after PDT, 5 cases developed metachronous lung cancer and were treated with surgical resection or radiation therapy. After these therapies 11 cases alive without recurrence, 1 case alive with recurrence, 1 case died from original disease, and 1 case died from other disease. Only one case suffered airway narrowing after PDT, but other 13 cases had no morbidity. **Conclusion:** We concluded PDT is a good treatment in early stage centrally located lung cancer with good outcomes and little morbidity rates.

Keywords: Photo Dynamic Therapy, early stage centrally located lung cancer

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-14 IMPACT OF SMOKING ON TREATMENT OUTCOME IN EARLY SQUAMOUS CELL LUNG CANCER (T1N0)

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Background: Smoking is the major risk factor for squamous cell lung cancer. However, squamous cell lung cancer in never-smoker is known to have poor survival outcomes. We compared clinicopathologic features and outcomes between smokers and never-smokers in resected early squamous cell lung cancer (T1N0). **Method:** An institutional database was reviewed retrospectively between 1994 and 2016 (N = 445). Eligible patients included completely resected squamous cell lung cancer, less than 3 cm in tumor size, and without N1 or N2 involvements. Patients were stratified by gender and smoking status. **Result:** 423 (95%) smokers and 20 (5%) never-smokers were identified. The median age of never-smokers was 66 years (range, 39 - 83), and 11 of these patients were female (55%). The median age of smokers was 66 (range, 42 - 84), and most of them were male (97.9%). The T stage were distributed equally in both groups. In smokers, 84 (19.9%) patients experienced recurrence whereas only 1 patient (5%) of never-smokers occurred distant metastasis ($p < 0.001$). Distant metastasis was most frequent recurrence pattern in smokers (n= 40), but locoregional recurrence also a fairly frequent pattern (n = 30). The 5-year overall survival rates and recurrence free survival rates were 70.9% and 61.5% in smokers and were 64.1% and 64.1% in never-smokers respectively (p = 0.65, and 0.34, respectively). **Conclusion:** There was no significant differences in clinicopathologic features and outcomes between smokers and never-smokers in early squamous cell lung cancer.

Keywords: squamous cell, never-smoker, NSCLC

P1.16-15 EVALUATION OF EMPHYSEMA SEVERITY BY 3D-CT FOR PREDICTING POSTOPERATIVE RESPIRATORY COMPLICATIONS AND PROGNOSIS OF LUNG CANCER

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Background: Emphysema is one of the main causes of respiratory complications and perioperative mortality and morbidity in lung cancer patients. We have used 3D-CT for depicting emphysematous areas as low attenuation areas (LAAs) and visual scores based on Goddard classification (Goddard score: GS). This study aimed to investigate the effectiveness of the 3D-CT function analysis of emphysema severity and its association with respiratory complications and prognostic outcomes. **Method:** The study included 504 patients who underwent preoperative 3D-CT for surgical simulation followed by resection for lung cancer from October 2010 to March 2015. GS and LAA% (LAA / total lung volume) were measured using 3D-CT data. We studied the relationship between the development of postoperative respiratory complications/ overall survival (OS) and independent variables including age, sex, forced expiratory volume in 1 second as percent forced vital capacity (FEV1%), histology, smoking status, surgical procedure, GS, and LAA%. **Result:** Postoperative respiratory complications were observed in 69 patients (13.6%). These included prolonged air leakage $\geq$ 7 days (n = 22), pneumonia (n = 13), bronchial fistula (n = 4), atelectasis (n = 5), pulmonary fibrosis (n = 3), empyema (n = 5), recurrent nerve paralysis (n = 2), chylothorax (n = 5), pleural effusion (n = 3) and other respiratory-related adverse events (n = 7). The ROC curves for respiratory complications determined using the GS and LAA% dichotomized at each cut-off level (1 and 0.7%, respectively) showed that the events were observed in 32% of the patients with GS $\geq$ 1 and in 25% of the patients with LAA% $\geq$ 0.7. On multivariate analyses, the GS or LAA% was significantly correlated with postoperative respiratory complications ($p < 0.001$ and $p = 0.016$, respectively). Univariate and multivariate analysis using the Cox regression model for prognosis also showed GS was significantly associated with unfavorable OS among 362 patients with pathological Stage I NSCLC patients ($p = 0.039$). Five-year OS rates in these patients with or without emphysema were 84.0% and 94.1%, respectively ($p < 0.001$). **Conclusion:** Preoperative measurement of GS and LAA% using 3D-CT in patients with lung cancer, particularly with the coexistence of emphysema, was beneficial for predicting postoperative respiratory complications and prognosis in lung cancer patients.

Keywords: complications, lung cancer surgery, emphysema

P1.16-16 AUTOMATIC INTRATUMOR SEGMENTATION IN CT OF NSCLC: AN ALTERNATIVE TO PET METABOLIC SUBREGIONS

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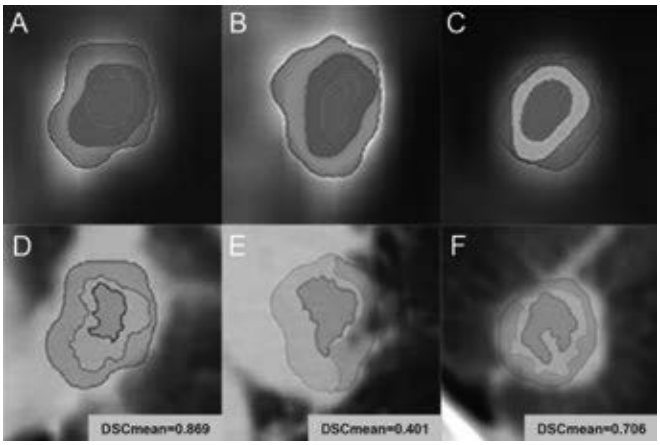
Background: PET images provide heterogeneous metabolic information in precision radiation treatment planning and the radiation dose given to high metabolic volumes should be escalated. However, PET scanning will increase the radiation dose received by patients. The aim of this study was to evaluated the feasibility of automatic intratumor segmentation in CT of NSCLC patients based on level-set evolution and cell automaton algorithm and assess the consistency with PET metabolic subregions. **Method:** The PET and plan-CT imaging data set of 17 patients who have diagnosed with NSCLC were randomly collected. First, the gross tumor volume (GTV) was defined using a threshold of 40% SUV_{max} on PET. Then, rigid registration was used to align PET images to plan-CT images and the GTV was mapped to the CT image subsequently. The subregions which describe heterogeneity of voxel gray-level intensities were then automatic segmented using an algorithm combined level-set evolution and cell automaton in GTV_{CT}. Meanwhile, the three metabolic subregions in GTV_{PET} were delineated using threshold interval a) 40%-60% SUV_{max}, b) 60%-80% SUV_{max}, and c) 80%-100% SUV_{max}. To evaluate the consistency with PET metabolic subregions, we calculated the spatial overlap by Dice's similarity coefficient (DSC). **Result:** In total, 21 GTV pairs acquired from CT and PET data set were used to evaluate the feasibility of method proposed in this study. The GTV_{CT} was automatically divided into three heterogenous subregions based on its difference on grays-level intensities and regional connectivity of voxel and 63 subregions were acquired. The average DSC value calculated from subregion in CT and PET is 0.725 with interval (0.321,0.905).



Conclusion: Our study revealed that there is a significant correlation between PET metabolic information and CT gray-level intensity. The automatic segmentation of subregion in CT images may can serve as an alternative to the metabolic region delineated in PET.

Keywords: Metabolic subregion, Automatic segmentation, NSCLC

P1.16-17 THE ROLE OF QUANTITATIVE METABOLIC METRICS ON FDG-PET/CT IN PREDICTING PATHOLOGICAL INVASIVE FACTORS IN CN0 LUNG ADENOCARCINOMA

T. Tanaka[1], Y. Shimada[1], Y. Makino[1], J. Maeda[1], M. Hagiwara[1], T. Okano[1], M. Kakihana[1], N. Kajiwara[1], T. Ohira[1], J. Matsubayashi[2], N. Ikeda[1]

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Background: Growing evidence suggests that FDG-PET/CT has greatly contributed the preoperative investigation of early-stage lung cancer. The maximum standardized uptake values (SUVmax) of the primary lesion is widely reported to be associated with prognosis in NSCLC while other metabolic metrics, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been explored as a measure of metabolic tumor burden in recent years. The purpose of this study is to investigate the role of quantitative metabolic metrics in predicting the incidence of pathological invasive factors including microscopic vascular invasion, pleural invasion, and lymph node metastasis in cN0 lung adenocarcinoma. **Method:** We examined 265 patients with clinical stage 0-II(cN0) adenocarcinoma. Pre-operative PET/CT and subsequent complete resection was performed for all the patients during the period from August 2012 to July 2017. The maximum tumor and solid-part diameter on HRCT and the three metabolic metrics on PET/CT measured by the SYNAPSE VINCENT (Fujifilm Medical, Tokyo, Japan) as the volume viewer softwarewere observed. In the current study, MTV was defined as the total tumor volume with an SUV $\geq$ 2.5 while TLG was calculated as meanSUV x MTV. We assessed the relationship between these parameters and the incidence of pathological invasive factors. **Result:** Among 265 patients, 18 (7%) patients were clinically staged as 0, 205 (77%) as IA, 32 (12%) as IB, and 10 (4%) as II, respectively. Pathological vascular invasion, pleural invasion, and lymph node metastasis were found in 100 (38%), 53 (20%), and 45 (17%) patients, respectively. SUVmax, MTV, and TLG were dichotomized at cut-off level by the receiver operating characteristic (ROC) curves for pathological invasive factors (SUVmax of 4.4, MTV of 0.75mm^3, and TLG of 2.6, respectively). ROC curve yielded area under the curve values of 0.812, 0.915, and 0.882 for SUVmax, MTV, and TLG, respectively. Univariate analysis showed that SUVmax (Hazard Ratio (HR), 27.185; p<0.001), MTV (HR, 24.580; p<0.001), TLG (HR, 24.580; p<0.001), maximum tumor size (HR, 2.495; p<0.001), solid-tumor size (HR, 7.830; p<0.001), c-stage (HR, 14.418; p<0.001), and sex (HR, 1.882; p=0.013) were significantly associated with the incidence of pathological invasive factors. Multivariate analysis showed that SUVmax was the independent predictor (HR, 7.006; p=0.001). The frequency of pathological invasive factors of patients with SUVmax $\geq$ 4.4, MTV $\geq$ 0.75mm^3, and TLG $\geq$ 2.6 were 82%, 84%, and 84%, respectively. **Conclusion:** In cN0 early-stage lung adenocarcinoma, the measurement of SUVmax, MTV, and TLG on FDG-PET/CT was beneficial for the prediction of pathological invasive factors.

Keywords: Adenocarcinoma, MTV, PET/CT

P1.16-18 ROLE OF ERCC1/2 SINGLE NUCLEOTIDE POLYMORPHISM (SNP) ON TREATMENT RESPONSE IN PATIENTS WITH LUNG CANCER UNDERGOING RADIATION THERAPY

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Background: Radiation therapy plays an important role in the treatment of lung cancer. The protein excision-repair cross-comlementation 1 (ERCC1) and protein excision-repair cross-comlementation 2 (ERCC2) are the key enzymes in NER pathway. Studies showed that ERCC1/2 were associated with susceptibility and efficacy of chemotherapy in lung cancer, but the association between ERCC1/2 SNPs and radiotherapy were seldom reported. **Method:** Eighty-seven peripheral blood samples were collected from patients with NSCLC before they received radiotherapy in our department from November 2014 to October 2017. The peripheral blood leukocyte DNA was isolated and SNP genotypes were detected by competitive allele-specific PCR. Seven SNPs in ERCC1/2 were analyzed. Data was collected both before and after radiotherapy from blood serum. Elisa was used to detect ERCC1 expression. The association between the changes of expression of ERCC1 during radiotherapy and efficacy, risk of RILI and SNPs in ERCC1 was analyzed. Result: ERCC1 re3212961 minor allele A was associated with a better response to radiotherapy in NSCLC patients. Survival analyses showed that G/G genotype had favorable OS than A/A genotype (P=0.012). Cox regression analysis indicated that ERCC1 rs11615 G/G genotype was associated with decreased risk of death. Subgroup analyses indicated that patients with G/G genotype who received high BED radiotherapy had better OS (median not reached vs. 21.5 months, 95%CI: 15.3-27.7, P=0.011) and PFS (median not reached vs. 19.9 months, 95%CI: 8.6-31.2, P<0.001) than low BED subgroup. There was no significant association between ERCC1/2 SNPs and RILI. The ERCC1 expression in serum was significantly increased after radiotherapy. However, the changes of ERCC1 expression showed no association with efficacy of radiotherapy, risk of RILI or SNPs of ERCC1/2. **Conclusion**: ERCC1 rs3212961 was related with short-term curative efficacy. ERCC1 rs11615 was an independent prognostic factor in NSCLC, which could serve as biomarker, because G/G genotype had favorable OS and PFS, and was associated with decreased risk of death. There was no significant correlation between ERCC1/2 SNPs and RILI. The changes of ERCC1 expression after radiotherapy showed no association with efficacy of radiotherapy, risk of RILI or SNPs of ERCC1/2.

Keywords: ERCC1/2, non-small cell lung cancer, SNPs

P1.16-19 NEITHER MAXIMUM TUMOR SIZE NOR SOLID COMPONENT SIZE WAS THE BEST PROGNOSTICATOR FOR SUBSOLID NODULE

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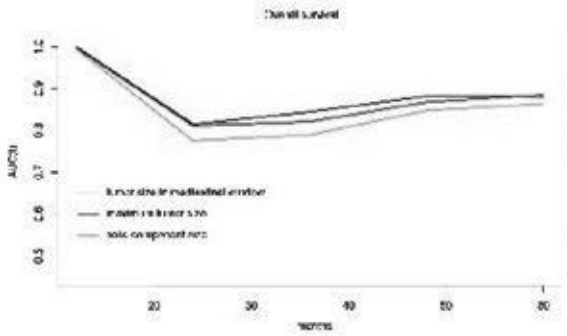
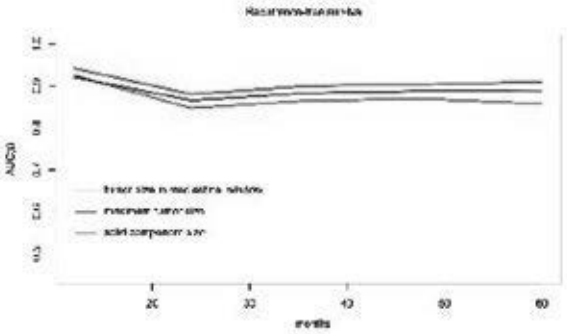
Background: Solid component size is used to define the T stage of subsolid nodule in the eighth edition TNM stage classification. Our study aimed to explore whether solid component size was the best parameter for T staging. **Method:** We retrospectively reviewed the clinical data of 431 cTis-T3N0M0 subsolid nodule from Shanghai Pulmonary Hospital. Maximum tumor size, solid component size and tumor size in mediastinal window were carefully recorded. Prognostic ability of different turmor size was compared by time-dependent receiver operating curve. **Result:** Survival revealed maximum tumor size, solid component size and tumor size in mediastinal window were statistical significant predictors. However, solid component size performed the worst of them, relatively

.

	DFS		OS		LN+	
	HR(95%CI)	P	HR(95%CI)	P	OR(95%CI)	P
All nodules						
Maximum tumor size (cm)	2.78 (2.17-3.56)	< 0.01	2.50 (1.93-3.23)	< 0.01	2.26 (1.58-3.24)	< 0.01
Solid component size (cm)	3.18 (2.36-4.29)	< 0.01	3.00 (2.05-4.40)	< 0.01	2.99 (2.00-4.47)	< 0.01
CTR (> 0.5)	14.4 (4.26-48.91)	< 0.01	5.82 (1.60-21.14)	< 0.01	13.20 (2.98-58.51)	< 0.01





Conclusion: Tumor size remains a common used parameter for nodule evaluation. Solid component size maybe not the best parameter for T staging.

Keywords: TNM, ground-glass opacity, Prognosis

P1.16-20 A SYSTEMATIC REVIEW AND META-ANALYSIS OF STEREOTACTIC BODY RADIATION THERAPY VERSUS SURGERY FOR PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Stereotactic body radiation therapy (SBRT) is the preferred treatment modality for patients with inoperable early-stage NSCLC. However, comparative outcomes of SBRT versus surgery for high-risk patients remain controversial. The primary aim of the present meta-analysis was to assess the overall survival of SBRT versus surgery in matched and unmatched patient cohorts. Secondary endpoints included cancer-specific survival, disease-free survival, disease recurrence, and perioperative outcomes. **Method:** A systematic review was performed through online databases using predefined criteria. The most updated studies were selected for meta-analysis according to unmatched and matched patient cohorts. **Result:** Thirty-two studies were identified in the systematic review. Surgery was associated with superior overall survival in both unmatched (OR 2.49, 95% CI 2.10–2.94, p<0.00001) and matched (OR 1.71, 95% CI 1.52–1.93, p<0.00001) cohorts. Cancer-specific survival, disease-free survival, and freedom from locoregional recurrence were found to be superior after surgery compared to SBRT, in both unmatched and matched cohorts. However, SBRT was associated with fewer perioperative mortalities.

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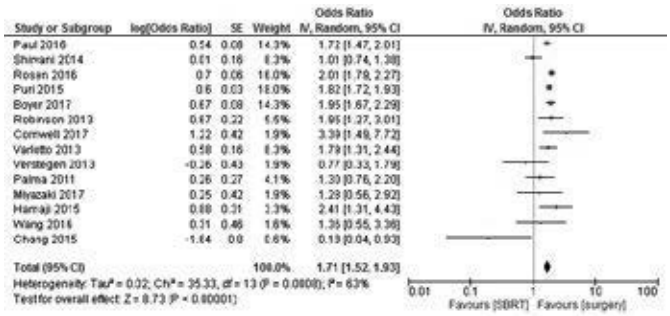

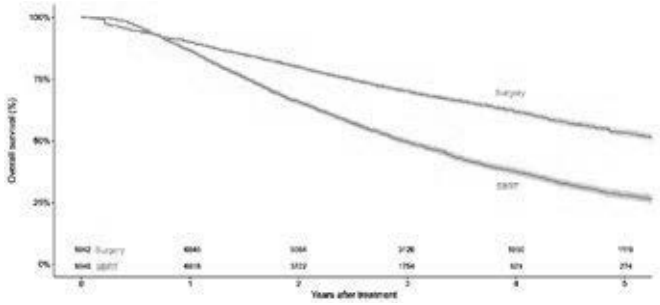

Conclusion: Current evidence suggests that surgery is superior to SBRT in mid- and long-term clinical outcomes. However, improved outcomes after surgery may at least be in part due to an imbalance of baseline characteristics. Mortality outcomes for SBRT were also more favorable in the perioperative period.

Keywords: Stereotactic body radiation therapy, meta-analysis, non-small cell lung cancer

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-21 PHASE I / II STUDY OF CARBOPLATIN, NAB-PACLITAXEL, AND CONCURRENT RADIOTHERAPY FOR PATIENTS WITH LOCALLY ADVANCED NSCLC

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Background: We performed an open-label, multicenter phase I/II study (UMIN ID 000012719) to prospectively evaluate the efficacy and safety of the combination of nab-paclitaxel plus carboplatin (nab-P/C) with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer. **Method:** In the phase I study (standard 3+3 design), escalating doses of weekly nab-paclitaxel were given along with weekly carboplatin area under the plasma concentration time curve (AUC) 2 and concurrent radiotherapy 60 Gy in 30 fractions, followed by 2 cycles of nab-paclitaxel (100 mg/m^2 on Days 1, 8 and 15) plus carboplatin (AUC 6 on Day 1). In the phase II study, nab-P/C at recommend dose (RD) was administered. **Result:** In the Phase I study, 11 patients were enrolled with 9 evaluable for dose limiting toxicity (DLT). At level 1 (nab-paclitaxel 40mg/m^2), none of 3 patients experienced DLT. At level 2 (nab-paclitaxel 50mg/ m^2), 1 of 6 patients experienced DLT: grade 3 leukopenia requiring a second consecutive skip in the administration of weekly nab-P/C. Level 2 was defined as the RD. A total of 56 patients including 6 patients who received at dose of RD, were evaluable for the efficacy and safety. Of the 56 patients for safety analysis, common toxicities in the concurrent phase included grade 3/4 leukopenia (60.7 %), neutropenia (26.8 %), anemia (7.1 %), anorexia (7.1 %), esophagitis (5.4 %) and febrile neutropenia (1.8 %). In one patient, grade 3 pneumonitis was observed. There were no treatment-related deaths. The objective response rate was 76.8 % (95% confidence interval (CI), 64.2 to 85.9 %). The median progression-free survival was 11.8 months (60% CI, 10.6 to 16.2 months, 95% CI, 8.2 to 20.8 months), and the median overall survival was not reached. **Conclusion:** This is the first study to demonstrate encouraging feasibility and activity for concurrent chemoradiation with nab-paclitaxel 50 mg/m^2 and CBDCA AUC 2 in patients with locally advanced NSCLC.

Keywords: locally adcanced NSCLC, nab-paclitaxel, chemoradiation

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-22 META-ANALYSIS OF STEREOTACTIC ABLATIVE RADIOTHERAPY VERSUS SURGERY FOR EARLY STAGELUNG CANCER.

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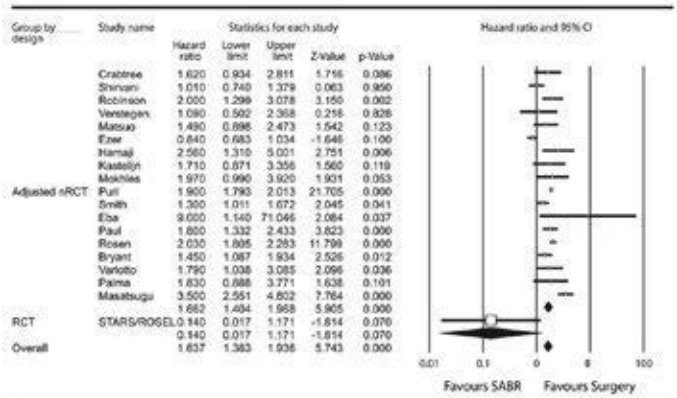
Background: The standard of care for operable, stage I, non-small-cell lung cancer (NSCLC) is lobectomy with mediastinal lymph node dissection or sampling. Stereotactic ablative radiotherapy (SABR) for inoperable stage I NSCLC has shown promising results, but two independent, randomised, phase 3 randomized controlled trials (RCTs) included few patients and closed early due to slow accrual. We aimed to assess overall survival with SABR versus surgery by pooling data from RCTs and adjusted observational studies. **Method:** We performed a systematic review and meta-anaysis according to PRISMA (Preferred Items Reporting for Systematic Reviews and Meta Analyses) guidelines. The search process covered a period untill 28th of February 2018. Search terms were: SABR, stereotactic body radiation therapy, radiotherapy, lung-, pulmonary-cancer. Studies comparing SABR vs surgery for NSCLC were ellegible if reported adjusted survival data. Approaches including propensity scoring, inverse probability weighting and multivariate regressions were only considered. Survival was calculated by pooling available Hazard Ratios (HRs) in random-effects model. Studies were then stratified based on their design (RCT[s] vs Adjusted nRCT[s]). HRs were digitized from the available Kaplan-Meier curves. **Result:** Nineteen studies were retrieved that enrolled 23,534 patients. Among them two RCTs (N=58 pts). In overall analysis SABR was associated with significantly worsened survival as compared to surgery group: HR (95%CIs): 1.64 (1.38-1.94); p<0.001; when analyzed separately, adjusted nRCT[s] favored surgery: HR for comparison SABR vs surgery: 1.66 (1.40-1.97); p<0.001; among RCTs only, SABR was associated with a statistical trend for improved survival: HR (95%CIs): 0.14 (0.02-1.17); p=0.07. There were significant statistical differences between RCTs and adjusted nRCTs $P_{interaction}$=0.02.



Conclusion: SABR could be an option for treating early stage NSCLC but there was significant discrepancy between RCTs and non-RCTs regarding survival after SABR as compared to surgery; more adequately powered randomized studies are needed before conclusions on efficacy of SABR can be drawn.

Keywords: survival meta-analysis, SABR, NSCLC

P1.16-23 LONG-TERM SURVIVAL ANALYSIS OF SURGERY IN POTENTIAL STEREOTACTIC ABLATIVE RADIOTHERAPY CANDIDATES OF NON-SMALL CELL LUNG CANCER

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Department of Thoracic Surgery II, Peking University Cancer Hospital & Institute, Beijing/CN

Background: The aims of this study were to evaluate the long-term survival outcomes and strengthen the primacy of surgery in potential stereotactic body radiotherapy candidates. **Method:** A total of 541 patients with clinical stage I peripheral non-small cell lung cancer from January 2005 to December 2014 were enrolled in the current study. All patients who were potential stereotactic ablative radiotherapy candidates underwent lobectomy and systematic lymph node dissection including level 13 and 14 without preoperative therapy. According to the recommendation of the 8th edition of TNM stage, combined with our own experience, we divided the N stage into N1a (only level 13-14 positive), N1b (level 10-12 positive), N2a1 (skip single N2), N2a2 (single N2 with N1) and N2b (multiple N2). Survival curves were estimated by the Kaplan–Meier method. **Result:** Among all patients, 25.0% had occult lymph node involvement, 12.8% were N1 and 12.2% were N2. Among 32 T1a patients only 1 case (3.0%) patients had N1a positive without other N positive. In 104 cases of T1b, the positive rates of N1a, N1b, N2a1, N2a2 and N2b were 0.8%, 5.9%, 0.8%, 2.5% and 1.7%, respectively. Among the 86 patients with T1c, the positive rate of each station was 5.4%, 11.5%, 3.8%, 8.5%, and 4.6%, respectively. Of the 184 patients with T2a, N1 accounted for 14.6% , and N2 accounted for 11.5%. The 3-year, 5-year and 10-year disease free survival (DFS) of all 541 clinical stage I patients were 82.8%, 74.0%, 64.7%, and the overall survival (OS) were 91.3%, 85.4% and 77.0% respectively. The 3-year, 5-year and 10-year DFS of postoperatively pathological stage I patients were 90.0%, 81.0%, 72.5%, and the OS were 94.4%, 91.1% and 85.0%, respectively.

T /N category	N0	N1a	N1b	N2a1	N2a2	N2b
1a	32 (97.0%)	1 (3.0%)	0	0	0	0
1b	104 (88.1%)	1 (0.8%)	7 (5.9%)	1 (0.8%)	3 (2.5%)	2 (1.7%)
1c	86 (66.2%)	7 (5.4%)	15 (11.5%)	5 (3.8%)	11 (8.5%)	6 (4.6%)
2a	184 (70.8%)	13 (5.0%)	25 (9.6%)	8 (3.1%)	12 (4.6%)	18 (6.9%)

Conclusion: In view of the high rate of lymph node metastasis in clinical stage I lung cancer, surgical resection is still the preferred treatment.

Keywords: lung cancer, Surgery, Stereotactic ablative radiotherapy

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-24 IMPACT OF TUMOR LOCATION & DOSIMETRIC PREDICTORS FOR CHEST WALL TOXICITY IN SINGLE FRACTION SBRT FOR STAGE I NON-SMALL CELL LUNG CANCER

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Background: Single fraction stereotactic body radiation therapy (SF-SBRT) is an acceptable regimen for treatment of peripheral Stage I Non-Small Cell Lung Cancer (NSCLC). Rates of chest wall toxicity (CWT) are not stratified by distance of tumor to chest wall (CW) and dosimetric parameters are not well defined. We sought to determine the relationship of tumor location and dosimetric parameters with CWT in SF-SBRT. **Method:** An IRB-approved prospective SBRT registry of 1,462 patients (pts) was used to identify pts treated with 30 Gy or 34 Gy in one fraction. Tumors were ≤ 5 cm, node-negative, and ≥ 2 cm from the proximal tracheo-bronchial tree. The CW was retrospectively contoured (3 cm soft-tissue structure). Gross tumor volume was measured as abutting, ≤ 1 cm, 1-2 cm or > 2 cm from the CW. CWT was graded according to CTCAE 3.0 criteria. Rates of CWT were compared using unpaired t-test. Logistic regression analysis was used to identify tumor and dosimetric parameters associated with CWT. **Result:** This study included 146 lesions treated with SF-SBRT. Median follow-up was 23.8 months. There were 80 pts (55%) treated with 30 Gy and 66 pts (45%) treated with 34 Gy. The rate of CWT was 30.6% for lesions abutting CW, 8.2% for ≤ 1 cm from CW, 3.8% for 1-2 cm from CW, and 5.7% for > 2 cm from CW. Grade ≥ 3 CWT was modest (1.4%). Tumor abutment (OR 6.5; p=0.0005), BMI (OR 1.1; p= 0.02), rib D1cc (OR 1.01 per Gy; p= 0.03), CW D1cc (OR= 1.08 per Gy; p=0.03), and CW D5cc (OR 1.10 per Gy; p= 0.01) were significant predictors for CWT on univariate analysis. Tumor abutment was the only significant predictor for CWT (OR 7.5; p= 0.007) on multivariate analysis. CWT occurred in only 1 out of 40 pts with CW D5cc < 18 Gy, while our model suggested a 15% risk of CWT with D5cc of 27.2 Gy to CW. **Conclusion:** The rate of CWT is significantly associated with distance from the CW. When considering lesions adjacent to the CW, the rate of CWT in this series (30.6%) does not appear to exceed rates in the published fractionated SBRT literature (20-33%). Location adjacent to CW should not be a contraindication to SF-SBRT. CW D1cc and D5cc may be used as predictors of CWT rates. As most CWT is low-grade and self-limited, these dosimetric parameters should be utilized as a guideline, rather than an absolute constraint.

Keywords: Stereotactic body radiation therapy, Single fraction, chest wall

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-25 A PROPENSITY SCORE MODEL FOR APPROPRIATE TREATMENT SELECTION (SUBLOBAR RESECTION VS. SBRT) IN PATIENTS WITH CSTAGE I NSCLC

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Background: Stereotactic body radiotherapy (SBRT) and sublobar resection (SLR) are current treatment options for patients with cStage I non-small-cell lung cancer (NSCLC) who are operable, but at high risk for lobectomy. However, optimal selection of the two treatments remains controversial. Purposes of this study are to identify pre-treatment factors affecting treatment decision and to evaluate their impact on outcomes. **Method:** We retrospectively reviewed patients who underwent SBRT or SLR for cStage I NSCLC because of medical comorbidity between 2003 and 2009. Patients who were with performance status of 2 or worse, those who had no data on pre-treatment pulmonary function test, or those who had no histological confirmation of NSCLC were excluded. A propensity score (PS) model of treatment decision (0 toward SBRT, and 1 toward SLR) was generated using stepwise logistic regression incorporating pre-treatment factors. **Result:** Ninety-two and 65 patients who underwent SBRT and SLR, respectively, were enrolled into this analysis. Median potential follow-up period was 8.6 years. The following factors remained in the PS model after stepwise selection: age, sex, Charlson comorbidity index (CCI), body mass index (BMI), forced expiratory volume in 1 second (FEV1) and tumor diameter. Old age, male, CCI of 1 or more, underweight BMI and large tumor had coefficients toward SBRT (Table). In a cohort with PS of 0.5 or more, overall survival was significantly better in SLR patients than in SBRT patients (79.5% and 47.5% at 5 years, respectively; P = 0.004). In a cohort with PS<0.5, whereas, overall survival was similar between SLR and SBRT (43.3% and 39.7% at 5 years, respectively; P = 0.805).

Coefficients for propensity score		
Factors		Coefficients
(Intercept)		(3.95)
Age	per 10y	-0.53
Sex	female	0 (ref)
	male	-0.62
CCI	0	0 (ref)
	1	-0.41
	>=2	-0.97
BMI	underweight	-0.98
	normal	0 (ref)
	overweight	0.44
FEV1	per 1L	0.84
Tumor diameter	per 1cm	-0.34

Conclusion: The PS model would help appropriate treatment selection for high-risk operable patients. Although patients with PS of 0.5 or more benefit from SLR, SBRT provides comparable outcomes for patients with PS<0.5.

Keywords: Propensity score, stereotactic body radiotherapy, sublobar resection

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-26 SAFETY OF SABR (STEREOTACTIC ABLATIVE BODY RADIOTHERAPY) FOR CENTRAL NON-SMALL CELL LUNG CANCERS (CNSCLC) WITH 50 GRAY IN 5 FRACTIONS (50GY/5F)

R. Rulach[1], J. Hicks[1], G. Lumsden[1], S. Mckay[1], V. Maclaren[1], J. Macphee[1], K. Moore[1], M. Omand[1], M. Sproule[2], S. Currie[1], A. Aitken[1], R. Ferguson[1], P. Houston[1], R. Valentine[1], S. Harrow[1]

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Background: SABR using 60Gy/3f (or equivalent) caused high toxicity when used for cNSCLC. To determine a safe SABR dose for cNSCLC, the phase I/II RTOG 0813 trial used 50Gy/5f as a baseline. From 2013, 50Gy/5f was adopted for inoperable early-stage cNSCLC at the West of Scotland Cancer Centre, a tertiary-level oncology unit. We report our prospectively collected toxicity and efficacy data. **Method:** Patients with cNSCLC were identified from the radiotherapy database. cNSCLC was defined as lung cancers within 2cm of the proximal bronchial tree, or the planning target volume (PTV) abutting the mediastinal pleura/pericardium. Patient and treatment characteristics were obtained from electronic medical records. All patients received 50Gy/5f on alternate days with a volumetric arc therapy plan using TrueBeam linear accelerators. Toxicity was assessed in a centralised follow-up clinic 2 weeks, 6 weeks, 3 months, 6 months, 1 and 2 years after treatment using Common Toxicity Criteria Adverse Events version 3. Patients had a CT scan at 3 months post-treatment. Subsequent CT scans were at the discretion of the treating clinician. **Result:** 50 patients (31 females, 19 males, median age 75.1 years old) were identified with T1-2N0M0 cNSCLC. 84% were medically unfit for surgery. 40% had biopsy-proven NSCLC. All patients completed treatment on schedule. Two patients died within 90 days of treatment, one from a chest infection, the other cause of death was unknown. Table 1 describes the early and late toxicity. Over a median follow-up of 24 months, there were 20 deaths, 8 unrelated to cancer, and 12 due to cancer recurrence. The median progression free survival and overall survival are 26.0 months (95% confidence interval: 16.4, 35.6 months) and 28.6 months (95% confidence interval: 21.3, 35.8 months) respectively.

	Early toxicity			Late toxicity
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 3 (%)
Fatigue	25 (50)	3 (6)	0 (0)	0 (0)
Dyspnoea	25 (50)	5 (10)	0 (0)	1 (2)
Cough	24 (48)	0 (0)	0 (0)	0 (0)
Sputum	12 (24)	0 (0)	0 (0)	0 (0)
Oesophagitis	6 (12)	0 (0)	1 (2)	0 (0)
Chest wall pain	7 (14)	0 (0)	0 (0)	0 (0)
Dermatitis	1 (2)	0 (0)	0 (0)	0 (0)
Brachial plexopathy	0 (0)	0 (0)	0 (0)	0 (0)

Table 1. Early (<90 days post treatment) and late (>90 days post treatment) toxicities encountered

Conclusion: This study has demonstrated that 50Gy/5f is a safe dose and fractionation for early-stage inoperable cNSCLC, with outcomes comparable to other series.

Keywords: Central NSCLC, SABR

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P1.16-27 USING RATES OF CLINICAL BRACHIAL PLEXOPATHY AFTER LUNG SBRT TO BETTER CHARACTERIZE THE TOLERANCE OF THE BRACHIAL PLEXUS

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Background: Treatment of apical lung tumors with stereotactic body radiation therapy (SBRT) can be challenging due to proximity to the brachial plexus (BP). We retrospectively investigated outcomes after treatment of apical lung tumors to compare the rate of brachial plexopathy (BPX) with what would be estimated based on published protocol-derived BP constraints. **Method:** Apical lung tumors were defined in this analysis as those whose lung SBRT target had a planning-derived PTV edge <1cm from the anatomic BP. We surveyed an IRB-approved prospective registry of 1,462 patients treated with SBRT for the interval 2003-2017 and included all patients who received definitive or salvage SBRT using dose/fractionation schedules of 50 Gy/5 fx, 60 Gy/5 fx, or 48 Gy/4 fx. Salvage SBRT included patients with local recurrence after conventional fractionation radiotherapy. Per RTOG protocols, the subclavian vein (SCV) ipsilateral to target was contoured as the BP surrogate. In this study, the ipsilateral subclavian artery (SCA), and BP were also contoured to characterize dosimetric differences between structures. Statistical analysis involved repeated measures ANOVA. **Result:** Sixty-four patients, which includes six patients (9.4%) receiving salvage SBRT, met inclusion criteria (median follow up of 21 months). No significant differences (p=0.77) were observed between maximum point doses to BP, SCV, and SCA. Within one year post-SBRT, two patients (3%) developed BPX (grade 2); both patients had exceeded 32 Gy to the BP and were treated with salvage SBRT. No patient treated with definitive SBRT (91%) developed BP, despite 17 of these exceeding recommended maximum doses. **Conclusion:** No BPX was observed for patients that exceeded a maximum dose of 32 Gy to the BP, unless they were treated as salvage SBRT. This suggests higher doses to the BP may be considered when clinically required for definitive SBRT. However, salvage SBRT may require more conservative BP constraints than used in the definitive setting.

Keywords: SBRT, brachial plexopathy, Brachial plexus

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-28 THE IMPACT OF SPIRONOLACTONE ON THE LUNG INJURY INDUCED BY CONCOMITANT TRASTUZUMAB AND THORACIC RADIOTHERAPY

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Background: Radiation-induced lung injury (RILI) is a potentially life-threatening and dose-limiting side effect of thoracic irradiation. Trastuzumab (T), a monoclonal antibody directed against HER2, improves overall survival in patients with HER2 positive breast cancer. T concurrently with radiation thus increases the antitumor effect of radiation. There are same clinical evidences in the literature that T also radiosensibilizes human healthy tissues and in this way it could increase the toxicity of the treatment. The incidence of T-induced pneumonitis is 0.4–0.6%. Although infrequent; pulmonary toxicity due to T may be life-threatening. Aldosterone, which is a physiological activator of MR, is partially responsible for increases in the extracellular matrix turnover, as observed in fibrosis of the cardiac, kidney and lung tissues, and exerts its effects primarily on lung epithelium. Spironolactone (S), an aldosterone receptor antagonist, may have the ability to ameliorate pulmonary fibrosis.We hypothesized that S would be effective in the treatment of both RT and T-induced lung injury by correcting pulmonary fibrosis **Method:** This study included 80 female Wistar-Albino rats (250-300 g); use of which was approved by the Ethical Committee. Rats were divided into eight groups: group (G) 1 was control group; G2, G3 and G4 were RT, S and T groups; G5, G6, G7 and G8 were RT+T, T+S, RT+S and RT+T+S groups respectively. RT was applied under general anesthesia with intraperitoneally administered 90 mg/kg ketamine hydrochloride and 10 mg/kg xylazine. A single dose of 15 Gy was applied to the both lungs. T (6 mg/kg) was administered intraperitoneally and S (80 mg/kg) was administered by oral gavage. Rats were sacrificed via cervical dislocation at 6th hour, 21st day and 100th day after RT and the lung samples were taken for microscopical examination. **Result:** By 100th days of RT inflammation score, lung fibrosis score and TGF- expression were significantly different within study groups (p values were 0.002, 0.001 and 0.043 respectively). Inflammation score of G8 was significantly lower than inflammation scores of G2 and G5 (p values: G2-G8= 0.004, and G5-G8=0.022). Inflammation score of G2 was significantly higher than G7 (p=0.028). There were significant differences regarding to fibrosis scores between G2-G8 (p=0.015), G2-G7 (p=0.017) and G5-G8 (p=0.011). TGF-β expression was higher in both G2 and G5 when compared to G8 (p = 0.038). **Conclusion:** Our results suggested that S is an effective treatment option for improving radiation-induced pulmonary

fibrosis. These findings should be clarified with further preclinical and clinical studies.

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-29 ACCELERATED HYPOFRACTIONATED RADIOTHERAPY FOR CENTRAL LUNG TUMORS UNSUITABLE FOR STEREOTACTIC BODY RADIOTHERAPY OR CONCURRENT CRT

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Background: In our institution, accelerated hypofractionated radiotherapy is a treatment option for 1) stage I lung non-small cell lung cancer (NSCLC) patients whose tumors are too bulky or central for SBRT; and 2) select stage II-III NSCLC patients not candidates for concurrent CRT. The purpose of this project was to review the clinical outcomes of a large single institutional experience of treating such patients with a dose of 60 Gy in 15 fractions in an era when SBRT was routinely used in clinical practice for early stage lung cancer. **Method:** Central tumors were defined as the gross target volume being in contact with mainstem bronchi, trachea, esophagus, great vessels, or heart. All patients who received 60 Gy in 15 fractions treated between 2008 and 2017 were reviewed. Competing risk analysis was used to calculate the cumulative incidence of local failure (LF), regional failure (RF), and distant failure (DF). Kaplan-Meier methodology was used to calculate overall survival (OS). Univariate analyses were used to look for potential predictive factors. **Result:** Eighty-nine patients were treated. Median follow-up was 24.0 months (range: 6.1-94.2 months). Median age was 79.4 years and most tumors were adenocarcinoma (n=47, 52.8%), followed by squamous cell carcinoma (n=31, 34.8%). Thirty patients (33.7%) had stage I disease, 47 patients (52.8%) had stage II-III disease, and 12 patients (13.5%) had stage 4 disease (mostly oligometastatic). Cumulative incidence of LF was 15.3% at 2 years. In those with stage I-III disease, cumulative incidence of RF and DF were 12.9%, and 28.5%, respectively at 2-years. OS was 74.9% at 2 years, with a median OS of 39.4 months for those with stage I-III disease. In the subset with stage II-III disease, median OS was 38.1 months and 2 year OS was 67.7%. Tumor stage, histology, EGFR mutation status, and location were not statistically significant predictors for any outcomes, although tumor size >3.5cm was borderline significant in predicting for a higher cumulative incidence of LF (subdistribution hazard ratio = 2.726; 95% confidence interval 0.995-7.469; p=0.051). The most common toxicity was radiation pneumonitis (n=6, 6.4%). The cumulative incidence of any grade 3 toxicity was 10.8% at ≥ 1 year. There were no deaths or hospitalizations directly attributed to treatment. **Conclusion:** Accelerated hypofractionated radiotherapy to a dose of 60 Gy in 15 fractions resulted in favorable outcomes in NSCLC patients who were not suitable for SBRT or concurrent CRT. Patients with Stage II-III disease had good OS despite not receiving concurrent chemotherapy. Severe toxicities were uncommon.

Keywords: accelerated hypofractionated radiotherapy, central lung tumors, local control

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P1.16-30 QUALITY OF LYMPHADENECTOMY DURING LOBECTOMY FOR NON-SMALL CELL LUNG CANCER: VATS VERSUS THORACOTOMY

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Background: Lobectomy by video-assisted thoracoscopic surgery (VATS) is preferred over thoracotomy in patients with early-stage non-small cell lung cancer (NSCLC). However, controversy still exists regarding the quality of the lymph node dissection accomplished using VATS. This study analyzed the lymphadenectomy by surgical approach and applied the International Association of the Study of Lung Cancer (IASLC) criteria of lobe-guided lymphadenectomy. **Method:** We performed a retrospective review of patients with stage I or II NSCLC who underwent lobectomy via thoracotomy (2003-2007, n=408) or VATS (2014-2017, n=754) at our institution. We compared the lymph node stations dissected by lobe-specific and the outcomes between the two approaches. **Result:** VATS was equal or superior to thoracotomy for dissection of all lymph node stations except stations 8R (p=0.0018) and 8L (p=0.0002) and was superior for subcarinal lymphadenectomy (p=<.0001). When examined by lung lobe(s), VATS was superior for lymphadenectomy during right upper lobectomies (p=<.0001) and at least equal to thoracotomy for all other lobes. Additionally, VATS was associated with less blood loss (p=<.0001), pneumonia (p=0.0008) and acute respiratory distress syndrome (p=0.0082), fewer air leaks (p=<.0001) and lower 30-day ortality (p=0.0308).

Table 1. Lymphadenectomy analysis

	VATS n (%)	Thoracotomy n (%)	p value
RUL +/- ML			
2R	92(26)	20(11)	<.0001
4R	274(79)	120(67)	0.0042
7	227(65)	98(55)	0.0231
2R, 4R, 7	79(23)	16(9)	<.0001
RLL +/- ML			
4R	63(52)	38(57)	0.5441
7	107(88)	48(72)	0.0094
8R	38(31)	37(55)	0.0018
9R	43(35)	19(28)	0.4183
4R,7, 8R/9R	33(27)	24(35)	0.2468
LUL			
5	150(80)	65(68)	0.0286
6	28(15)	4(4)	0.0055
7	85(45)	31(32)	0.0414
5, 6, 7	14(7)	2(2)	0.0995
LLL			
7	64(67)	31(47)	0.0151
8L	17(18)	30(45)	0.0002
9L	64(67)	35(53)	0.1011
7, 8L, 9L	5(5)	9(14)	0.0865
All lobectomies			
7	483(64)	208(51)	<.0001

RUL: right upper lobe; ML: middle lobe; RLL: right lower lobe
LUL: left upper lobe; LLL: left lower lobe

Conclusion: At our institution, the transition from thoracotomy to VATS lobectomy for early-stage NSCLC did not negatively impact the quality of the lymph node dissection. Moreover, VATS significantly improved surgical outcomes.

Keywords: non smal cell lung cancer, lobe-guided lymphadenectomy, early stage lung cancer

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-31 SURGICALLY RESECTED ACINAR ADENOCARCINOMA OF THE LUNG: ANALYSIS OF DIFFERENT PROGNOSTIC GROUPS.

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Background: Adenocarcinoma has become the most frequently diagnosed histotype of Non-Small cell Lung Cancer (NSCLC). Nevertheless, the latest classification of lung adenocarcinoma issued by IASLC/ATS/ERS identified different subtypes with different prognostic impact; concurrently, different subtypes might mingle influencing biological features and behavior. We focused on surgically treated stage I and II predominantly acinar lung adenocarcinoma analyzing outcomes and prognostic factors according to the second main histological pattern. **Method:** We retrospectively collected all lung adenocarcinoma with a predominant acinar histological pattern operated on between October 2012 and September 2017 in our institution. We selected all patients in pathological stage I A-B and II A-B with full preoperative staging procedures performed at our institution. All clinical and pathological features were registered. We analyzed outcomes according to the histological sub pattern and we focused on main prognostic factors.

Result: During the study period we performed 153 lung resections for patients affected by NSCLC. Among them we found 93 adenocarcinoma and 55 had a predominant acinar pattern. Among selected patients, there were 33 female and the mean age was 68.2 (SD±9.3) years. The histology report showed a solely acinar pattern in 11 cases (20.0%), while a second main sub-pattern was seen in the remaining cases: papillary or micropapillary in 7 cases (12.7%); lepidic in 27 cases (49.1%) and solid in 10 (18.2%). Mean Overall Survival (OS) and Disease-Free Survival (DFS) of all the cohort of patients were 66.1 (CI 95% 59.7-72.4) and 51.9 (CI 95% 42.7-61.2) months respectively. According to the secondary histological pattern, papillary and micropapillary subtypes showed a significant worse OS (p=0.029) and DFS (p=0.015) compared to all the other subtypes; concurrently they showed a significant higher mean Standard Uptake Value of T component at the preoperative PET-CT (11.8 vs 6.4, p=0.007) and had a higher rate of vascular invasion at the specimen (P=0.002). Beyond papillary and micropapillary subtypes, vascular invasion showed to be a significant prognostic factor both for OS and DFS. **Conclusion:** Lung adenocarcinoma encompasses different sub-histotypes. In our experience, stage I and II resected predominantly acinar adenocarcinoma with papillary or micropapillary component showed higher rate of vascular invasion in the specimen and worse long-term outcomes compared to other subtypes, which might be related with a higher aggressiveness. In conclusion, our results suggest that different postoperative management should be adopted according to adenocarcinoma histological subtypes pattern; histology patterns should also be considered as a prognostic factor to be included in the NSCLC staging system.

Keywords: lung adenocarcinoma, NSCLC

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-32 LUNG CANCER COMPLETENESS OF RESECTION IN UNIPORTAL VERSUS MULTIPORTAL VIDEO-ASSISTED THORACOSCOPIC SURGERY LOBECTOMY

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Background: In 2005, the International Association for the Study of Lung Cancer (IASLC) added a new category to complete and incomplete resection for residual tumor classification (R): uncertain resection (R(un)). R status has a major prognostic impact, and the prognosis of patients with a R(un) resection differs from that of patients with either complete (R0) or incomplete resection (R1 or R2). The aim of this study was to measure R status with the expanded classification system when performing lobectomy for non-small cell lung cancer (NSCLC) using a uniportal (U-VATS) or multiportal (M-VATS) video-assisted thoracoscopic surgery. **Method:** From August 2014 through December 2017, 672 VATS lobectomies were performed for the primary treatment of clinical stage I and II NSCLC, 43 patients with ground glass opacity or complex cases were excluded. Patients were analyzed according to ports used (one or multiple), R status, lobe-specific lymphadenectomy, subcarinal lymphadenectomy, length of hospital stay and length of thoracic drainage. A propensity-matched analysis was planned however, all variables were evenly distributed in both groups. **Result:** Of 629 VATS lobectomies, 234 (37%) were performed with U-VATS and 395 (63%) with M-VATS. Most resections were classified as R(un) (84%); 2% were incomplete. When compared with M-VATS, U-VATS was associated with superior completeness of resection (p=0.0159), superior lobe-specific lymphadenectomy (p=0.0004), and superior subcarinal lymphadenectomy (p=0.0064). The highest mediastinal lymph node station dissected was not different between the approaches. The patients who underwent U-VATS had shorter hospital stays (mean: 4.4 days vs 6.2 days, p=0.0001) and less thoracic drainage (mean: 4.7 days vs 5.8 days, p=0.0004). There was no difference in operative mortality (p=0.3024) (Table 1).

Table 1: Primary and secondary outcomes

Variables	Uniportal VATS (N = 234)	Multiportal VATS (N = 395)	p-value
Oncologic			
R status (%)			
Complete (R0)	45 (19)	44 (11)	
Uncertain (R(un))	185 (79)	345 (87)	0.0159
Incomplete (R1 or R2)	4 (2)	6 (2)	
Lope-specific lymphadenectomy, n (%)	55 (24)	49 (12)	0.0004
Station 7 dissected, n (%)	163 (70)	232 (59)	0.0064
Positive highest mediastinal station, n (%)	12 (5)	10 (3)	0.1146
Positive margin, n (%)	4 (2)	6 (2)	1.0000
Perioperative			
Bleeding, in ml[a]	94 ± 176	125 ± 143	0.0001
Surgery duration, in hours[a]	2.2 ± 0.7	2.7 ± 0.8	0.0001
Conversion to thoracotomy, n (%)	5 (2)	20 (5)	0.0902
Length of hospital stay, in days[a]	4.4 ± 4.1	6.2 ± 5.0	0.0001
Length of thoracic drainage, in days[a]	4.7 ± 6.7	5.8 ± 6.3	0.0004
30-day mortality, n (%)	0 (0)	4 (1)	0.3024

[a]mean ± standard deviation. VATS, video-assisted thoracoscopic surgery.

Conclusion: In our institution, most VATS lobectomies were uncertain resections due to the lymph node evaluation by IASLC definition. Using U-VATS is not inferior to M-VATS in accomplishing a complete oncologic resection thoracoscopically.

Keywords: non small cell lung cancer, early stage lung cancer, complete resection

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-33 OCCULT LYMPH NODE METASTASES IN EARLY STAGE NSCLC PATIENTS: WHERE DO WE STAND NOW? A PROPOSAL FOR A PREOPERATIVE RISK MODEL

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Background: Notwithstanding mediastinal lymphadenectomy is a cornerstone of surgical management of primary lung tumors, results and evidences are still debated for clinical stage I disease. In this aspect, current guidelines appear conflicting, as being both radical lymph node dissection and systematic node sampling equally advocated by several Authors. However, though lymphadenectomies are not risk-free procedures, N-status is an undoubted and significant prognostic factor in NSCLC patients. For these reasons, the adoption of a preoperative predictive non-invasive model should be clinically useful to stratify patients according to risk of lymphatic metastases. **Method:** A multicentre retrospective study from January 2014 to June 2017 enrolling 2502 early stage NSCLC patients (up to cIB disease) with a mean age of 67.35 ± 8.89 years was conducted by analysing demographic, radiological and pathological features and correlating themselves to pN+ disease through a bivariate analysis, relative risk estimation and Receiver Operative Curves estimation. Diagnostic performance of a derived risk coefficient (RC = Σ factors) was finally evaluated. **Result:** With a mean Charlson's Comorbidity Score of 4.34 ± 1.80 and an excellent ECOG Status (ECOG 0-1) in 98.1%, 66.2% presented a very early stage disease (cT1a/b N0 M0) with predominant solid nodule density at chest CT (n. 1992 – 79.6%) and a mean SUVmax of 4.37± 4.95. Each patient underwent a R0 video-assisted thoracoscopic lobectomy with a radical node dissection in 69.9% and a systematic lymph node sampling in remaining cases. Concerning with histology, primary pulmonary invasive adenocarcinoma was the predominant pattern (n. 1417 56.6%) and a cumulative incidence of occult hilar-mediastinal lymph node metastases of 8.8% was reported. At bivariate analysis and relative risk estimation, male gender (p=0.033), clinical T-stage (p=0.000), nodule diameter (p=0.000), nodule density (p=0.005), the presence of visceral pleura or bronchial invasion (p=0.000) and a SUV max >3.5 (p=0.001) significantly correlated with pN+ disease. By deriving a risk coefficient function and adopting it to general population through a ROC curve, a RC > 58 presented a not negligible predictive value (sensibility: 82.73%, specificity 74.36%, PPV 23.73%, NPV 97.81%). **Conclusion:** Although a prospective study is needed, a preoperative clinically easily reproducible predictive model for early stage NSCLC patients should represent a useful tool for a proper stratification of pN+ high risk patients. In particular, by considering its high negative predictive value, the aforementioned risk coefficient could allow to discriminate low risk cohort patients amenable to limited lymph node assessment rather than radical dissections with their fearsome related risks.

Keywords: OCCULT LYMPH NODE METASTASES, Preoperative risk model, early stage NSCLC

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-34 THE IMPACT OF PATHOLOGY, STAGING AND OPERATIVE RESECTION ON SURVIVAL AND CT EVIDENCE OF RECURRENCE OF EARLY NSCLC

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Background: The purpose of this study is to determine the impact of histopathology, staging and extent of operative resection on survival and CT evidence of recurrence of early NSCLC excised with VATS wedge resection guided by preoperative CT-guided microcoil localization (CTML) and intra-operative fluoroscopic guidance. **Method:** Between April 2003, to June 2012, 106 of 154 patients who underwent CTML and VATS resection of suspicious pulmonary nodules were found to have NSCLC. Serial chest CTs of the 106 patients with confirmed NSCLC were reviewed by 2 chest radiologists for development of recurrence of the original cancer at the resection margin, lung or mediastinum and the development of new primary lung cancer. 53 patients underwent CTML and VATS resection alone and 53 had CTML, VATS diagnostic resection followed by VATS therapeutic lobectomy. An experienced chest pathologist determined pathologic resection margins, histological subtype and staging. **Result:** The male/female ratio was 47/59. Median age was 63 (34-81) years. Smoking history obtained in 91/106. Median follow-up was 82 (32-136) months. Histology consisted of 99 adenocarcinomas and 7 squamous carcinomas. Staging (AJCC 8th edition) was Stage 0 (11), IA1 (77), IA2 (2), IA3 (3) IB (8), IIB (4) & IV (1). Both surgical groups were similar for demographics, tumor characteristics, histopathology and stage at surgery; there was no 90-day mortality. Multivariate analysis showed adverse effects on: 1) Local recurrence of cancer (n=3) by positive resection margin (n=2) ***. 2) Any recurrence of original cancer (n=10) by lymph node stage ***, positive resection margin ***, visceral pleural invasion (VPI) *** but not age, gender, smoking history, nodule shape on CT, histopathology, tumor invasive size, STAS, lymphovascular invasion or extent of resection. 3) Development of a new primary NSCLC (n=19) by wedge resection alone* (12/19). The new primary was resected in 13/19 patients. 4) Disease free survival at 3 (89%), 5 (74%) & 9 years (61%) by a positive resection margin ***, VPI **, lymph node stage*, or wedge resection alone *. Overall 5-year survival was 85%. (p<.05 *,p<.01 **, p<.001***) **Conclusion:** In patients with early NSCLC, CTML accurately identifies the cancer margins resulting in a low radiologic local recurrence rate of 3%. Ten patients had recurrence of their original cancer associated with lymph node involvement, positive resection margin, and VPI. Second primary lung cancers are prevalent in long-term survivors, particularly if treated with wedge resection. Completion therapeutic lobectomy following diagnostic wedge resection of NSLC improves disease-free survival.

Keywords: Microcoil, recurrence, NSCLC

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-35 SLEEVE LOBECTOMY VERSUS PNEUMONECTOMY FOR NON-SMALL CELL LUNG CANCER, A CUMULATIVE UPDATED META-ANALYSIS

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Background: Sleeve lobectomy (SL) is an appealing alternative to pneumonectomy (PN) for central or locally advanced non-small cell lung cancer (NSCLC). The purpose of this study was to investigate the benefits of SL versus PN for NSCLC through cumulative meta-analysis. **Method:** A systematic review and cumulative analysis of comparative studies reporting both postoperative and survival outcomes of SL and PN was performed through a comprehensive search of PubMed, EMBASE and the Cochrane library electronic databases from inception to April 2018 **Result:** A total of 9153 patients (SL: 3658, PN: 5495) from thirty-two studies were included. Meta-analysis was conducted for hazard ratio (HR), postoperative mortality, postoperative morbidity, local recurrence, and overall survival. PN was inferior to SL in terms of hazard ratio (HR=0.66, 95% confidence interval [CI]=0.59 to 0.75, I^2=56%). Lower postoperative mortality was found in SL group (OR=0.45, 95% CI=0.36 to 0.56, I^2=0.0%). While SL and PN showed no significant difference in local recurrence (OR=0.86, 95% [CI]=0.69 to 1.07, I^2=45.0%) or postoperative morbidity (OR=0.92, 95% [CI]=0.78 to 1.09, I^2=29.0%). Moreover, the 1-, and 5-years survival rates (1-yr: OR=2.19, 95% CI=1.93 to 2.5, I^2=14.0%) (5-yrs: OR=1.94, 95% CI=1.61 to 2.35, I^2=52.0%) and survival in patients with pN0 or pN1 at 5-years (OR=1.79, 95% CI=1.19 to 2.67, I^2=3.0%) in the SL group were significantly higher than that in the PN group. As demonstrated in our cumulative meta-analysis, these effects were consistent over the years. **Conclusion:** SL could be considered an acceptable alternative to PN for the treatment of NSCLC.

Keywords: sleeve lobectomy, pneumonectomy, NSCLC

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-36 REAL-TIME CT GUIDED VIDEO ASSISTED THORACOSCOPIC PARTIAL RESECTION OF PERIPHERAL SMALL-SIZED LUNG TUMORS.

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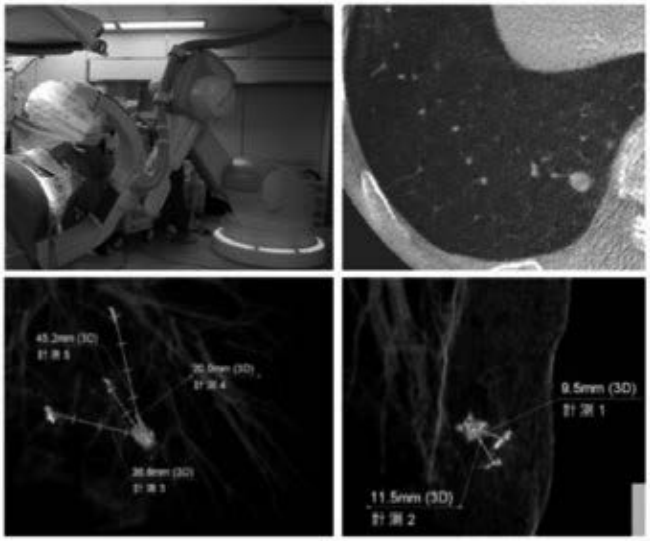
Background: As pulmonary resection for small and grand-grass opacity (GGO) dominant pulmonary nodules have been increasing, various navigation systems to detect these nodules have been reported. The aim of this study is to evaluate feasibility of real-time CT guided pulmonary resection for impalpable small pulmonary nodules. **Method:** From July to November in 2017, 11 patients were eligible for pulmonary resection for lung cancer or malignancy suspected lesions, which was expected to be difficult to detect during operation. These nodules were defined as GGO-dominant (>50%) tumor with a diameter of 3cm or lower (GGO-dominant type), and tumor with a diameter of 2cm or lower, which is located deeper than the diameter of the tumor from visceral pleura (deep solid type). First, we put several surgical clips as first marker on the visceral pleura of the tumor-located lobethrough 3-ports VATS approach. The tumor and the first markers were visualized by cone beam CT, then the second marker was put just on the tumor based on the image. Pulmonary resection was performed according to second marker guided by automated staplers. CT scanning was also performed for confirmation of the complete resection. **Result:** These procedures were performed for 4 men and 7 women (mean age: 58 years (39-71)). Tumors were located in the right upper lobe/right lower lobe/left upper lobe/left lower lobe in 5/2/2/2 patients. Diameters of tumors were 1.5cm or less. Six tumors were GGO-dominant types whereas 5 were solid types located in the deep from the visceral pleura; therefore all tumors couldn't be detected by video-scopic observation. The average number of cone beam CT scanning is 2.7 times. All patients accomplished macroscopic and microscopic complete resection with no adverse events during perioperative periods. **Conclusion:** This feasibility study suggested that cone beam CT was safe and useful guide forvideo assisted thoracoscopic partial resection for impalpable peripheral pulmonary nodules.



Keywords: small pulmonary nodules, Image-guided surgery, Cone beam CT

P1.16-37 CLINICOPATHOLOGICAL CHARACTERISTICS AND PROGNOSTIC FACTORS OF OPERABLE NON-SMALL CELL LUNG CANCER PATIENTS WITH THE DIABETES MELLITUS

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Background: Lung cancer patients have a high frequency of comorbidity. The diabetes mellitus (DM) has been reported to be associated with postoperative complication and survival in several types of cancers. The aim of this study was to investigate the impact of DM on postoperative complication and survival in operable non-small cell lung cancer (NSCLC) patients. **Method:** We retrospectively reviewed 1231 patients who underwent surgical resection for NSCLC between 1996 and 2012. The outcomes were compared between the patients with DM (DM group, n=139) and without it (Non-DM group, n=1092). Patients were assigned to DM group if following conditions were identified; 1) a history of DM or medication use, and 2) preoperatively elevated fasting glucose (>126 mg/dL) or hemoglobin A1c (National Glycohemoglobin Standardization Program) level (≥ 6.5 %) in spite of the unrevealed history of DM. However, diabetes of all patients in DM group was controlled by dietary or sliding-scale insulin therapy. Postoperative complications were defined as events of grade 2 or more according to the Clavien-Dindo classification. A multivariate Logistic regression model was used to identify clinical factors associated with postoperative complication. Survival was evaluated by overall, relapse-free, and disease-specific survivals using Kaplan-Meier method, and a multivariate Cox proportional hazard model was used to identify prognostic factors. **Result:** DM group included more elderly patients, males, smokers, patients with ischemic heart disease, patients taking antiplatelet or anticoagulant drugs, squamous cell carcinomas than non-DM group. DM group showed higher incidence of postoperative complications than non-DM group (28% vs. 21%, p=0.047). Logistic regression analysis showed that DM was an independent predictor for postoperative complication (OR: 1.851, 95% CI: 1.189-2.884). But, no signficant difference was observed in thirty-day mortality between the two groups (2% vs. 1%, p=0.061). DM group showed a worse overall survival than non-DM group (p=0.024), and multivariate Cox analysis showed that DM was identified as an independent poor prognostic factor for overall survival (HR: 1.492, 95% CI: 1.053-2.113). DM group included more death from other disease than non-DM group (50% vs. 35%, p=0.048), and there was no significant difference in relapse-free and disease-specific survival between the two groups. **Conclusion:** The present study demonstrated that operable NSCLC patients with DM have distinct clinicopathological features. Although the presence of preoperative DM was associated with postoperative morbidity and worse overall survival, it did not increase perioperative and lung cancer-related mortalities. Operable NSCLC patients with DM can be still indicated for curative surgery if their perioperative diabetes was controlled.

Keywords: Diabetes Mellitus, non-small cell lung cancer, prognostic factor

P1.16-38 META-ANALYSIS OF UNPLANNED READMISSIONS FOLLOWING THORACOSCOPIC VERSUS OPEN LUNG CANCER RESECTION

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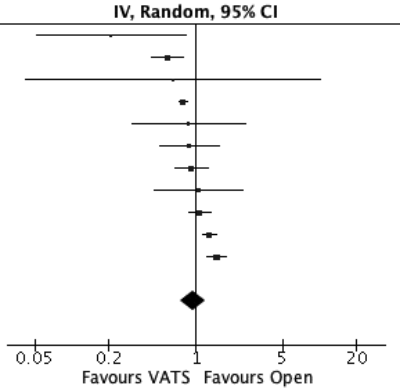
Background: Approximately 7.4% of patients experience unplanned readmission within 30 days following pulmonary resection. Although video-assisted thoracic surgery (VATS) is able to improve short-term outcomes in both cancer patients and noncancer patients, surprisingly, several recent big registry studies showed significantly increased readmission rates. **Method:** We performed a systematic review and meta-anaysis according to PRISMA (Preferred Items Reporting for Systematic Reviews and Meta-Analyses) guidelines. The search process covered a period untill 31st of March 2018. Search keywords were: VATS, lobectomy, segmentectomy, open, thoracotomy, readmission*, readmit*. Studies were to compare VATS vs open thoracotomy and reporting 30-90 days readmission rates. Only reports in English were included and retrieved as full-txts. Data were pooled in DerSimmonian and Laird Inverse Variance random effects model and reported as Risk Ratios (RR) with corresponding 95% Confidence Intervals (CIs). **Result:** A systematic search yielded 16 potentially elegible reports, of which 5 were further excluded because they did not report crude readmission rates across VATS vs open thoracotomy. Eleven studies remained enrolling 60,146 patients undergoing VATS (39.3%) and open thoracotomy (60.7%). Unplanned readmissions followed in 7.8% (1,843/23,632) and 8.1% (2,944/36,514) of patienst undergoing VATS and open thoracotomy respectively; there was no statistical differences between two appraoches: RR (95%CIs): 0.94 (0.75-1.19); p=0.63. Substantial heterogeneity was present (p<0.001, I^2=87%) in the analysis though. No single study influenced direction nor magnitude of the estimates in number of sensitivity analyses. In meta-regression analyses we demonstrated that patients' age, disease's local advancement and centre volume did not influence the results (p>0.05). On the other hand number of complications across single study pooled n. of patients was negatively

Study or Subgroup	VATS Events	VATS Total	Open Events	Open Total	Weight	Risk Ratio IV, Random, 95% CI
Handy Jr. JR et al. 2010 [LCSOS]	2	49	38	192	2.4%	0.21 [0.05, 0.83]
Shargall Y et al. [ICC]	50	306	104	378	12.0%	0.59 [0.44, 0.80]
Surendrakumar V et al. 2017	1	52	1	34	0.7%	0.65 [0.04, 10.10]
Stiles BM et al. 2015 [SID HCUP]	981	9327	1770	13320	14.8%	0.79 [0.74, 0.85]
King M et al. 2017	9	49	4	19	3.7%	0.87 [0.30, 2.50]
Werner A et al. 2013	15	118	46	323	8.2%	0.89 [0.52, 1.54]
Rajaram R et al. 2015 [ACS NSQIP 2011-]	61	724	82	899	11.8%	0.92 [0.67, 1.27]
Quero-Valenzuela F et al. 2017	8	125	15	247	5.1%	1.05 [0.46, 2.42]
Boffa DJ et al. 2014 [STS]	149	2156	167	2607	13.3%	1.08 [0.87, 1.34]
Medbery RL et al. 2016 [NCDB]	294	5791	546	13920	14.3%	1.29 [1.13, 1.49]
Bhagat R et al. 2017 [ACS NSQIP 2012-2015]	273	4935	171	4575	13.7%	1.48 [1.23, 1.78]
Total (95% CI)		**23632**		**36514**	**100.0%**	**0.94 [0.75, 1.19]**
Total events	1843		2944			

Heterogeneity: Tau² = 0.09; Chi² = 79.22, df = 10 (P < 0.00001); I² = 87%
Test for overall effect: Z = 0.49 (P = 0.63)



Conclusion: There was no apparent difference between VATS and open thoracotomy with regard to number of unplanned readmissions. Future studies should focus on reducing complication rates in the open thoacotomy group rather than reducing readmission rates after VATS.

P1.16-39 A NOMOGRAM FOR PREDICTING SURVIVAL OF TNM8 STAGE I NON-SMALL CELL LUNG CANCER PATIENTS TO TAILOR POTENTIAL CHEMOTHERAPY CANDIDATES

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Background: The 8th TNM stage I non–small-cell lung cancer (NSCLC) patients are not considered as candidates for adjuvant chemotherapy (ad-Chemo). This study aimed to develop a nomogram for predicting cancer specific survival (CSS) of these patients and identifying those who might benefit from ad-Chemo. **Method:** NSCLC cases between 1998 and 2013 were extracted from the SEER database and randomly divided into training and validation cohorts. We identified and integrated the recurrence-associated factors to build a nomogram. We determined the cut-off for the high-risk group by matching the nomogram-predicted 5-year CSS with that of the current 4-5 cm stage IIA cases. The difference in benefit from chemotherapy between risk groups was examined using both SEER and NCDB cohort. **Result:** A total of 30,475 patients with stage I were included for analysis. Six independent prognostic factors were identified and integrated into the model. The calibration curves showed good agreement. The C-index of the nomogram was higher than that of the staging system (IA1, IA2, IA3, IB) (training set, 0.59 vs. 0.56, P < 0.01; validation set, 0.62 vs. 0.57, P < 0.01). Specifically, 26.9% stage IB patients (8.1% of all stage I) were categorized into the high-risk group (score>29) and had inferior CSS compared with stage IIA patients. In addition, chemotherapy was associated with significantly better OS (HR, 0.739; P = 0.047) than no-chemotherapy in the high-risk group.

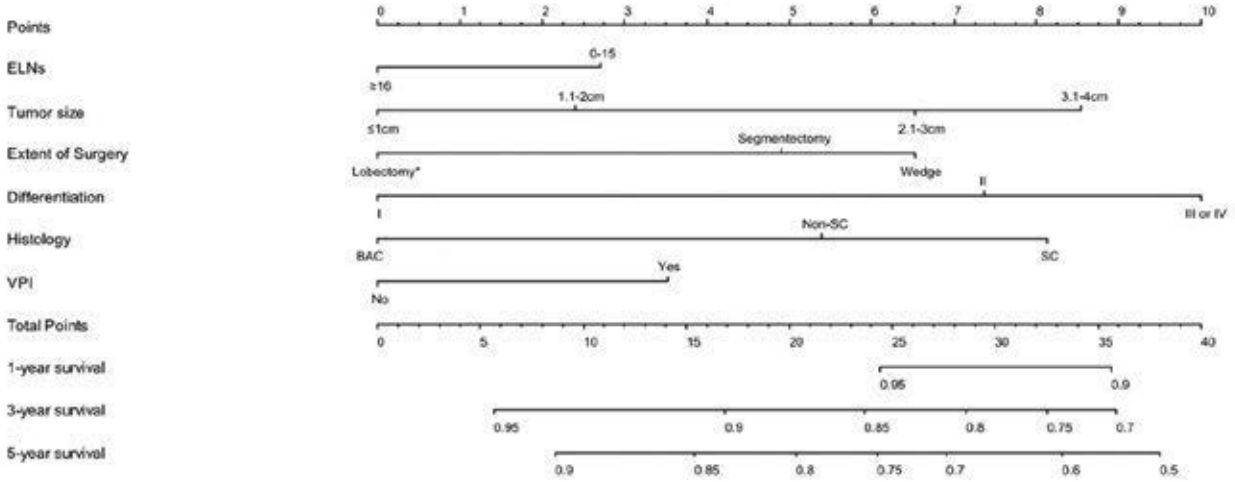

Figure 1. Postoperative prognostic nomogram for patients with stage I. ELNs, examined lymph nodes; BAC, bronchioloalveolar carcinoma; SC, squamous carcinoma; VPI, visceral pleural invasion; Lobectomy* includes lobectomy, pneumonectomy, and bronchial sleeve resection.

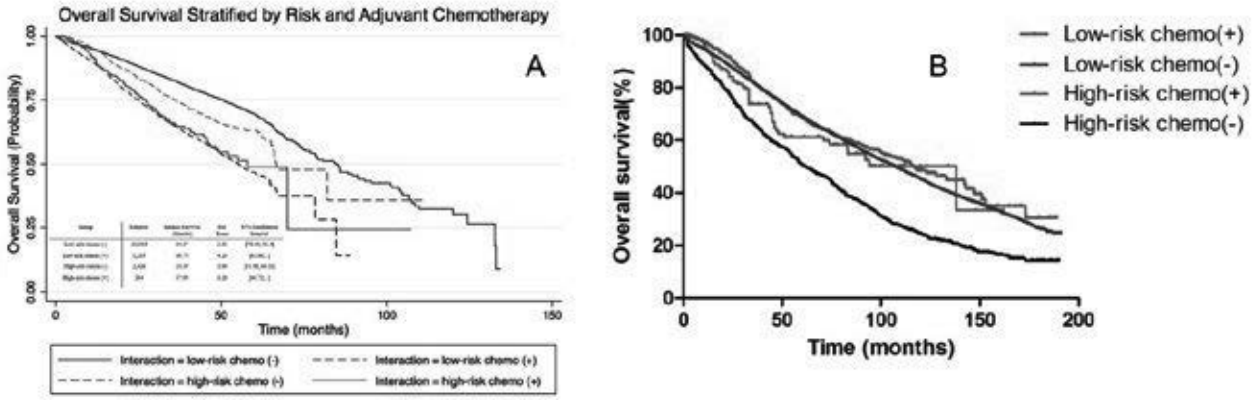

Figure 2. Overall survival stratified by risk and adjuvant chemotherapy of patients with stage I non–small-cell lung cancer (NSCLC) in (A) NCDB and (B) SEER

Conclusion: We established a practical and economical nomogram to predict CSS for 8th edition stage I NSCLC, and identified a subset of patients at relatively high risk for recurrence who might benefit from ad-Chemo.

P1.16-40 EVALUATING THE TUMOR HETEROGENEITY IN LUNG CANCER BY CONSTRUCTING TUMOR HETEROGENEITY INDEX (THI) FROM MAGNETIC RESONANCE IMAGING

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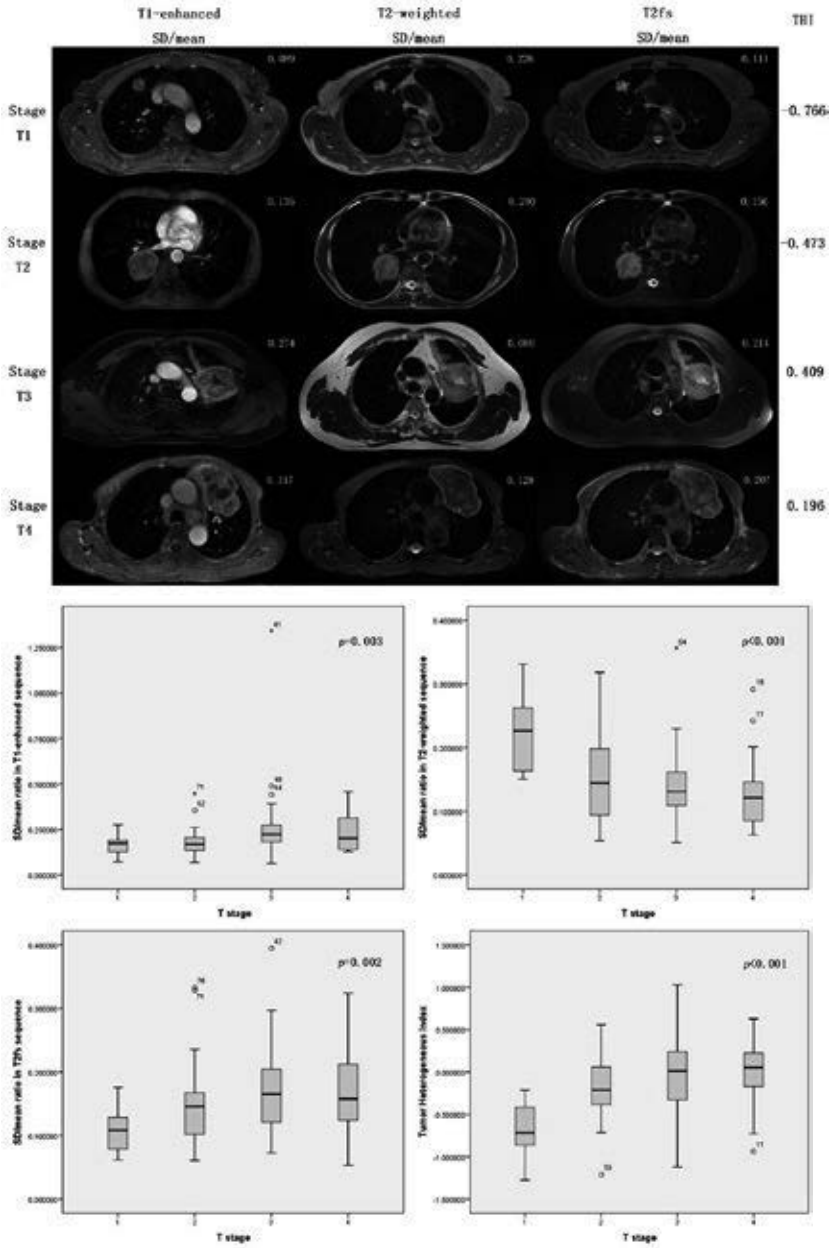
Background: To improve the evaluation of primary lung cancer heterogeneity using clinical routine magnetic resonance imaging (MRI), we proposed a method based on basic measurements from T1- and T2-weighted MRI. **Method:** As a novel technique of magnetic resonance imaging analysis, we investigated a total of 203 patients with biopsy-proven primary lung cancer and with different T stages. All patients previously received positron emission tomography/computed tomography (PET/CT) scan. Gross lesions were manually contoured on T1-weighted, T1-enhanced, T2-weighted and T2 fat suppression (T2fs) images. The ratios of standard deviation (SD) / mean tumor value from each sequence were calculated. Correlation analyses were performed between T stages and the ratios. P value <0.05 was defined as statistical significant. Then a linear regression was performed to determine the weight of each related ratio. A model was built to calculate Tumor Heterogeneous Index (THI). One hundred and one patients were analyzed as the training set and another 102 as validating set. **Result:** There were 56 patients diagnosed with T1 disease, 60 with T2 disease, 51 with T3 disease and 36 with T4 disease. Pair matching was performed between training set and validating set. As a result of the correlation analyses, SD/mean ratio showed significantly correlations with T stages in T1-enhanced (p=0.003), T2-weighted (p<0.0001) and T2fs sequences (p=0.002). Based on a linear regression model, THI was established for assessing the heterogeneity of lung tumor, consisting the three ratio measurements. Correlation analysis demonstrated that Higher THI was significantly related to more advanced T stages (p<0.0001).



Conclusion: The proposed SD/mean ratio measurements and the calculation of THI according to clinical routine MR images could be clinical biomarkers that correlated with T stages, and were capable of evaluating heterogeneity of lung cancers.

Keywords: tumor heterogeneity index, T stage, MRI

P1.16-41 THE ROLE OF SURGERY IN PULMONARY LARGE CELL NEUROENDOCRINE CARCINOMA: A PROPENSITY-SCORE MATCHING ANALYSIS OF SEER DATABASE

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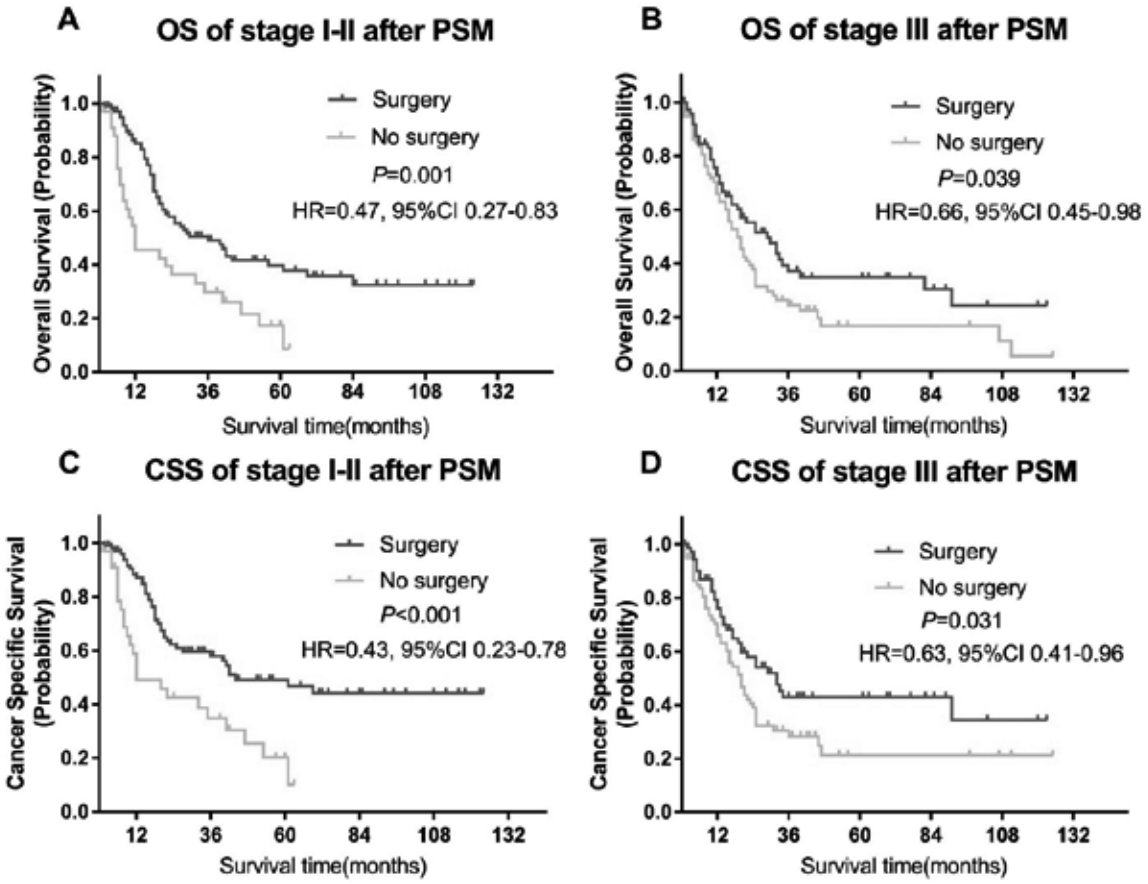
Background: Pulmonary large cell neuroendocrine carcinoma (LCNEC) is a rare and aggressive subset of non-small-cell lung cancer with poor prognosis. Due to its rarity, the optimal therapy strategy for pulmonary LCNEC remains undefined. We aimed to evaluate the role of surgery for stage I-III LCNEC using the Surveillance, Epidemiology, and End Results (SEER) database. **Method:** Patients with stage I-III LCNEC were extracted from the SEER database (2004-2014). Propensity-score matching was performed to reduce the effect of potential confounders. Kaplan-Meier curves were constructed for overall survival (OS) and cancer-specific survival (CSS) for patient strata based on surgery use or nonuse. Multivariable Cox-regression was used to explore the efficacy of different treatment strategies. **Result:** A total of 944 LCNEC patients were identified, of which 674 (71.4%) received surgery. Both OS and CSS of surgery use group were superior to surgery nonuse group in the whole cohort (HR=0.48, *P*<0.001 and HR=0.41, *P*<0.001, respectively). Among matched cohort, significantly greater benefits in OS and CSS (Figure 1) from surgery was observed in both stage I-II (HR=0.47, *P*=0.001 and HR=0.43 *P*<0.001, respectively) and stage III (HR=0.66, *P*=0.039 and HR=0.63, *P*=0.031, respectively). On multivariable analysis of surgical group, there was no significant difference in either OS or CSS between surgery alone and the addition of chemotherapy or (and) radiation for stage I-II patients, whereas favorable survival outcomes of surgery plus chemotherapy (OS: HR=0.26, *P*<0.001; CSS: HR=0.30, *P*=0.001) and surgery plus chemotherapy and radiation (OS: HR=0.33, *P*<0.001; CSS: HR=0.34, *P*=0.002) were significantly evident for stage III patients.



Conclusion: This is the largest study exploring the benefit of surgery for stage I-III pulmonary LCNEC. Regardless of stage, surgery showed remarkable survival benefits for LCNEC patients. It is suggested that surgery alone may be sufficient for stage I-II, whereas the multimodal combination of surgery and other therapies should be considered for stage III disease.

Keywords: Pulmonary large cell neuroendocrine carcinoma, Surgery, survival

P1.16-42 INDOCYANINE GREEN INTERSEGMENTAL VISUALIZATION DURING FLUORESCENCE IMAGING OF THORACOSCOPIC ANATOMIC SEGMENTECTOMY: A NOVEL APPROACH

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Background: Anatomic segmentectomy (AS) of the lung is a more complex operative procedure than standard lobectomy, especially when performed as a complete thoracoscopic surgery. Identification of the intersegmental boundary line (IBL) is a technical imperative, allowing surgeons to develop this plane during segmentectomy. Although several methods of IBL identification (IBL-ID) have been reported, our general usage of an intravenous indocyanine green (ICG) fluorescence system is alternative. In examining 83 patients by conventional ICG method (CIM), the IBL-ID success rate was high (98.8%), but intersegmental visibility was diminished due to smoking and emphysema. We also examined 29 patients using the Spectra A method (SAM), which heightened intersegmental contrast (IC) and preserved segment brightness (PB), compared with CIM, thus improving intersegmental visibility. To effect further improvement, a trial of the novel SAM with xenon light (SAM-X) was undertaken. **Method:** We prospectively studied 106 consecutive patients who underwent complete thoracoscopic AS of 111 lung segments (including subsegments) at our Hospital between October 2015 and October 2017. Following intraoperative transection of the segmental artery, vein and bronchi, 5 mg/body weight of ICG was administered intravenously, and fluorescence images were generated using the ICG system. Both the CIM with xenon light (CIM-X) and the SAM-X were simultaneously obtained in concert for IBL-ID, quantifying intersegmental visibility for histogram representation. **Result:** The patient population (men, 50; women, 56) had a mean age of 67.4±10.7 years and a mean Brinkman index of 446.6±650.7, harboring malignant lung tumors (primary, 77; metastatic, 29, other, 5) as follows: right upper, 28; right middle, 1; right lower, 20; left upper, 38; left lower, 24. IBL-ID was achieved in all patients (100%). As with the SAM apparatus, the SAM-X provided significantly better accentuation of green fluorescence in RGB light analysis, compared with the CIM-X ($p<0.01$). Furthermore, both IC and PB showed significant increases ($p<0.01$ each), whether comparing SAM-X with CIM-X or with SAM; and SAM-X was strong (R=0.8), surpassing that of CIM-X (R=0.39) as for the correlation between IC and PB. **Conclusion:** The SAM-X device stabilized visibility and improved contrast between resected and non-resected segments and brightness of both resected and non-resected segments during thoracoscopic intersegmental identification.

Keywords: segmentectomy, VATS, ICG

P1.16-43 ANALYSES OF LONG-TERM OUTCOMES AND PROGNOSTIC FACTORS IN SURGICALLY RESECTED ALK-REARRANGED LUNG ADENOCARCINOMA

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Background: Anaplastic lymphoma kinase (ALK)-rearrangement (ALK+) in lung cancer has made an epoch in the molecular classification. Specific inhibitors of the kinase activity of ALK have been developed as therapeutic drugs for lung cancer with ALK+. Long-term outcomes and prognostic factors, however, in surgically resected cases are unclear. We evaluated the survival rate, and investigated association between prognosis of surgically resected lung adenocarcinoma (AC) with ALK+ and clinicopathological features. **Method:** From 1996 to 2013, clinical data of 62 AC patients with ALK+ were retrospectively analyzed. The median follow up time was 73 months. Relationships between the patients' clinicopathological features (i.e. age, gender, smoking history, operative procedure, administration of adjuvant therapy, tumor size, c-stage, p-stage, pleural invasion, Ly/V invasion, intrapulmonary metastasis, histologic predominant subtypes, and histologic grade), and their recurrence-free survival (RFS), post-recurrence survival (PRS) and overall survival (OS) rates were assessed. **Result:** The 5-year RFS and OS were 69% and 92%, respectively. For OS, advanced p-stage (IIIA and IV) and pleural invasion were independent poor prognostic factors in multivariate analyses, but 5-year OS for even Stage IIIA was 85%, nevertheless (Figure). 20 patients had recurrence. 8 of the 20 patients were treated with ALK-tyrosine kinase inhibitors (TKIs), and 12 were without. The median PRS was 54 months. Patients treated with AKL-TKIs had longer PRS and OS than without (65 vs. 38 months, p=0.01, and 80 vs. 74 months, p=0.04, respectively).

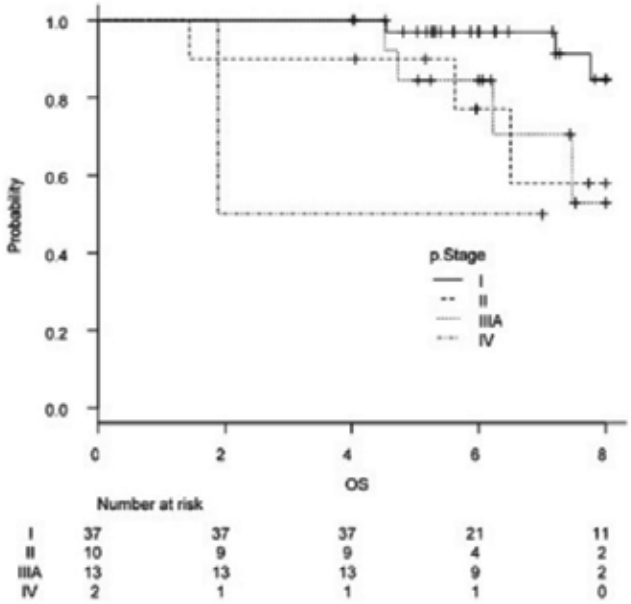

Figure. Overall survival (OS) curve for each stages.

Conclusion: Long-term outcomes in surgically resected ALK+ AC were excellent even so advanced stage. ALK-TKIs are certainly effective for post-recurrence status. For the resectable ALK+ AC treatment strategy, ALK-TKIs might play an important role.

Keywords: Anaplastic lymphoma kinase, Surgical resection, Prognosis

P1.16-44 MINUTE VENTILATION-TO-CARBON DIOXIDE SLOPE IS ASSOCIATED WITH EARLY AND LONG TERM SURVIVALS FOLLOWING ANATOMICAL PULMONARY RESECTION

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[1]*St. James'S University Hospital, Leeds/GB,* [2]*Surgical Oncology, Nagasaki Graduate School of Medicine, Nagasaki/JP*

Background: The aim of study was to identify that ventilation-to-carbon dioxide output (VE/V CO2) slope obtained from cardiopulmonary exercise test (CPET) was an independent prognostic factor of short and long term survival after lobectomy or segmentectomy.The aim of study was to identify that ventilation-to-carbon dioxide output (VE/V CO2) slope obtained from cardiopulmonary exercise test (CPET) was an independent prognostic factor of short and long term survival after lobectomy or segmentectomy. **Method:** 974 patients including lobectomy (n=887) or segmentectomy (n=87) were performed from April 2014 to March 2018. 209 (22%) underwent CPET, and pulmonary function and several clinical factors including age, sex, performance status and comorbidities were retrospectively investigated to identify the prognostic factors with a multivariable Cox regression analysis. **Result:** Among patients with CPET, 95 patients (46%) had VO2max<15 mL/kg/min. Compared to patients with higher VO2max, they had similar cardiopulmonary complication rates (32% vs. 29%, p=0.68) and 90 day mortality (9.5% vs. 6.2%, p=0.43). 172 patients had measured VE/V CO2. The incidence of cardiopulmonary complications in patients with VE/V CO2 slope >40 was 37% (19 of 51) vs. 27% (33 of 121) in those with lower slope values (p=0.19). However, 90-day mortality in patients with high VE/V CO2 slope (n=8) was 3-fold higher (16% vs. 5.0%) compared to those with lower (n=6) values (p=0.03). Cox regression analysis showed that higher VE/V CO2 values were significantly associated with poorer 2-year survival (HR 1.07, 95% CI 1.01-1.13, p=0.009) **Conclusion:** We found VE/V CO2 slope was associated with increased 90-day mortality and poorer 2-year survival in patients submitted to anatomical pulmonary resection for non-small

cell lung cancer. These findings may assist the multidisciplinary team in selecting the most appropriate radical treatment in high-risk patients.

Keywords: Cardiopulmoary exercise test, lung cancer, Surgery

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-45 THORACOSCOPIC STAPLER-BASED COMPLEX SEGMENTECTOMY ASSISTED BY VIRTUAL ASSISTED LUNG MAPPING

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Background: Anatomical segmentectomies play an important role for the patients with small ground-glass lung cancer and metastatic lung tumors. Virtual assisted lung mapping (VAL-MAP) assists to localize hardly palpable lung tumors and to define the resection lines. VAL-MAPhas been found to be useful in thoracoscopic segmentectomies, particularly complex segmentectomies. VAL-MAP is a novel preoperative bronchoscopic multi-spot dye-marking technique to provide "geometric information" to the lung surface, using three-dimensional virtual images.The multiple spots (tattooing) of VAL-MAP assists not only to localize hardly palpable lung tumors but to define appropriate resection lines in sublobar lung resections including wedge resections and segmentectomies. The purpose of the study is to evaluate the role of VAL-MAP in simple and complex thoracoscopic segmentectomy. **Method:** VAL-MAP was conducted before surgery as follows: the target bronchi were identified using radiology workstation; 1 ml of indigo carmine was injected through a catheter by bronchoscopy under fluoroscopy; another CT scan was taken to confirm marking locations. Segmentectomies were conducted thoracoscopically and intersegmental planes were made using staplers (Figure). Anatomical segmentectomies using VAL-MAP conducted were retrospectively analyzed (2014-2017). Simple segmentectomy was defined as a resection of anatomical single segment or combined segments. Other anatomical segmentectomies were defined as complex segmentectomy (Table). Successful resection rates, surgical margins, and post-operative course were compared between simple segmentectomy and complex segmentectomy. **Result:** Atotal of 43 patients were included in the study (42% women; median age 68 yr (48-83 yrs.). The median tumor size was 12 mm. The average number of markings via VAL-MAP was 4.2 (1-8) points. Post-VAL-MAP complications identified in CT included 5 pneumothorax, 3 airway bleeding, and 2 mediastinal emphysema, although none needed additional treatment. Simple segmentectomy was conducted in 18 patients, while complex segmentectomy was conducted in 25 patients. There was no significant difference in operation time (simple vs. complex; 233±100 vs. 266±8 min), length of chest tube drainage (2.3±0.33 vs. 2.5±0.25 days), or margin/tumor diameter ratio (2.10±0.28 vs. 1.89±0.23). Minor postoperative complicationswere found in 4 patients (2 collapse lung after removed chest tube; 2 pneumonia and inflammatory reaction). No pleurodesis was needed postoperatively.Final pathology included 24 lung cancer, 15 metastatic tumors, and 3 others. **Conclusion:** VAL-MAP-assisted stapler-based thoracoscopic segmentectomies were safely and effectively conducted even in complex ones. The bronchoscopic approach of VAL-MAP made the anatomical liberty available to surgeons. The "map" drawn with VAL-MAP not only helps to identify the tumor, but also helps to determine oncologically appropriate resection lines.

Keywords: Virtual assisted lung mapping, complex segmentectomy, thoracoscopic segmentectomy

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-46 A POPULATION-BASED VALIDATION STUDY OF THE PROPOSED 'R-FACTOR' CLASSIFICATION IN A LUNG CANCER-ENDEMIC REGION OF THE US.

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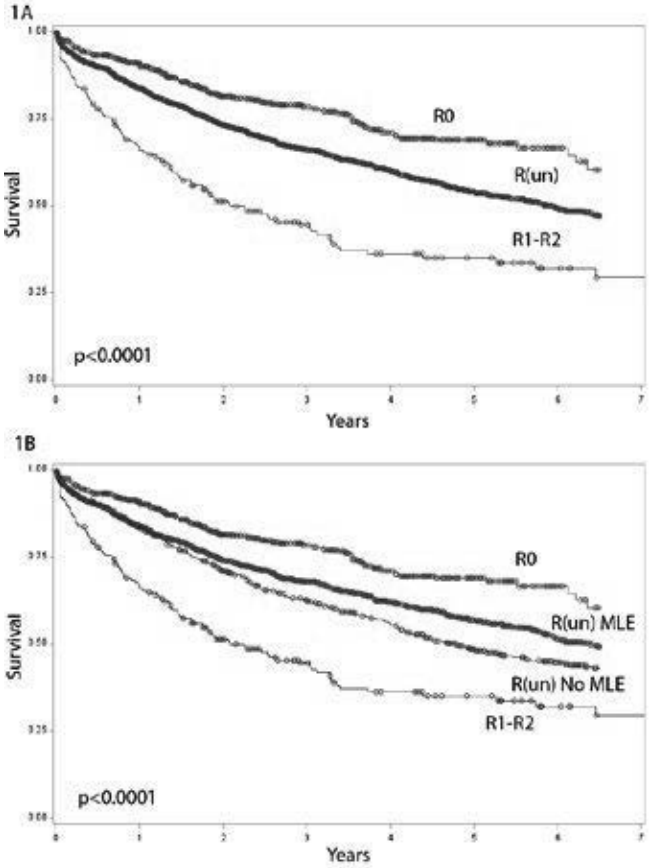
Background: The IASLC has proposed a definition of completeness of surgical resection beyond margin status. We sought to validate the proposed classification in a US cohort, and evaluated the impact of a lymph node (LN) specimen collection kit on resection status. **Method:** The population-based Mid-South Quality of Surgical Resection cohort includes >95% of lung cancer resections in 4 contiguous US Dartmouth Hospital Referral Regions from 2009-2018. Resections were classified as Complete (R0), Uncertain (R[un]), or Incomplete (R1-R2) based on the proposed classifications. We evaluated overall survival (OS) using the Kaplan-Meier method and proportional hazards models. Adjusted models included age, sex, histology, extent of resection, pTNM categories, and co-morbidities. A subset of resections used a LN specimen collection kit. **Result:** Of 3,099 resections, 18% were R0, 76% R(un), and 6% R1-R2. 5-year OS was 69%/54%/35% for R0/R(un)/R1-R2 (p<0.0001, Figure 1A). Compared to R0, the increased hazard of death for R(un)/R1-R2 was 1.6/3.0 overall, 1.5/2.3 in node negative patients, 1.7/3.1 in node positive patients, and 1.5/1.9 in fully adjusted models (all p<0.0001). Of 2,351 R(un) resections, the highest mediastinal LN positive increased the hazard of death 1.6 times (vs. negative, p=0.0008). However, 626 (27%) had no mediastinal LN examined (MLE). R(un) resections with 0 MLE had 1.2 times the hazard of death compared to R(un) with >1 MLE (p=0.0212, Figure 1B). Use of the LN kit intervention resulted in R0 in 40% of cases, compared to 6% without the kit (p<0.0001). Kit cases had improved OS across the entire cohort (p=0.0002), but when restricted to R0 patients, OS did not differ based on kit use (p=0.96).



Conclusion: The proposed 'R-factor' classifications are prognostic. R(un) rates were high, but significantly lower in cases where a LN collection kit was used. Further delineation of R(un) cases based on MLE should be considered.

P1.16-47 ADJUVANT TARGETED THERAPY FOLLOWING STANDARD ADJUVANT THERAPY FOR RESECTED NSCLC: AN INITIAL REPORT FROM ALCHEMIST (ALLIANCE A151216)

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Background: The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) was launched in 2014 across the National Clinical Trials Network (NCTN) of the National Cancer Institute (NCI). This trial platform aims to enroll up to 8300 patients with resected high-risk non-small cell lung cancer (NSCLC) to facilitate enrollment to adjuvant targeted therapy trials following completion of standard adjuvant therapy, and to collect biospecimens for clinical and investigational genomics. On 5/1/2016, the study was expanded to include squamous NSCLC and PDL1 testing to facilitate enrollment to a new immunotherapy study. **Method:** Eligible patients have completely resected NSCLC, stage IB (>4cm) to IIIA by AJCC 7. Eligibility window extends 75-285 days post-op depending upon receipt of adjuvant chemotherapy and/or radiation. Molecular testing of EGFR, ALK, PDL1 is performed centrally (depending on the histology and testing results) and results are returned to sites within 7-21 days. FFPE tissue and blood are collected by the NCI for genomic analysis. Appropriate patients may then enroll to one of three therapeutic trials studying single agent adjuvant targeted therapy (erlotinib NCT02193282, crizotinib NCT02201992, or nivolumab NCT02595944) versus observation. **Result:** As of March 19, 2018, 2945 patients have been enrolled from 575 sites within the US, with a median enrollment of 98/month (range: 71-133) in 2017. Central molecular testing was completed in 83%-92% of appropriate patients: EGFR L858R/19del was detected in 395 of 2468 patients (16.0%), ALK FISH was positive in 106 of 2458 patients (4.3%), and PDL1 IHC was >1% in 902 of 1464 patients (61.6%). Adequate tissue and blood for whole exome sequencing (WES) was collected on 1928 patients (65.5%), and enrollment plasma (added January 2017) has been collected on 885 patients (30.1%). Of 1960 patients deemed to be eligible for the adjuvant treatment trials with sufficient follow-up, 560 (28.6%) were enrolled; those enrolled were younger (p=0.01) and had higher N stage (<0.01) than those not enrolled. The primary reason for eligible patients not enrolling to treatment trials was lack of interest in further adjuvant therapy (53%). **Conclusion:** ALCHEMIST has achieved an enrollment of ~100 patients/month with resected high-risk NSCLC. This initial report demonstrates the feasibility of central molecular testing for enrollment to adjuvant targeted therapies. Efforts are ongoing to plan clinically-informed genomic analyses of tumor and plasma, as well as the planning of new treatment arms that leverage this ongoing trial platform. **Support:** U10CA180821, U10CA180882, U10CA180820, U10CA180868, U10CA180888; **ClinicalTrials.gov Identifier:** NCT02194738

Keywords: Adjuvant therapy, NSCLC, Genomics

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-48 THE IMPACT OF SEGMENTECTOMY VERSUS LOBECTOMY ON PULMONARY FUNCTION OF PATIENTS WITH NON-SMALL CELL LUNG CANCER: A META-ANALYSIS

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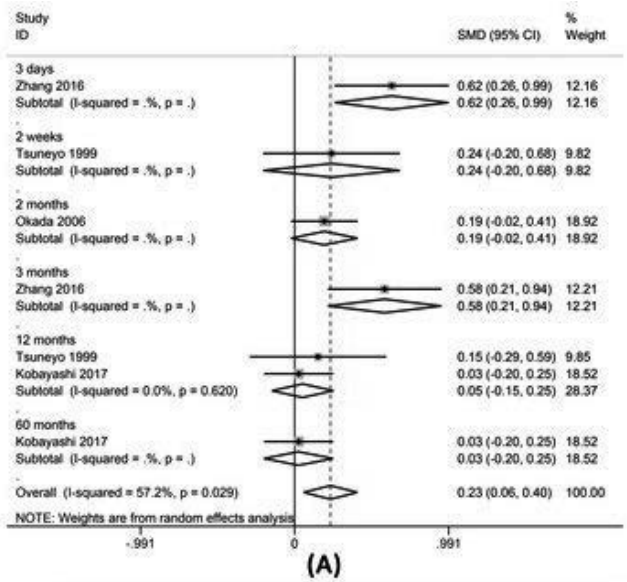
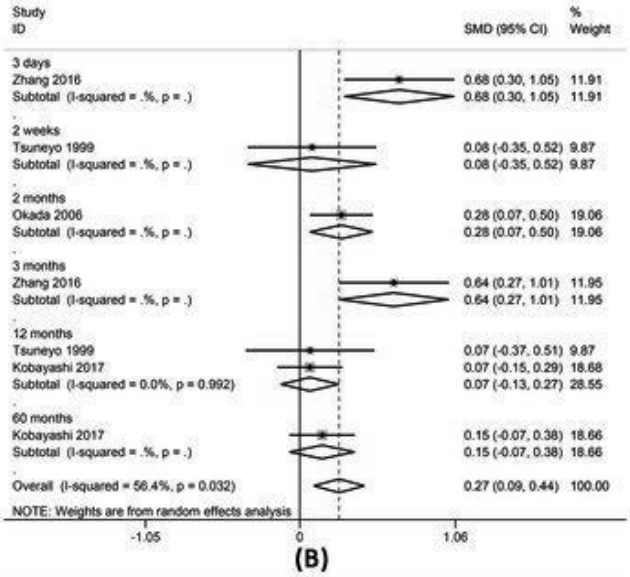
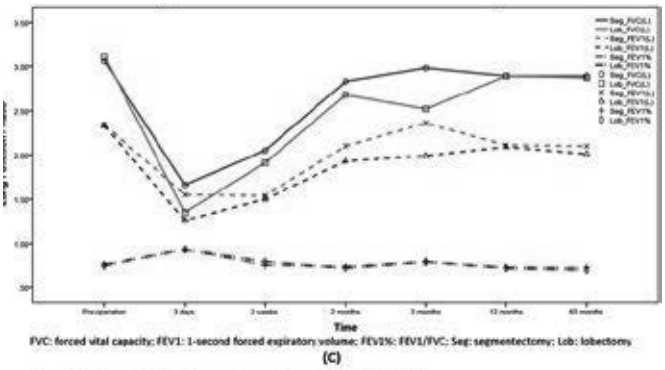
Background: Lobectomy (Lob) and lymph node dissection is considered as the standard surgical procedure for non-small cell lung cancer (NSCLC). Segmentectomy (Seg) has been recently regarded as an alternative in early peripheral NSCLC owing to its advantages of lung function reservation. Thus, we performed a meta-analysis with the aim of evaluating whether Seg offers a better lung functional advantage over Lob. **Method:** A comprehensive search of online databases was performed. Perioperative outcomes and lung functional index and were synthesized. The odds ratio (OR) or SMD and its 95% CI was calculated using a random effects model. Subgroup was conducted according to different time points. Single-arm meta-analysis was conducted for lung function at each visit time. Repeated-measures analysis of variance (ANOVA) was used to compare the lung function between at each visit. **Result:** A total of 5 eligible studies including 958 patients were recruited. There were no significant differences according to baseline characteristics before surgery between groups (Seg and Lob). Seg correlated with a greater postoperative preserved pulmonary function than Lob in FVC (SMD=0.23, p=0.009) (Figure A) and FEV1 (SMD=0.27, p=0.002) (Figure B), especially before 12 months. ANOVA showed there were no differences between two groups in FVC (p=0.647) and FEV1 (p=0.468) according to each visit time (Figure C). Seg group showed significantly less postoperative complications compared with the Lob. (OR=0.64, p=0.045) and the recurrence rate were same between groups (OR=0.89, p=0.623).







Conclusion: Seg offers a better lung functional preservation in short time and reduces postoperative complication compared with Lob. However, two groups showed no significant difference on lung function and tumor relapse according to long follow up.

Keywords: segmentectomy, lobectomy, non-small cell lung cancer(NSCLC)

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-49 TREATMENT OF NSCLC PATIENTS WITH CLINICAL N1 DISEASE: IS THERE AN ADVANTAGE TO NEOADJUVANT THERAPY?

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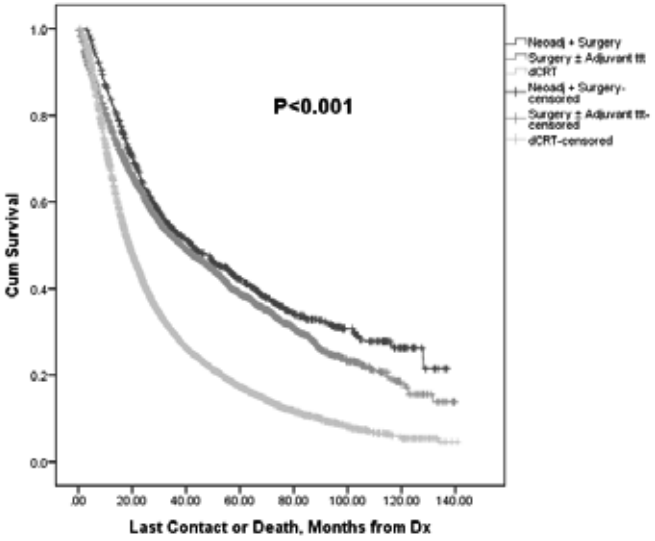
Background: Treatment options for clinical N1 patients with non-small cell lung cancer (NSCLC) include neoadjuvant therapy and surgery, surgery with adjuvant therapy, or definitive chemoradiation (dCRT). We sought to evaluate the rates of use of each strategy and associated outcomes in patients in the National Cancer Database (NCDB). **Method:** The NCDB (2004-2014) was reviewed for patients with clinical N1 NSCLC, excluding those with multiple primary tumors, unknown treatment modality/sequence, and clinical M1 disease. Overall survival (OS) of different treatment modalities was compared using log rank test in Kaplan Meier curves. Logistic and Cox regressions were performed to identify predictors of OS among cN1 cohorts respectively. **Result:** We identified 14,934 cN1 patients undergoing curative treatment. Median age was 67 (IQR 59-73) and median tumor size 4.5 cm (IQR 3-6.4). This included 1,040 patients (7%) undergoing neoadjuvant therapy followed by surgery, 4,398 patients (29.4%) undergoing surgery +/- adjuvant therapy, and 9,496 patients (63.6%) undergoing dCRT. Predictors of neoadjuvant therapy were age (OR=0.96,CI=0.95-0.96), white race (OR=1.54,CI=1.23-1.93), year of diagnosis (OR=0.92,CI=0.90-0.94), Charlson Comorbidity Index (CCI)<2 (OR=1.282,CI=1.004-1.637), adenocarcinoma (OR=1.30,CI=1.12-1.51), larger tumor size (OR=1.002,CI=1.001-1.003, and private insurance (OR=1.51, CI=1.29-1.77). Superior OS was achieved following neoadjuvant therapy and surgery (median-OS=42.1±3.4 months) compared to surgery ± adjuvant therapy (38.4±1.5 months, p=0.002). dCRT was associated with the worst survival (18.9± 0.30 months). By MVA, predictors of poor survival in the cohort were older age (HR=1.015,CI=1.012-1.018), male gender (HR=1.20,CI=1.13-1.26), lack of insurance (HR=1.26,CI=1.08-1.46), higher comorbidities (CCI=2, HR=1.29, CI=1.19-1.40), larger tumors (HR=1.002, CI=1.001-1.002), and the use of dCRT (HR=1.75,CI=1.58-1.95). **Conclusion:** Neoadjuvant therapy followed by surgery is associated with superior survival compared to upfront surgery +/- adjuvant therapy in this large cohort of patients. dCRT, although used most commonly in patients with cN1 disease, demonstrates the worst survival rates.



Keywords: Neoadjuvant treatment, National Cancer Database (NCDB), survival

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-50 THE ROLE OF ADJUVANT THERAPY FOR PATIENTS WITH EARLY STAGE LARGE CELL NEUROENDOCRINE LUNG CANCER: A NATIONAL ANALYSIS

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Background: Although large cell neuroendocrine lung cancer (LCNEC) generally has a worse prognosis than other non-small cell lung cancer histologies, data regarding the role of adjuvant therapy in completely resected stage I LCNEC are extremely limited and current guidelines do not routinely recommend adjuvant therapy. This U.S. National Cancer Data Base (NCDB) analysis was performed to improve the evidence guiding decision-making regarding postoperative therapy for early stage LCNEC. **Method:** Overall survival of patients with pathologic T1-2aN0 LCNEC who underwent resection in the NCDB from 2003 to 2015 was evaluated using Kaplan-Meier and multivariable Cox proportional hazard analysis. Patients who died within 30 days of surgery were excluded. These prospective data were acquired by certified tumor registrars, and include over 80% of cancer diagnoses annually in the U.S. **Result:** Of the 5,177 patients who met study criteria, adjuvant therapy was given to 31% of patients (n=1585): 20% received chemotherapy (n=1039), 8% chemoradiation (n=400), and 3% radiation (n=146). In stage IA LCNEC, adjuvant chemotherapy was associated with improved survival when compared to no adjuvant therapy in unadjusted analysis (five-year survival 55% vs. 53%; p=0.03) but not after multivariable adjustment (hazard ratio [HR] 0.81; 95% CI 0.64 to 1.02). Of note, adjuvant chemoradiation (HR 1.66; 95% CI 1.11 to 2.48) and adjuvant radiation (HR 1.55; 95% CI 1.06 to 2.25) were associated with worse survival when compared to no adjuvant therapy. In stage IB LCNEC, adjuvant chemotherapy was associated with improved survival when compared with no adjuvant therapy in both univariate (five-year survival 60% vs. 43%; p<0.0001; Figure) and multivariable (HR 0.65; 95% CI 0.48 to 0.88) analyses.

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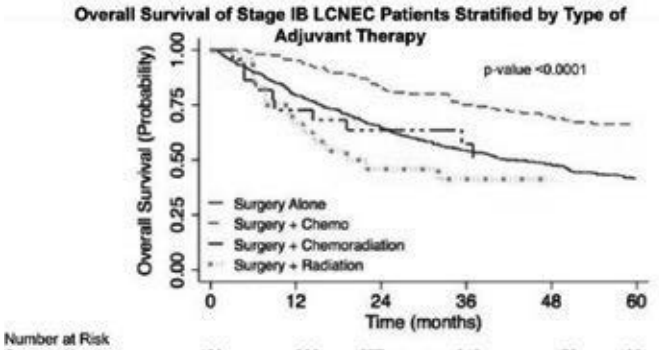

Conclusion: In this NCDB study of resected stage I LCNEC, adjuvant chemotherapy was associated with improved survival after resection of stage IB but not stage IA LCNEC.

Keywords: adjuvant chemotherapy, large cell neuroendocrine lung cancer, early stage lung cancer

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-51 PREOP NUTRITION-ENHANCED RECOVERY AFTER SURGERY PROTOCOL FOR THORACIC CANCER RESECTIONS DECREASES HOSPITAL DAYS AND CHARGES

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Background: Numerous studies over the last decade have documented that the preoperative nutritional status strongly influences perioperative outcomes. Based on published surgical studies, we instituted a preoperative enhanced nutritional support protocol for thoracic cancer resection patients and compared the results to a historical control cohort from the year immediately prior to starting this nutrition program. **Method:** Patients undergoing thoracic cancer resections from July 15, 2016 to July 14, 2017 underwent a preoperative nutritional-enhanced recovery after surgery protocol (N-ERAS) of daily probiotics, five days of an oral immunonutrition drink and a complex carbohydrate loading drink the night prior to surgery. Historical controls were from patients undergoing surgery the 12 months prior (Pre-N-ERAS), all operated on by the same surgical team. Non-parametric statistical tests were employed for this retrospective analysis. **Result:** Data from 234 patients were analyzed. For the Pre-N-ERAS group, there were 121 patients (48/73 men/women), mean age 67.5 (range 24-88), mean post-bronchodilator %FEV1 86.7±19.9 (range 41-126), mean serum albumin 4.3±0.3gm/dl (range 3.2-5.1) and mean Charlson Co-Morbidity Index 4.3±2.2 (range 0-11). For the N-ERAS group, there were 113 patients (50/63 men/women), mean age 67.5 (range 43-85), mean post-bronchodilator %FEV1 89.4±19.7 (range 43-146), mean serum albumin 4.3±0.3gm/dl (range 3.3-5.0) and mean Charlson Co-Morbidity Index 4.8±2.2 (range 1-11). There were no significant differences among the groups for demographics. For both groups, no mortalities, empyemas, wound infections or reoperations for any cause were reported. The N-ERAS nutrition protocol patient compliance was 100% with no toxicity. Compared to the Pre-N-ERAS patients, the N-ERAS group had significantly less time to return of bowel function (mean 1.30 days versus 1.11 days, p<0.001), shorter hospital stays (mean/median 4.57/4 days versus 3.63/3 days, p=0.001) and less total hospital mean charges/patient ($47,403 versus $42,979, p=0.037), respectively. This translated into approximately a 9.3% decrease ($4,424) in mean charges/patient using the N-ERAS protocol. Consequently, for the N-ERAS cohort, hospital charges were likely $499,912 lower than expected for the 113 patients. **Conclusion:** Use of this patient-compliant N-ERAS preoperative nutrition protocol in normally nourished thoracic cancer surgical patients is associated with accelerated bowel function recovery, decreased hospital stays and lower charges. While a prospective clinical trial is warranted, thoracic surgeons should consider using N-ERAS in their major surgical patients with an expectation of improved clinical results at a lower cost--an important consideration when exploring ways to decrease charges in the prospective payment environment.

Keywords: Cost of Care, Preoperative nutrition, Thoracic Surgery

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-52 LONG-TERM IMPACT OF POSTOPERATIVE COMPLICATIONS FOLLOWING LUNG RESECTION AMONG PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Postoperative complications following lung resection are fatal and common. The immediate effects of postoperative complications are clearly associated with poor prognosis; however, the long-term effects remain unclear. The aim of this study was to investigate the long-term effect of postoperative complications in patients with non-small cell lung cancer following lung resection. **Method:** This investigation was designed as a retrospective cohort study including 345 consecutive patients with non-small cell lung cancer who underwent lung resection as the curative surgery at a single institution between 2007 and 2016. Three patients who had surgery related deaths which is defined as the event within hospital stay or within 30days after surgery was excluded. Postoperative complications were graded according to the Clavien-Dindo classification. Postoperative complications included a grade of greater than and equal to 2. We devided two groups among patients with complications(n=109) and without complications (n=233), and evaluate the deta between two groups. Clinical characteristics, pathological features, and causes of death were analysed. Survival analysis was conducted by the Kaplan-Meier method. Prognostic factors were analysed by a Cox proportional hazard model. **Result:** Throughout the study, 253 patients (74.0%) survived and 89 died (26.0%). The median length of follow-up was 51.8 months. Postoperative complications were observed in 109 patients (31.9%). Operation time, smoking index (pack-year), the rate of COPD, and lymphatic invasion were significantly higher in patients with complications than those withtout complications (p=0.001, <0.001, <0.001 and 0.02, respectively). FEV1.0% was lower in the complications group (p <0.001). In comparison to an absence of complications, the presence of complications resulted in worse 5-year overall survival (68.3% vs. 79.5%; p=0.001), worse recurrence-free survival (48.4% vs. 71.0%; p<0.001), and worse cause-specific survival (84.4% vs. 90.5%; p=0.003). There are no significant differences between two groups in concerning non-cause-specific survival (81.0% vs. 94.7%; p=0.095). Patients with complications had higher rates of lung cancer death (15.6% vs. 9.0%; p=0.030). The 5-year overall survival in patients with pulmonary complications tended to be poorer than among those without them, although the difference was not significant (64.2% vs. 70.4%; p=0.072). The Cox proportional hazards model for OS adjusted for age, sex, pathological staging, Charlson comorbdity index, COPD, vascular invasion, lymphatic invasion, pleural invasion, CEA ≥5 ng/ml, and lobectomy showed that postoperative complications are associated with a poorer overall survival (hazard ratio 1.78; 95%CI=1.15–2.19; p =0.010). **Conclusion:** Our findings indicate that postoperative complications were associated with poor overall survival due to the increase in cause-specific deaths.

Keywords: non-small cell lung cancer, Prognosis, postoperative complications

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-53 COUNTY-LEVEL VARIATIONS AND CONTRIBUTING FACTORS IN RECEIPT OF SURGERY FOR EARLY-STAGE NON-SMALL CELL LUNG CANCER IN THE US

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Background: Previous studies have reported geographic variations in receipt of curative-intent surgery for early-stage non-small cell lung cancer (NSCLC) across states or regions in the United States. However, little is known about the extent of county-level variations in the receipt of care within and across states, and factors contributing to these variations. We examined county-level variations in receipt of curative-intent surgical treatment, and factors contributing to such variations, for patients with early-stage NSCLC in the United States. **Method:** Patients with stage I or II NSCLC diagnosed in 2007–2014 were identified from 40 states and the District of Colombia population-based cancer registries compiled by the North American Association of Central Cancer Registries. A total of 179,189 patients residing in 2,263 counties were included. Percentage of patients who underwent curative-intent surgery was calculated for each county with 20 or more cases. Adjusted means were generated using mixed effects model accounting for covariates that were significant in three sequential models (model 1: age, sex, race/ethnicity; model

2: race/ethnicity, tumor size, grade; model 3: race/ethnicity, percent below poverty level, urban/rural status, surgeon-to-population ratio). Surgeon-to-population ratio was calculated using the 2010 county-level data from the Area Health Resources Files, by dividing the total number of surgeons (general and thoracic surgeons) by the total population age 35 years and older in the county. **Result:** Receipt of curative-intent surgery for early-stage NSCLC during 2007-2014 by county ranged from 12.8% to 91.7% (sevenfold difference), with a median of 64.5% (interquartile range, 58.8%-71.2%). Higher proportion of non-Hispanic blacks, uninsured patients, and patients residing in high poverty census tracts and in low surgeon-to-population ratio counties were at the lowest quartile of county-level percentage in receipt of curative-intent surgery. In the adjusted means, poverty level, surgeon-to-population ratio, and urban/rural status were independent predictors of receipt of surgery by county. For example, there was a 12% significant difference in adjusted mean between patients residing in affluent and poor neighborhoods. **Conclusion:** Receipt of curative-intent surgery for early-stage NSCLC varied substantially across counties in the United States. Area-level socioeconomic status and surgeon availability were significantly associated with this variation, which may therefore be amenable to corrective intervention. Further studies are needed to identify and address gaps in access to surgical treatment of early-stage NSCLC.

Keywords: County-level, non-small cell lung cancer, Surgery

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-54 THE SIGNIFICANCE OF MULTIPLE LUNG CANCER OCCURRENCE IN SURGICALLY-TREATED CLINCAL STAGE I LUNG CANCER

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Background: Advancements in lung cancer early detection and treatment are leading to an increase in patients with diagnoses of multiple primary lung cancers or lung cancers with multiple pulmonary sites of involvement. While lobectomy is considered the standard for surgical treatment in early stage non-small cell lung cancer, the optimal treatment strategies in such cases are not well known. **Method:** From February 2012 to February 2017, 370 consecutive c-stage I non-small cell lung cancer patients were surgically treated with lobectomy or segmentectomy and systematic lymph node dissection. A retrospective review was conducted for cases with multiple lung cancers. Multiple lung cancers (MLC) were defined as multiple pulmonary nodules with no clear evidence of either lesion to be a metastasis from the other, and with no lymph node or distant metastases at presentation of the secondary lesion. Cases with multiple pulmonary nodules with ground glass features were also considered MLC if they met the above criteria. Clinical characteristics and outcomes were reviewed. **Result:** Sixty-five cases (17%) were considered (synchronous and/or metachronous) MLC. The secondary lesion occupied the opposite lung in 32 cases, the same lobe in 24 cases, and other lobes of the same lung in 17 cases. Multiple adenocarcinomas with ground glass features were frequently seen as synchronous lesions (33/40), and the majority (69%) of synchronous cases were found in the same lobe. MLC were resected in a single surgical procedure in 22 cases. A second procedure was given in 21, and a third in 2. The initial surgery was lobectomy in 53% of cases and segmentectomy in 47%. The second procedure was segmentectomy in 14 (67%) cases, partial resection in 6, and lobectomy in 1. In 12 cases, multiple sites of lung cancer were treated with initial surgery and a subsequent non-surgical procedure (SBRT, cryotherapy, etc.). Lung cancer recurrence following surgical resection for MLC occurred in 3 cases, two of which had lymph node involvement at time of surgery. Three-year survival following final surgery was 89.5% (median follow-up 1142 days) in all cases, and was 94.6% in cases with MLC. **Conclusion:** Multiple lung cancer occurrence is not rare among c-stage I lung cancer cases. Repeated lung-sparing resections seem feasible as part of their treatment. Aggressive local therapy may lead to prolonged survival.

Keywords: Clinical stage I non-small cell lung cancer, multiple lung cancer, Local treatment

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-55 SURGICAL TREATMENT FOR LUNG CANCER. SUBAORTIC (PARA-AORTIC) LYMPH NODES INVOLVEMENT - N1 OR N2 DISEASE?

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Background: In patients with cN2 disease surgical treatment alone is not recommended because it often indicates systemic disease. Qualification to undergo a surgery patients with clinical manifestation of subaortic (#5)/para-aortic (#6) nodes malignant involvement remains controversial. The aim of this study is to compare survivals of patients with single station metastases to #5(#6) lymph nodes, patients with interlobar (#11) and lobar (#12) nodes involvement (pN1) and patients with right lower paratracheal (#4R) and subcarinal (#7) nodes involvement (pN2) after received lung resection. **Method:** Material was collected rectospectively from an online-survey-based database of the Polish Lung Cancer Group and included patients who underwent a surgical treatment due to lung cancer at multi-institution in Poland between 2007 and 2017. The 8th Edition of the Staging Classification System (TNM, 2017) was used to determine staging. **Result:** There were 34 870 patients (35,52% females and 64,48% males) who received surgical treatment for lung cancer. 27 321 (78,35%) underwent lobectomy, 1 063 (3,04%) segmentectomy, 4 658 (13,35%) pneumonectomy, 1 768 (5,07%) wedge resection. Histologic types included: non-small cell lung cancer (n= 475), adenocarcinoma (n=13 515), squamous cell carcinoma (n=14 273), large cell carcinoma (2 127), carcinoid (n=1 428) and others (n=2 934). Stage IA1 disease presented 683 (1,97%) patients, IA2 - 4442 (12,79%), IA3 - 3674 (10,58%), IB - 7150 (20,59%). Stage IIA disease presented 2493 (7,18%) patients, IIB - 7442 (21,43%). 6804 (19,59%) patients were in stage IIIA disease, 1529 (4,4%) in IIIB and 475 (1,37%) in IVA, 12 (0,03%) in IVB disease. The majority of patients were diagnosed with N0 disease (n: 24388, 70,23%). N1 disease was reported in 5913 (17,03%) cases, N2 disease in 4 412 (12,71%). Among patients with N1 disease there were 3543 cases with confirmed metastases only in #11 or #12 nodes. 3-, 5-, 7- and over 7-year survivals in this group were 70,03%, 15,33%, 8,41%, 6,24%. Among patients with N2 disease there were 1202 cases with exclusive involvement of #4R or #7 nodes. 3-, 5-, 7- and over 7-year survivals in this group were 73,21%, 14,14%, 7,74%, 4,91%. Malignant involvement of #5 or #6 nodes were reported in 1047 cases. 3-, 5-, 7- and over 7-year survivals here were 75,17%, 14,04%, 6,59%, 4,2%. **Conclusion:** According to the study there is no significant difference in survival of patients with #5(6) nodes invasion comparing to those with N2 and N1 disease. Controversy followed from classification #5(6) nodes as N2 remains unsettled.

Keywords: lung cancer, subaortic lymph nodes, surgery

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-56 PROGNOSTIC ABILITY OF NEW T1 DESCRIPTORS IN THE TNM CLASSIFICATION OF SURGICALLY TREATED NON-SMALL CELL LUNG CANCER

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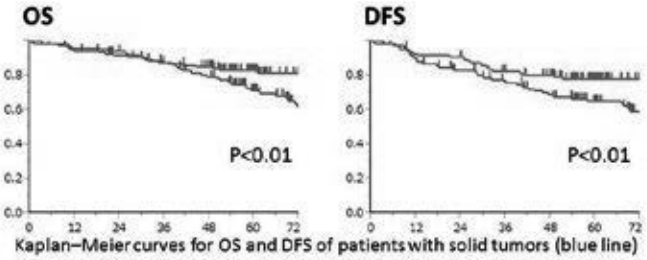
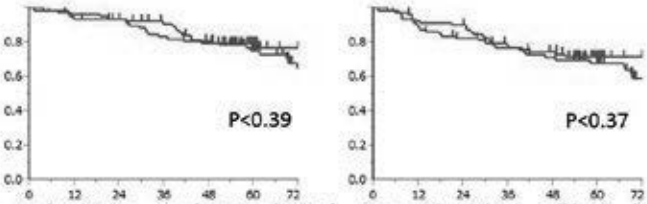
Background: In the tumor, node, and metastasis (TNM) classification (8th edition) of non-small cell lung cancer (NSCLC), T (tumor size) is determined solely according to the size of the solid component determined using computed tomography (CT). However, it is unclear if tumors of equal size but with differing solid and part-solid components should be similarly treated. Here we assessed the prognostic significance of the newly proposed T1 descriptors with respect to the size of the solid component. **Method:** We analyzed overall survival (OS) and disease-free survival (DFS) between groups of patients (n = 255) with solid or part-solid tumors. Propensity score matching (PSM) was added as an exploratory analysis of survival among patients with solid tumors and part-solid tumors to balance the size of the solid. The new staging system was used for classification and comparison of survival. **Result:**

(See next page)



Kaplan–Meier curves for OS and DFS of patients with solid tumors (blue line) and those with part-solid tumors (red line).



Kaplan–Meier curves for OS and DFS of patients with solid tumors (blue line) and those with part-solid tumors (red line) according to propensity score matching cohort.

Chest CT detected 7 non-solid tumors, 123 part-solid tumors and 125 solid tumors. All patients underwent pulmonary lobectomy. The 5-year OS and DFS rates differed significantly between the solid tumor (OS, 71.2%; DFS, 65.4%) and part-solid tumor (OS, 83.2%; DFS, 78.2%) groups. However, among 81 PSM pairs, their 5-year survival rates did not significantly differ as follows: 5-year OS, solid tumor group = 75.1% vs part-solid group = 79.6% (P=0.39); and 5-year DFS, solid tumor group = 68.2% vs part-solid group = 71.9% (P=0.37). Using the 8th TNM edition, 5-year OS rates were patients diagnosed with cIA1 disease: 88.0%; cIA2: 79.4%; and cIA3: 67.6%. **Conclusion:** PSM did not detect a significant difference in survival between the groups with solid tumors and those with part-solid tumors when matched according to the size of the solid component. The new T descriptors included in the 8th edition of the TNM provide a detailed classification of patients with NSCLC ≤3 cm in diameter.

Keywords: TNM staging, Surgical resection, non-small cell lung

cancerP1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-57 OUTCOMES OF PULMONARY RESECTION IN ELDERLY NON-SMALL CELL LUNG CANCER PATIENT

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Background: Because of increasing in life span and more than third-fourth of lung cancer patients being age > 60-65 years old, appropriate treatment of old lung cancer patients has become an important issue. The aim of this study is to evaluate the short and long-term surgical outcomes in elderly patients, and to identify prognostic factors of overall mortality. **Method:** Medical records of patients with non-small cell lung cancer (NSCLC) who underwent pulmonary resection at Chiang Mai University Hospital from January 2002 through December 2016 were retrospectively reviewed. Patients were divided into two groups; age less than 70 years (non-elderly group) and 70 years or more (elderly group). Primary outcome was major post-operative complications and in-hospital death; secondary outcome was long-term survival. Logistic regression and cox proportional hazard model were used to analyze data. **Result:** This study included 583 patients; 167 in elderly group, and 416 in non-elderly group. Patients in elderly group were more likely to have government insurance, be active smoker, and have a diagnosis of COPD, an abnormal ECG, to undergo a sublobar resection, lymph node sampling, and no chemotherapy treatment than those in the non-elderly group. There were no differences in term of in-hospital mortality, composite post-operative complications, and overall mortality. At multivariable analysis, the composite post-operative complications in the elderly group was not statistically different from the non-elderly group (Adjusted odd ratios = 0.52, 95% CI=0.21-1.28), however the elderly group was more likely to die (HR_{adj})=2.44, 95%CI=1.26-4.74). Adverse prognostic factors for overall mortality in elderly patients were a poorly differentiated tumor (HR_{adj}=3.53, 95%CI=1.45-8.61) and the presence with perineural invasion (HR_{adj}=3.95, 95%CI=1.14-13.77) Table 1 prognostic factors for overall mortality of elderly NSCLC patients after pulmonary resection

Variables	Hazard Ratio	95% CI	p-value
Male vs Female	1.43	0.62-3.26	0.401
Smoking amount			
≥20 pack-year	0.91	0.45-1.82	0.783
Stage of cancer			
Stage I	1.00	Reference	
Stage II	0.76	0.36-1.57	0.452
Stage III	2.18	0.92-5.16	0.077
Stage IV	1.70	0.53-5.46	0.373
Grading of cell differentiation			
Well	1.00	Reference	
Moderately	0.80	0.39-1.67	0.558
Poorly	3.53	1.45-8.61	0.006
Undifferentiated	1.72	0.41-7.31	0.462
Intratumoral lymphatic invasion	2.73	0.99-7.52	0.052
Intratumoral vascular invasion	1.76	0.91-3.39	0.092
Perineural invasion	3.95	1.14-13.77	0.031
SLND versus SLNS	0.51	0.24-1.10	0.084
Chemotherapy			
No chemotherapy	1.00	Reference	
Adjuvant or induction therapy	0.69	0.33-1.46	0.330
1st-line treatment	0.76	0.15-3.80	0.734
Sublobar resection versus lobectomy	1.78	0.65-4.90	0.261

Conclusion: Surgery in elderly NSCLC is a safe procedure. Patients presenting with perineural invasion and poorly differentiated tumor should be further considered for possible adjuvant treatment.

Keywords: Postoperative Morbidity, lung resection, old patient

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-58 HOSPITAL LUNG SURGERY VOLUME AND PATIENT OUTCOMES IN VICTORIA

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Background: Surgical resection remains the primary curative option for early stage non-small cell lung cancer (NSCLC) with lobectomies considered the gold standard due to a reduction in local recurrence and improved overall survival. There has been growing evidence of an association between patient outcomes and the number of cancer surgeries performed at a hospital since the seminal paper by Luft *et al* in 1979. To our knowledge, there are no Australian data on hospital cancer surgery volumes and patient outcomes by procedure, and few data worldwide on specific lung surgery procedures and outcomes. We evaluated the relationship between hospital NSCLC surgery volume and patient outcomes in Victoria. **Method:** Victorians with a primary diagnosis of NSCLC between 2008 and 2014 were identified in the Victorian Cancer Registry (n=15,469), 3,420 (22%) of whom had surgery. Primary outcome was death within 90 days of surgery and secondary outcomes were overall survival, use of postoperative ventilation, ≥24hours spent in ICU and length of stay >17days. Hospital volume was measured as the average number of lung surgeries performed per year, with quartiles Q1: 1-17, Q2: 18-34, Q3: 35-58 and Q4: 59+. **Result:** 57% (1,941/3,420) lung cancer patients underwent lobectomy, 38% (1,299/3,420) sub-lobar resection and 5% (180/3,420) pneumonectomy. The overall 90-day mortality after lung surgery was 3.5%, and was 2.6% for patients undergoing lobectomy compared with 4.5% for those undergoing sub-lobar resection. There was no difference in 90-day mortality between low- and high-volume centres

regardless of procedure. Patients operated in lower volume centres had more admissions to ICU ≥24hours (Q1. 55% vs. Q4. 11%, p-trend <0.001). Median overall survival was 6.2 years, 5.4 years and 5.8 years for lobectomy, sub-lobar resection and pneumonectomy, respectively. The distribution of ASA scores differed between patients attending public and private hospitals. A higher proportion of patients attending private hospitals (19%) had an ASA score of 4 compared with patients attending a public hospital (9%). **Conclusion:** We observed no evidence of survival differences between lung cancer patients attending low- and high-volume hospitals for surgery, regardless of surgical procedure. Median overall survival in Victorian is substantially better compared to interstate and international data. Of interest, a higher proportion of patients had an ICU admission ≥24hours in lower volume centres. We also observed a higher proportion of patients with an ASA score of 4 in private hospitals compared to public hospitals; the reasons for this are unclear and warrant further investigation.

Keywords: NSCLC, Surgery, volume

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-59 A PHASE II STUDY OF ADJUVANT CHEMOTHERAPY WITH TEGAFUR-URACIL FOR VESSEL INVASION POSITIVE STAGE IA NON-SMALL CELL LUNG CANCER (LOGIK0602)

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Background: Vessel invasion, which includes vascular or lymphatic invasions, is a representative prognostic factor in lung cancer therapy. Even in the patients with resected stage IA non-small cell lung cancer (NSCLC), vessel invasion is a significant poor prognostic factor. The pathological analysis of 322 cases of resected stage IA NSCLC in Oita Prefectural Hospital revealed that the 5-yr overall survival rate was 71.8% in the vessel invasion-positive group and significantly worse than the 89.6% in the vessel invasion-negative group. Interestingly, the 5-yr overall survival rate of the oral tegafur-uracil adjuvant chemotherapy group was 93.3% and significantly better than the 66.6% of the untreated group. Tegafur-uracil is known to affect vascular endothelial growth factor overexpressing tumours. Therefore, to estimate the positive effect of adjuvant tegafur-uracil in patients with vessel invasion-positive stage IA NSCLC, we conducted a multi-center single-arm phase II study (LOGIK0602). **Method:** The patients with completely resected vessel invasion-positive stage IA NSCLC were registered at the Lung Oncology Group in Kyushu (LOGIK). Vessel invasion was diagnosed by two of the three pathologists. Adjuvant chemotherapy consisted of 2 years of oral tegafur-uracil at 250 mg/m^2/day. Fifty-five patients from 7 institutions were enrolled from June 2007 to September 2012. The primary endpoint was the 5-yr overall survival rate. Secondary endpoints were the rate of accomplishment of scheduled adjuvant chemotherapy, incidence and grade of adverse reactions, 3-yr overall and relapse-free survival rates, and 5-yr relapse-free survival rate. **Result:** Among the 52 eligible patients, 16 (30.8%) discontinued tegafur-uracil administration and 36 (69.2%) completed the treatment course. The observation period was calculated as 562 to 3107 days and median observation period as 1947 days using the reverse Kaplan-Meier method. There were 39 male and 13 female patients. The 3-yr and 5-yr overall survival rates were 96.2% and 94.2% respectively, which were obviously better than the historical data of 28% to 78.7% in 8 reports. The 3-yr and 5-yr relapse-free survival rates were 92.3% and 88.5%, respectively. Eighteen adverse reactions were observed including 4 cases of grade 3 hepatic function disorder (7.7%) and 5 cases of grade 2 anorexia (9.6%). No grade 4 adverse effect was encountered. Five recurrences were observed including 1 distant metastasis (adrenal) and 4 local recurrences (lung: 2, lymph node: 2). **Conclusion:** A 2-year course of oral tegafur-uracil administration is feasible and might have a significant benefit in the adjuvant treatment of vessel invasion-positive stage IA NSCLC.

Keywords: Vessel invasion, tegafur-uracil, adjuvant chemotherapy

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-60 A HIGH RISK OF RECURRENCE AFTER THE RESECTION OF LOWER LOBE ADENOCARCINOMA

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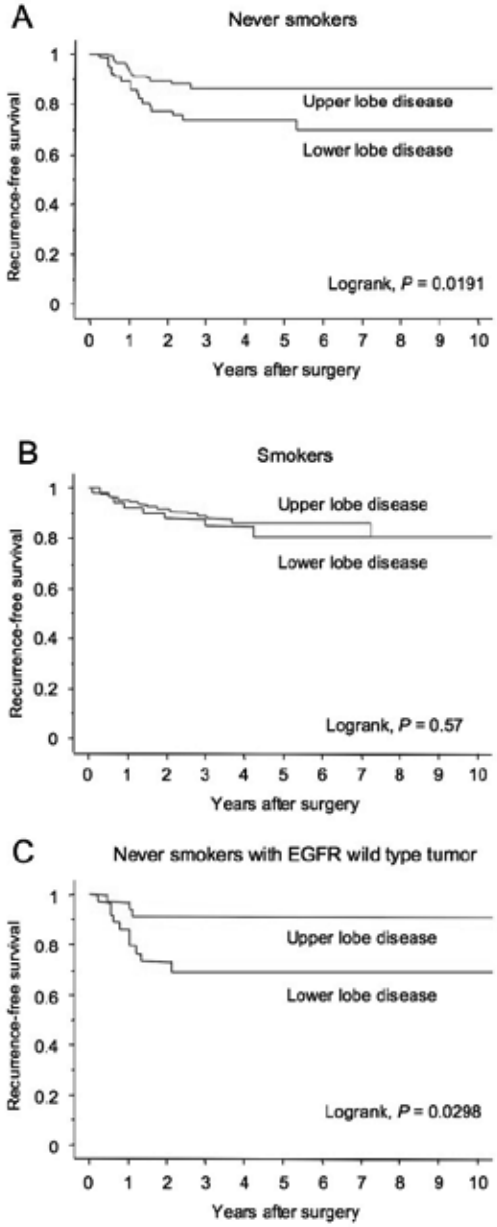
Background: According to previous reports, non-small cell lung cancers arising in the lower lobe are associated with a worse prognosis than those arising in the upper lobe; however, the reason remains to be elucidated. Thus, we attempted to identify high-risk population in patients with lower lobe disease, that may substantially cause poor prognosis of lower lobe disease. **Method:** We retrospectively reviewed a consecutive series of 400 patients with completely resected lung adenocarcinoma who were treated between January 2006 and December 2015. All patients underwent major lung resection and lymph node dissection. The clinicopathological factors that were investigated included the solid component size, the pathological subtype (pre-invasive, minimally invasive/invasive), the epidermal growth factor receptor (EGFR) mutation status, and some other characteristics (TNM 8th edition). **Result:**



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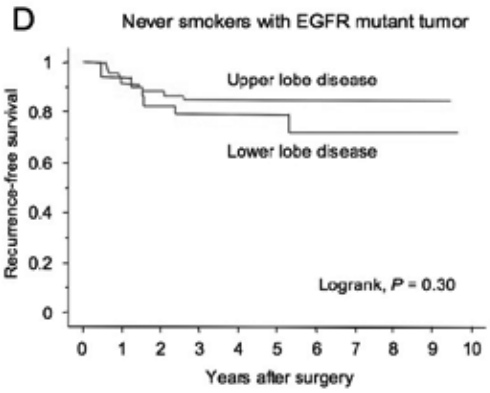

The proportion of never-smokers among patients with lower lobe disease was significantly higher than that among those with upper lobe disease. According to a multivariate proportional hazards analysis, primary site (upper/lower) was an independent predictor of early recurrence, along with the solid component size, pleural lavage cytology results, pathological pleural invasion, and pathological lymph node metastasis. However, although lower lobe disease was associated with early recurrence in never smokers (Fig 1A), it was not in smokers (Fig 1B). Furthermore, although lower lobe disease was associated with early recurrence in never smokers with EGFR wild-type tumors (Fig 1C), it was not in never smokers with EGFR mutant tumors (Fig 1D). EGFR wild-type tumors were more frequently detected in patients with lower lobe disease than in those with upper lobe disease when the analysis was restricted to never smokers. **Conclusion:** Patients with lower lobe cancer, particularly those without a smoking history or those with EGFR wild-type tumors, showed a higher risk of recurrence than their counterparts with upper lobe disease. Further studies that include the molecular profiling of such aggressive lesions, are warranted.

Keywords: prognostic factor, Adenocarcinoma

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-61 INTERMITTENT CHEST TUBE CLAMPING SHORTENS CHEST TUBE DURATION AFTER LUNG CANCER SURGERY: AN INTERIM ANALYSIS OF RANDOMIZED CLINICAL TRIAL

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Background: Postoperative pleural drainage markedly influences the length of hospital stay and the financial costs of medical care. Our previous retrospective study proved the safety and effectiveness of chest tube clamping in the term of shortening chest tube duration. This study aims to determine if intermittent chest tube clamping could decrease chest tube duration and total drainage volume after lung cancer surgery in randomized clinical trial. This trial is registered with ClinicalTrials.gov (NCT03379350). **Method:** All the patients were managed with gravity drainage (water seal only, without suction) during the first 12–24 h (depending on the time of surgery completion) after surgery. Once a radiograph confirmed re-expansion of the lung on the morning of the POD1 and no air leak was detected, patients were randomly assigned to intermittent chest tube clamping as study arm or traditional chest tube management as control arm. Patients in control arm were unchangeably managed with gravity drainage. In clamping arm, the chest tube would be clamped, and the nurses would check the patient every 6 h. If the patient had no problems with compliance, the clamp was removed for 30 minutes in the morning to record the drainage volume every 24 h. The criterion for chest tube removal was drainage volume <250 mL in 24 h. **Result:** Seven-two consecutive patients with operable lung cancer treated using lobectomy were randomized, all of them were eligible and evaluable. Thirty-seven and 35 patients were randomly assigned to clamping arm and control arm, respectively. There were no significant differences between two groups in terms of demographics, such of age, gender and the percentage of neoadjuvant treatment. Analyses were performed to compare drainage duration between two groups. Chest tube drainage duration was significantly shorter in clamping group than in control group (2.3±0.5 days vs. 2.7±0.9 days, p = 0.011). Total drainage volume was significantly less in clamping group than in control group (411.0±183.1 ml vs. 553.7±333.6 ml, p = 0.030). Only one patient in clamping group underwent thoracocentesis after chest tube removal due to chylothorax, which was probably caused by excess high-fat diet. No pyrexia relevant to chest tube clamping occurred. There was some degree of improvement on plasma albumin declination at discharge in clamping group over control group (7.5±2.5 g/L vs. 8.6±3.6 g/L, p = 0.119), but without a significant statistical difference. **Conclusion:** Intermittent postoperative chest tube clamping decreases chest tube duration and total drainage volume while maintaining patient safety. Further investigation is warranted.

Keywords: lung cancer surgery, chest tube clamping, chest tube duration

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.16-62 A NOMOGRAM TO PREDICT DISEASE-FREE SURVIVAL AFTER CURATIVE RESECTION OF NON-SMALL CELL LUNG CANCER

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Background: The aim of this study was to find clinicopathologic variables associated with disease-free survival (DSF) and develop a prognostic nomogram for patients with curative resected non-small-cell lung cancer (NSCLC) and compare the value of the nomogram to the seventh AJCC TNM classification. **Method:** A nomogram to predict DFS following surgical resection of NSCLC was constructed using a single-institutional cohort of 805 patients who underwent curative resection of lung adenocarcinoma in the Cancer Hospital of the Chinese Academy of Medical Sciences (Beijing, China) between January 2003 and December 2013. For nomogram construction and validation, we randomly assigned two thirds of the patients to the training cohort (n=605) and one third to the validation cohort (n=260). The median age of training cohort was 57 years (range, 25-76) and the proportion of male and female patients was 64.8% vs. 35.2%. Half of the patients (49.8%) presented with early-stage disease and 85.3% patients received adjuvant chemotherapy alone. The predictive discriminative and calibration were measured by concordance index (C-index), risk group stratification and calibration plot. **Result:** The median disease-free survival for the total cohort was 23.2 months (95% CI, 21.3-26.4 months). The 1-, 3- and 5-year disease-free survival was 71.3%, 39.5% and 32.3%, respectively. The nomogram included 8 important variables based on a Cox proportional hazards regression modeling of the training cohort: histology, differentiation, nodal status, AJCC T category, primary tumor location, type of surgical resection, adjuvant radiotherapy and regimen. Each patient with a higher score had a worse prognosis. Prognostic discrimination was performed by dividing the predicted nomogram score into quartiles that were then used to plot Kaplan-Meier curves. The nomogram was able to stratify patients into 4 distinct incremental 3-year prognostic groups (quartile 1, 73.0%; quartile 2, 49.6%; quartile 3, 30.6%; and quartile 4, 9.3% [P <0.001]). Both in the training and validation cohort, the C-index of the nomogram for DFS prediction was superior to the TNM category prediction (training cohort, 0.694 vs. 0.640; P<0.01 and validation cohort, 0.662 vs. 0.602; P<0.01). The 200-sample bootstrapped calibration curves for probability of 3- and 5-year disease-free survival (PFS) showed optimal agreement between nomogram prediction and actual observation. **Conclusion:** This novel nomogram provides an individualized prediction of DFS in NSCLC patients after radical surgery and may assist the clinical treatment decision making and clinical trials designing.

Keywords: Disease-free survival, Non-small-cell lung cancer, Nomogram

P1.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P1.16-63 THE VALUE OF ADJUVANT CHEMOTHERAPY IN PATIENTS WITH RESECTED STAGE IB SOLID PREDOMINANT AND SOLID NON-PREDOMINANT LUNG ADENOCARCINOMA

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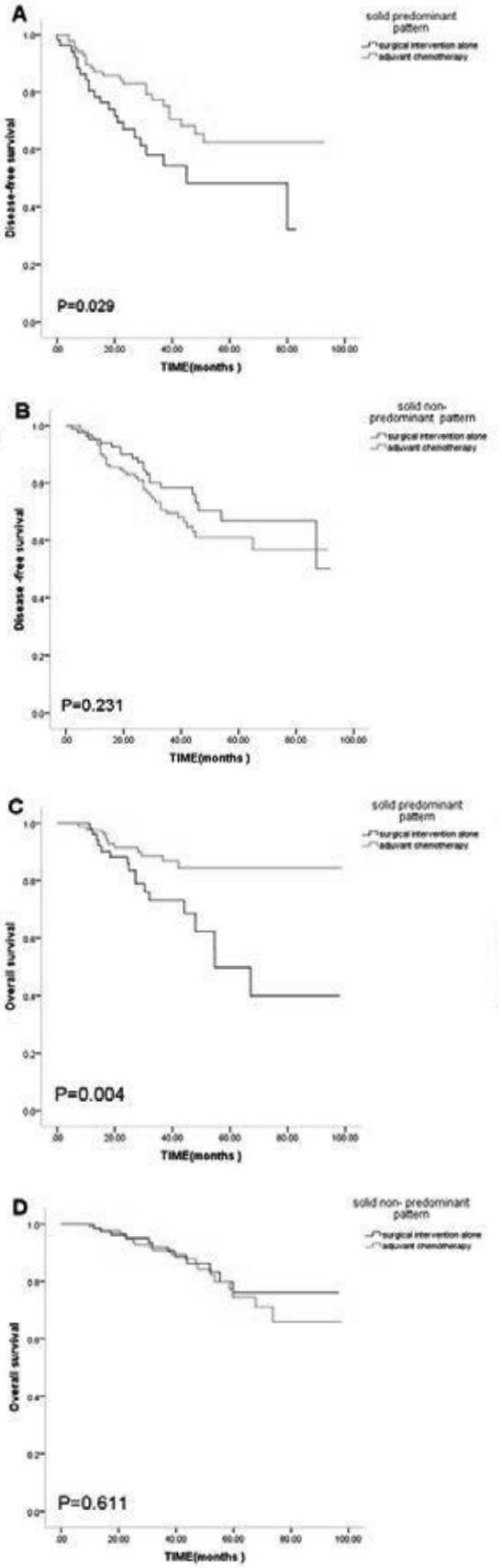
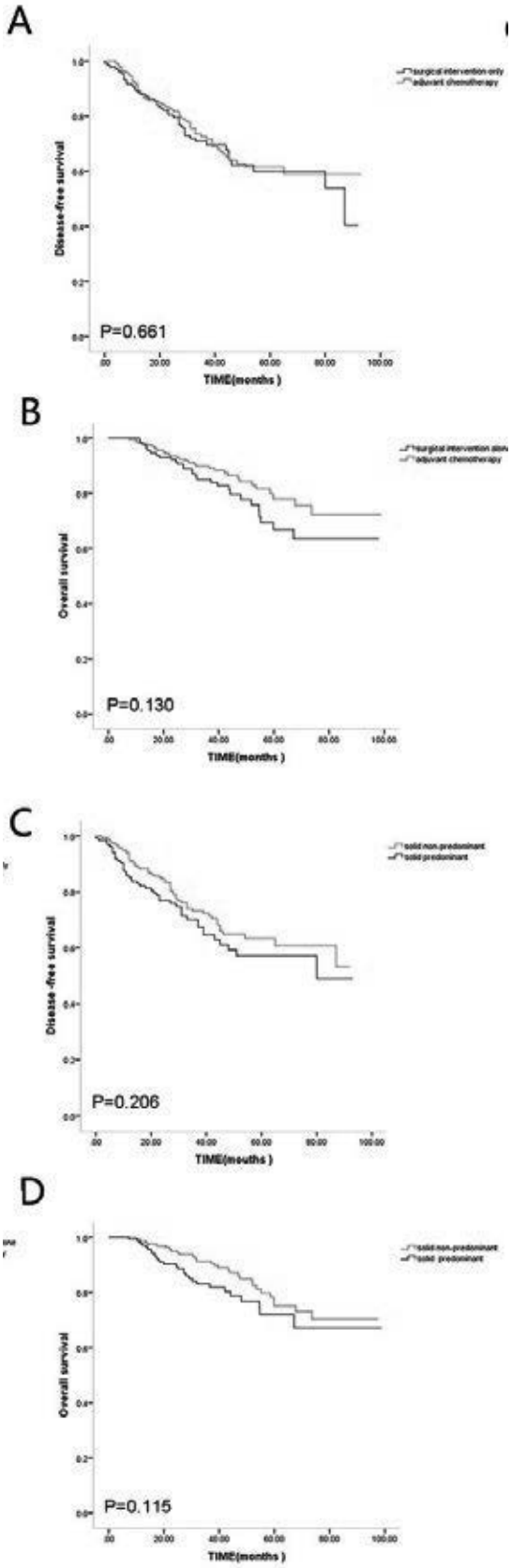
Background: The adjuvant chemotherapy(ACT) of stage IB lung adenocarcinoma remain controversial. We are intended to explore the benefits adjuvant chemotherapy made on patients in IB with solid ingredients. **Method:** A number of 334 completely resected patients with lung adenocarcinoma in stage IB from 2006 to 2015 were reviewed. All the pathological slides were evaluated with solid ingredients composed. **Result:** Our data showed that although disease-free survival (DFS)

(p=0.661) and overall survival (OS)(p=0.130) were not significantly different in solid growth pattern with or without ACT, patients with solid predominant patterns tend to have longer DFS [hazard ratio (HR) 0.403, p=0.021)]and OS (HR 0.286, p=0.009) with ACT. In patients with solid non-predominant patterns, receiving ACT had no influence in DFS(p=0.231) and OS (p=0.611).





Conclusion: The solid predominant pattern in postoperative patients of stage IB could benefit from adjuvant, and solid non-predominant pattern couldn't.

Keywords: lung cancer, adjuvant chemotherapy, solid predominant

P1.16-64 THE HISTOLOGICAL PREDOMINANT PATTERN COULD PREDICT SITE OF RECURRENCE AND METASTASIS IN SURGICALLY TREATED STAGE I ADENOCARCINOMA OF THE LUNG

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Background: Pattern-based subtyping of adenocarcinoma of the lung is currently recommended due to prognostic implications. We aimed to evaluate whether predominant pattern subtype in surgically treated stage I adenocarcinoma of the lung can predict first site of recurrence or metastasis. **Method:** We retrospectively reviewed clinical information, radiological findings, PET/CT-records, and pathological features (classified by IASLC/ATS/ERS subtyping criteria) of 906 Stage-I adenocarcinoma of the lung, who underwent surgery in 7 Centers. Patients were classified by histologic grade according to the IASLC/ATS/ERS classification as follow: intermediate grade (Invasive Lepidic, Acinar, Papillary) *vs.* high grade (Micropapillary, Solid) *vs.* NOS. The date of recurrence or metastases was defined as the first radiographic evidence of cancer relapse upon imaging or pathological tumour evidence from a biopsy. Univariate and multivariate logistic analysis were used to identify predictors of first site of recurrence or metastasis. **Result:** A total of 248 (27%) patients developed recurrence or distant metastasis. The most commonly observed first location of recurrence was ipsilateral thorax (133 cases, 44%), followed by brain (27, 11%), contralateral lung (24, 10%), bones (11, 4%), liver and adrenal gland (10, 4%). Forty-three patients (17%) presented recurrence or metastasis in multiple sites simultaneously at the time of diagnosis. At multivariate analysis, patients with intermediate-grade histology developed intra-thoracic recurrence more frequently compared to the remainder of the cohort (odds ratio (OR) 1.85, 95% confidence interval (CI): 1.1– 3.18, P=0.038). Patients with high-grade histology developed contralateral lung metastasis (OR 2.1, 95%CI 1.1-4.2, P= 0.044) and brain metastasis (OR 2.5, 95%CI 1.3-5.1, P<0.01) more frequently compared to the low-grade ones. **Conclusion:** Predominant pattern subtype seems to predict site-specific recurrence and metastasis in surgically treated Stage I adenocarcinoma of the lung.

Keywords: non-small cell lung cancer, Surgery, histology

P1.17-01 ROBUSTNESS OF AN IMAGE-BASED DATA MINING APPROACH IN LUNG CANCER PATIENTS

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Background: Image-based data mining (IBDM) enables exploring the correlation of dose distributions and outcomes in large cohorts of patients without the requirement of additional contouring. IBDM has recently identified the dose to the base of the heart as an important predictor for overall survival (OS) in lung cancer patients receiving radiotherapy [McWilliam et al EJC 2017]. IBDM relies on non-rigid registration to set inter-patient dosimetric data into a common reference anatomy or reference patient. Here, we investigated the uncertainties associated with the choice of reference patient, and their influence on the correlation between incidental dose to the base of the heart and OS. **Method:** In previous work, 1101 NSCLC patients (55Gy / 20 fractions) were randomly selected, and their planning CT images non-rigidly registered to a reference patient CT scan using NiftyReg (http://cmictig.cs.ucl.ac.uk/wiki/) as part of IBDM process. In this work, 5 additional patients with small cell lung cancer (i.e. without a large tumour burden) were used as "reference patients" and the IBDM analysis in the whole cohort was repeated for each reference patient. Permutation testing with 100 iterations was applied to assess statistical significance. **Result:** Figure 1 shows the regions of highly significant correlation between dose and OS for each reference patient. In spite of large variations in anatomy between the reference patients, each analysis identified similar anatomical regions as significantly associated with OS (t>5). Moreover, permutation testing was consistent with the original findings.

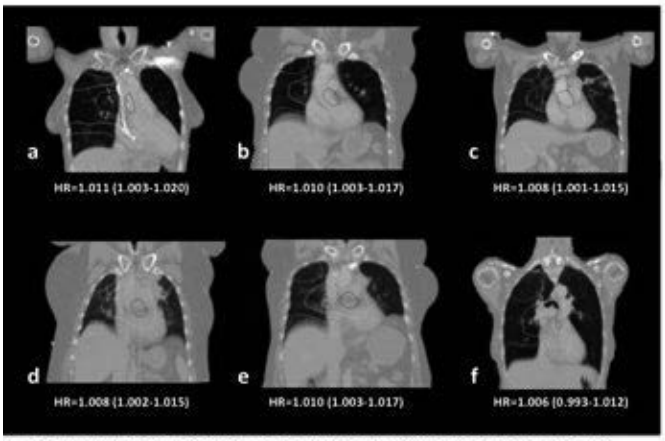

Figure 1. T-maps resulting from IBDM for a) original patient reference, b-f) 5 additional reference patients. T-isolines are 3 (dark green), 4 (light green), 5 (orange) and 6 (red). Hazard ratios (HR) per Gray and 95% confidence intervals from multivariate Cox regression analysis for the dose to the region of high T value are presented for

Conclusion: IBDM is a robust approach and, in this analysis, does not appear to be sensitive to the choice of reference patient for the investigated dose-effect correlation. Prospective studies are necessary to confirm the correlation between dose to the base of the heart and OS in NSCLC patients. Methodological studies are needed to determine the level of effect strength and region size that this general technique can identify.

Keywords: Radiotherapy for NSCLC, data mining, survival analysis

Keywords: Radiotherapy for NSCLC, data mining, survival analysis

P1.17-02 LOW PROGNOSTIC NUTRITIONAL INDEX PREDICTS POOR SURVIVAL IN STAGE IIIB NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH CHEMORADIOTHERAPY

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Background: The prognostic role of prognostic nutritional index (PNI) has been widely investigated and showed in many types of cancer. However, to our best knowledge, the significance of PNI has never been investigated in locally advanced non-small cell lung cancer (NSCLC) who were treated with concurrent chemoradiotherapy (CCRT). Therefore in this current study, we aimed to investigate the prognostic impact of PNI on survival outcomes of locally advanced NSCLC undergoing CCRT. **Method:** The data of 358 patients with stage IIIB NSCLC treated with CCRT were analyzed retrospectively. All patients received 60 to 66 Gy (2 Gy per fraction) thoracic radiotherapy and at least one course of platinum-based doublet chemotherapy concomitantly. For each patient PNI was calculated by the known formula in blood samples those were available prior to CCRT: [PNI=10×serum albumin (g/dl) + 0.005×total lymphocyte count (mm^3)]. The primary endpoint was the association between PNI and overall survival (OS). Secondary endpoints were locoregional progression-free survival (LPFS) and progression-free survival (PFS). The survival curves were calculated by Kaplan-Meier method and log-rank test. The cutoff value of the PNI was analyzed by receiver operating curve (ROC). **Result:** At a median follow-up of 22.5 months (2.4-123.5 months) 108 patients (30.2%) were still alive. For the whole study cohort median OS was 25.2 months (95 % CI: 22.7-27.7). The median LPFS and PFS were 15.4 months (95% CI: 14.4-16.4) and 10.7 months (95% CI: 9.7-11.7) respectively. In ROC analysis, calculated cutoff value of PNI was 40.1 (AUC: 67.8% (62.0-73.6); sensitivity: 73.1; specificity: 68.4, p<0.001). According to this, patients were grouped as follows, group 1: PNI>40 and group 2: PNI<40. Accordingly, for the patients in group 1, OS (36.7 vs. 16.8 months, p<0.001), LPFS (19.5 vs. 11.5 months, p<0.001) and PFS (13.6 vs. 8.6 months, p<0.001) times were significantly better as compared to patients in group 2. Results of the multivariate analysis demonstrated that the prognostic worth of

PNI was independent of the other covariates (p<0.001, for each survival endpoints). **Conclusion:** Being the first of its kind study the result of this current investigation revealed that the PNI which is easy to calculate, easily achievable with no additional cost has a strong prognostic value in prognostic stratification of the stage IIIB NSCLC patients undergoing to CCRT.

Keywords: Prognostic nutritional index, non-small cell lung cancer, Chemoradiotherapy

P1.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.17-03 POTENTIAL ASSOCIATED SNPS BY GWAS WITH RADIATION PNEUMONITIS (RP) IN PATIENTS WITH LUNG CANCER TREATED WITH RADIOTHERAPY

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Background: Lung cancer is one of the most prevalent cancers and the leading cause of cancer-related deaths in China and worldwide. Radiation therapy plays a remarkable role in lung cancer treatment, and approximately 60%~70% lung cancer patients receive radiation treatment. Whereas, radiation pneumonitis is one of the most critical dose-limiting toxicities of thoracic radiation. Single nucleotide polymorphisms (SNPs) in inflammation-related, DNA repair-related, oxidative stress response-related and angiogenesis-related genes and so on were proved to be associated with RP, with different underlying mechanisms. Previous limited studies reported few SNP sites that may be used a biomarker for prediction of RP risk. However these studies mainly focused on previously reported sites and only limited sites were tested. Here, the purpose of this study was to evaluate the potential related SNPs by whole genome sequencing and radiation pneumonitis (RP) development. **Method:** We recruited a total of 132 patients with lung cancer receiving intensity modulated radiation therapy (IMRT). We collected the blood sample and sequenced the whole genomes in all patients. RP events were prospectively scored using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Kaplan-Meier analysis was used to determine the cumulative probability of RP of grade ≥ 2. Genomes-Wide Association Study (GWAS) was carried out to look for potential SNPs associated with risk of RP grade ≥ 2. **Result:** The incidence of RP of grade ≥ 2 was 29.2%. Using SNP information by Genomes-Wide Association Study (GWAS), we discovered 73 SNPs that showed significant difference with cutting off p-value of 0.001. Most of them are previously not reported. **Conclusion:** This result established a set of biomarkers which can be used for prognosis predictions for radiation-induced pneumonitis.

Keywords: single nucleotide polymorphisms, Radiation pneumonitis, Genomes-Wide Association Study

P1.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.17-04 CURATIVE INTENT TREATMENT FOR STAGE III NSCLC IN ENGLAND

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Background: The National Lung Cancer Audit (NLCA) produces annual reports detailing standards of care for lung cancer. This further analysis investigates the use of curative intent multi-modality treatment for people in England diagnosed with stage III NSCLC during 2016, including, for the first time, details about use of concurrent and sequential chemoradiation (cRT). **Method:** Data on patients diagnosed during 2016 with stage III NSCLC in England were extracted from the National Cancer Registration and Analysis Service (NCRAS); information submitted through the Cancer Outcome and Services Dataset (COSD) were linked to other NCRAS datasets, including Hospital Episode Statistics (HES), the National Radiotherapy Dataset (RTDS) and the Systemic Anti-Cancer Dataset (SACT). **Result:** 6,288 cases of stage III NSCLC were analysed, 3839 Stage IIIA and 2449 Stage IIIB (Table 1). 813 (13%) people underwent surgery with 447 (7%) of these also receiving chemotherapy (predominantly adjuvant). 1047 (17%) people were treated with radical radiotherapy with 676 (11%) of these also receiving chemotherapy. For the 589/676 cRT cases where complete treatment dates were available, 199 (34%) received concurrent and 390 (66%) received sequential chemoRT (37% and 63% for stage IIIA). For 481/589 cases with performance status (PS) available, 171 (36%) PS0-1 cases received concurrent and 310 (64%) received sequential cRT (38% and 62% for stage IIIA) Of note, 2148 (34%) people received anti-cancer treatment of palliative intent and 2290 (36%) received supportive care only. Survival data will also be presented. Table 1

Total by Stage	Stage IIIA 3839	Stage IIIB 2449
Groups	Number (n)	Number (n)
Group 1: Surgery	770	43
Surgery	302	19
Surgery and Adjuvant Chemotherapy	356	12
Neoadjuvant chemotherapy and surgery	34	2
Surgery and Radiotherapy	37	8
Triple therapy	41	2
Group 2: Radical Radiotherapy	712	335
Radical Radiotherapy	291	80
Radical Radiotherapy and Chemotherapy	421	255
Group 3: Palliative intent treatment	1023	1125
Palliative radiotherapy and chemothera	182	234
Palliative radiotherapy	396	321
Chemotherapy alone	445	570
Group 4: Best Supportive Care (No treat	1334	946

Conclusion: Multi-modality treatment with either surgery or radical radiotherapy combined with chemotherapy was delivered to 1123 (18%) patients with stage III NSCLC. Concurrent cRT, optimal cRT based on meta-analysis, was delivered to just over one third of people receiving cRT, including for patients of good PS0-1. This analysis provides a baseline for future quality improvement initiatives to optimise treatment and outcomes for patients with stage III NSCLC.

Keywords: multi-modality treatment, sequential chemoradiotherapy, Concurrent Chemoradiation

P1.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.17-05 ACCELERATED RADIOTHERAPY FOR NON-SMALL CELL LUNG CANCER: A 12 YEAR RETROSPECTIVE REVIEW OF TWO DOSE FRACTIONATION SCHEDULES

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Background: Numerous dose fractionation regimes have been used for inoperable NSCLC patients and there is evidence that accelerated schedules can produce better outcome than conventionally fractionated treatment (1). Continuous hyperfractionated accelerated radiotherapy (CHART, 54Gy in 36 fractions over 12 days) and accelerated hypofractionated radiotherapy (55Gy in 20 fractions over 4 weeks) have been routinely used in Sheffield over the past decade, with schedule selection largely down to patient choice (in-patient vs out-patient treatment). In this single-centre retrospective analysis, we present the outcomes for all patients treated with these two schedules between 2003 to 2015. Ref 1. LePechoux C, Mauguen A, Baumann M, et al. Hyperfractionated or Accelerated Radiotherapy in Lung Cancer: An Individual Patient Data Meta-Analysis. JCO 2012;30:2788-2797. **Method:** In this audit details on patient demographics, tumour characteristics and survival data was collected from the electronic hospital records and supplemented by information from patient notes. Dosimetric data for tumour and organs at risk were collated automatically via the Varian Eclipse Scripting application programming interface. Descriptive statistical analysis was performed using the SSPS package with clinical and dosimetric variables assessed using independent samples t-tests and survival via a log-rank test. Multivariate survival analysis was performed using Cox regression. **Result:** We identified 883 eligible patients, of which 45% received CHART and 55% hypofractionated radiotherapy. Mean age was 70 years and 58% were male. PET staging was performed in 87% with 30%, 15%, 51% and 4% being stage I, II, III and IV, respectively. 63% had a WHO performance status of 0-1. 38% of patients underwent induction chemotherapy. 99% completed their prescribed radiotherapy treatment with an overall response rate of 60%. Relapse was observed in 50% of patients with median disease-free survival of 19.4 months. 2-year overall survival was 47% with a median overall survival of 23.2 months. Multivariate analysis identified histology, stage, performance status, use

of chemotherapy as independent predictors of survival. No significant differences between the two radiotherapy regimes was seen for any parameters. **Conclusion:** This audit has confirmed that both CHART and hypofractionated accelerated radiotherapy are deliverable and well tolerated schedules when used in day to day practice. We have detected no significant difference in outcome between the two schedules and there is the need to explore avenues, eg dose escalation, that develop these schedules to match outcomes reported by recent concurrent chemo-radiation studies.

Keywords: NSCLC, Accelerated radiotherapy

P1.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.17-06 SALVAGE SURGERY AFTER CHEMOTHERAPY AND/OR RADIOTHERAPY INCLUDING SBRT AND PROTON: CONSECUTIVE ANALYSIS OF 46 PATIENTS

A. Kobayashi[1], H. Horinouchi[2], Y. Nakayama[3], Y. Ohe[4], M. Yotsukura[1], S. Uchida[1], K. Asakura[5], Y. Yoshida[1], K. Nakagawa[1], S. Watanabe[1]

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Background: Local recurrence after definitive chemotherapy and/or radiotherapy with curative intent is frequently experienced in patients with locally advanced lung cancer. We evaluated the frequency, feasibility, and efficacy of salvage pulmonary resection after definitive chemotherapy and/or radiotherapy. **Method:** We analyzed the characteristics and medical courses of consecutive patients who had undergone salvage pulmonary resection after local relapse or progression after chemotherapy, chemoradiotherapy and radiotherapy including stereotactic body radiation therapy (SBRT) and proton beam therapy (PBT). In this analysis, local relapse or progression were defined as increase in remaining tumor size or detection of new lesions by CT and/or FDG/PET-CT. Indications of resectability was assessed by multidisciplinary tumor board. **Result:** Between January 2000 and January 2018, 46 patients (0.63%) received salvage surgery out of 7,290 patients underwent surgery for primary lung cancer at National Cancer Center Hospital, Tokyo, Japan. Median follow-up time was 24.5 months (range, 2-157.6). Of 46 patients evaluated, 30 (65.2%) were men, the median age was 64.5 years (range, 20-78 years), 22 (47.8%) underwent chemotherapy, 18 (39.1%) underwent resection after definitive chemoradiotherapy, 3 (6.5%) underwent resection after SBRT and 3 (6.5%) underwent resection after PBT. The number of patients undergoing salvage surgery has increased in recent years: 9 patients were between 2000 and 2009, whereas 37 patients were between 2010 and 2018. Method of surgical resection was as follows: 28 lobectomies (2 bilobectomy, 15 right upper, 1 right middle, 6 right lower, 2 left upper, 2 left lower), 10 pneumonectomies (left:right=7:3). One patient received a wedge resection, and one recieved wedge resection with chest well resection, and 2 segmentectomy and lymphadectomy for residual lymph nodes respectively. A complete resection (R0) was achieved in 42 cases (91.3%). Postoperative complications were observed in 3 patients (6.5%): prolonged air leakage, bronchopleural fistula, and atrial fibrillation. There were no post-operative deaths within 30 days after surgery. The five-year progression free and overall survival rate after surgical resection was 39.1% (95% CI.: 19.9-57.9) and 64.1% (95% CI.: 39.3-80.9), respectively. **Conclusion:** The frequency of salvage surgery after initial treatment has been increasing possibly due to a better treatment course using novel medical and radiation oncology technique. Salvage pulmonary resections demonstrated acceptable morbidity and mortality with promising long-term efficacy in selected patients.

Keywords: Chemoradiotherapy, salvage surgery

P1.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.17-07 THE PROGNOSTIC VALUE OF VOLUMETRIC CHANGES OF THE GTV MEASURED ON CBCT DURING RADIOTHERAPY FOR CCRT IN NSCLC PATIENTS

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Background: To pursue personalized cancer care, it is important to determine tumor response during treatment and associate these with outcomes. Previously published literature reported that adenocarcinoma and squamous cell carcinoma have different treatment response and outcome. Therefore, the aim of this study is to examine the prognostic value of volumetric changes of the primary tumor measured on Cone Beam-CT (CBCT) during radiotherapy for locally advanced NSCLC patients treated with concurrent chemoradiation (CCRT). **Method:** 394 NSCLC-patients treated with CCRT between 2007-2013 were included. To determine GTV during treatment, deformable image registration of the planning-CT to all CBCTs was performed. To assess the association of volumetric changes of the gross tumor volume (GTV) with overall survival (OS), progression free survival (PFS) and local regional control (LRC), multivariate cox regression analyses were performed, accounting for potential confounders. Furthermore, the entire group was stratified based on adenocarcinoma and non-adenocarcinoma and an additional log rank and multivariate cox regression analysis based on pathology was performed. **Result:** In patients with adenocarcinoma, GTV reduction during CCRT was significantly associated with worse OS (HR=1.55, Figure 1). GTV reduction was not significantly associated with PFS and LRC in either subgroup. For the entire group no significant association was found between GTV volume change and OS, PFS or LRC.

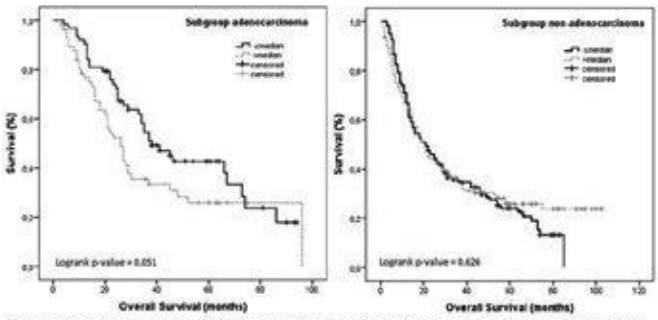

Figure 1: Kaplan Meier curves for Overall Survival for the subgroup analysis adeno-carcinoma and non-adenocarcinoma on the basis of the relative GTV-change between first CBCT and the last CBCT of the last week, dichotomized on the median of the entire group.

Conclusion: Surprisingly, no associations between GTV changes and outcomes were found for the entire treatment group. In patients with adenocarcinoma, GTV changes during concurrent chemoradiaton measured on CBCT were a significant predictor for OS.

Keywords: ConeBeamCT, volumetric changes prediction model, Concurrent chemo radiation NSCLC

P1.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.17-08 GENETIC PREDICTORS OF RESPONSE TO CHEMORADIATION IN STAGE III NON-SMALL-CELL LUNG CANCER

L. Luo[1], R. Samstein[1], R. Dick-Godfrey[1], B. Sidiqi[1], C. Wang[1], F. Oro[1], M. Sonnick[1], P. Paik[2], J. Chaft[2], A. Rimner[1], A. Wu[3]

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Background: Radiation with platinum-based doublet chemotherapy is the standard of care for patients with unresectable stage III non-small-cell lung cancer (NSCLC). Despite aggressive treatment, progression-free survival and overall survival remain poor. It is unclear whether any tumor genetic alterations are associated with response to therapy. **Method:** We retrospectively reviewed clinical outcomes of patients with stage III NSCLC treated with definitive radiation, who had undergone tumor molecular profiling through an institutional next-generation sequencing platform. This platform is an FDA-approved, targeted-DNA-sequencing panel that contains 341 (now expanded to 468) somatic mutations and other genetic alterations. Basic patient and tumor characteristics, clinical outcomes including loco-regional recurrence, distant recurrence, and overall survival, were collected. Overall and recurrence-free survivals were estimated using the Kaplan-Meier method. Cox proportional hazards model was used to investigate association between clinical outcome and genetic alterations. **Result:** We identified 110 patients with stage III NSCLC who were treated with definitive radiation between 2013 and 2017 and underwent tumor molecular profiling. Fifty-one patients (46%) had stage IIIA disease and 59 patients (54%) had stage IIIB disease. Median radiation dose delivered was 60Gy in 30 fractions (range 48.6Gy to 74Gy). Either concurrent or sequential chemotherapy was given in 104 patients (95%) with 83 patients (75%) receiving concurrently. One

patient received induction crizotinib and one patient died before start of chemotherapy. With a median follow-up time of 15.3 months, the median overall survival was 31.2 months. Several genetic mutations were significantly associated with worse overall survival after therapy, including AKT2 any mutation (Hazard ratio 13.71, p<0.001), KMT2C truncating mutations (HR 13.42, p<0.001), KMT2D truncating mutations (HR 6.97, p<0.001), ARID1A frameshift mutations (HR 8.54, p<0.001), and FLT1 any mutation (HR 6.62, p<0.001). These genes were also associated with increased loco-regional recurrence. Mutation in the PIK3C2G gene was significantly associated with improved overall survival. Association of other common genetic alterations such as EGFR mutation with response to therapy was not observed. **Conclusion:** This study coupled multiplex targeted sequencing with clinical outcome information to identify several potential genetic predictors of response to chemotherapy and radiation in locally advanced NSCLC. KMT2C and KMT2D encode two subunits of a histone methyltransferase, and mutations of KMD2 have been shown to correlate with worse survival in locally advanced and advanced NSCLC patients. Further studies including in vitro validations are necessary to confirm the findings.

Keywords: non-small cell lung cancer, biomarker, genetic predictor

P1.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.17-09 V30 MAY BETTER PREDICT RADIATION PNEUMONITIS AFTER INTENSITY-MODULATED RADIATION THERAPY FOR LUNG CANCER

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Background: V20 and MLD are the most commonly used dose constraints for radiation pneumonitis (RP) prediction. However, intensity-modulated radiation therapy (IMRT) has unrestricted beam arrangements, an infinite number of very different dose distributions could be generated in the lung volume outside the planning target volume (PTV). Conventional dose constraints from traditional 3D conformal RT may not be valid for IMRT treatment. We hypothesize that lung dosimetric parameters may have different RP predictive values from that of traditional constraints (largely generated from 3D treatment) in IMRT treated lung cancer patients. **Method:** We retrospectively enrolled184 IMRT treated lung cancer patients from January 2014 to October 2017. The primary endpoint was acute grade 2 or higher symptomatic radiation pneumonitis (RP2), based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03). Vdose (from V5 to V50) and MLD were generated from the lung volume outside PTV. Univariate and multivariate logistic regression analysis was used to evaluate the association between the dose parameters outside PTV to RP2. We employed area under the curve (AUC) for the receiver operating characteristic curve (ROC) to assess prediction accuracy for the single or multi-variate model. **Result:** 26 out of 184 lung cancer patients (14.1%) developed RP2 within 3 months after the end of IMRT treatment. In univariate logistic regression, although none of the clinical parameters was significantly associated with RP2, female gender (P=0.051) and chemotherapy (P=0.151) had a trend of correlation. V5 (P=0.007), V10(P=0.012) V20 (P=0.004), V30 (P=0.003) and MLD (P=0.004) were significantly associated with RP2 incidence. From ROC curve, the largest AUC of 0.67 was generated from V30, which showed a better predictive value compared with other dosimetric factors. Multivariate logistic regression analysis showed the only significant dosimetric factor is V30 (P=0.021). Combining gender and chemotherapy factors, V30 has an AUC of 0.71 which is the largest among all the other dosimetric factors. **Conclusion:** For IMRT treated lung cancer patients, V30 generated from lung volume outside PTV may predict RP more accurately than traditional dosimetric parameters.

Keywords: intensity-modulated radiation therapy (IMRT), Predict, Radiation pneumonitis (RP)

P1.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.17-10 CONSOLIDATION CHEMOTHERAPY IN STAGE III NON-SMALL CELL LUNG CANCER: STILL A CRITICAL PIECE OF THE PUZZLE

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Background: Despite lack of proven survival benefit, national guidelines recommend that patients with stage III non-small cell lung cancer (NSCLC) treated with chemoradiation (CRT) using weekly regimens receive two additional cycles of full dose consolidation chemotherapy (cCT). We seek to explore the benefit of cCT in our mature annotated cohort of stage III NSCLC patients treated with modern radiation therapy (RT) and predominantly weekly carboplatin/paclitaxel-based CRT. **Method:** In this retrospective analysis, 355 consecutive patients with stage III NSCLC treated with either definitive CRT alone (bimodality) or followed by surgery (trimodality), between the years 2000-2013 were analyzed. Median age of the patients was 60 years (range: 30-86). Stage grouping was IIIA: 56.3%, T3/4: 49%, N2: 61.4%; N3: 21.4%. Histology was evenly distributed between squamous, adenocarcinoma, other or not specified. Concurrent CRT was delivered in 92.1% of the patients, 74% receiving weekly carboplatin/paclitaxel. Median radiation dose was 63Gy (range 10.8-81.6Gy). Data on cCT use was available in 304 patients, 69.7% receiving cCT. Logistic regression was performed to assess predictors for the use of cCT. Kaplan-Meier method and Cox proportional hazards model was used to estimate the overall (OS) and freedom-from-recurrence (FFR) adjusted for age, gender, marital status, insurance status, smoking history, COPD diagnosis, performance status, Charlson score, year of diagnosis, concurrent vs sequential CRT, RT technique, RT dose and surgery. **Result:** With a median follow up of 15 months (range: 1-184 months), OS (median/5-year) with and without cCT was 30.2 months/ 30.5% and 15.3 months/ 12.9%, respectively (multivariate adjusted HR for death: 0.50; 95% CI: 0.37-0.69, p < 0.001). Corresponding values for FFR were 19 months/ 27% and 11.2 months/ 11.4% (adjusted HR: 0.54; 95% CI: 0.37-0.77, p = 0.001). On subset analysis, the OS benefit was seen in patients undergoing bimodality therapy (HR: 0.57; 95% CI: 0.40-0.83, p = 0.003) but not for trimodality therapy (p = 0.124). Similarly, an OS benefit was seen in stage IIIA (HR: 0.35; 95% CI: 0.23-0.55, p < 0.001) but not for stage IIIB patients (p = 0.071). The only factor predicting the use of cCT was primary treatment: bimodality vs trimodality (OR: 2.2; 95% CI: 1.1-4.3, p = 0.018 favoring bimodality). **Conclusion:** Consolidation chemotherapy should continue to be strongly considered for stage III NSCLC patients, especially those undergoing bimodality therapy receiving weekly sensitizing doses of carboplatin-paclitaxel and with stage IIIA disease. The relative benefit of cCT in the setting of maintenance durvalumab (or other immunotherapy) needs further evaluation.

Keywords: consolidation chemotherapy, loco-regional NSCLC

P1.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.17-11 PATTERN AND SURVIVAL IMPACT OF NEOADJUVANT TREATMENT OF NON-SMALL CELL LUNG CANCER (NSCLC) IN A PROSPECTIVE LUNG RESECTION COHORT

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Background: Neoadjuvant therapy may benefit locally-advanced NSCLC patients. We evaluated patterns of neoadjuvant therapy and the impact on stage-shift and survival. **Method:** All curative-intent NSCLC resections were collected from 12 hospitals in 4 contiguous Dartmouth Hospital Referral Regions in mid-Southern USA from 2009-2018. Comparisons made using Chi-square tests and non-parametric t-tests, survival impact assessed using Cox-proportional hazard models. **Result:** 182 of 3,297 resections (5.5%) had neoadjuvant therapy: 118 (64.8%) chemoradiation, 47 (25.8%) chemotherapy, and 17 (9.3%) radiation. Neoadjuvantly treated patients were younger, more likely to be commercially insured, have immediate preoperative brain MRI, and invasive mediastinal staging than those with primary resection (p<0.001 for all, Table 1). They also had more advanced stage, but 27% were clinical stage IA/IB. Despite evidence of more difficult surgery, perioperative complications, hospital length of stay and postoperative mortality rates were similar to the primary resection cohort. Despite delay to surgery, they had significantly greater down-staging (p<0.001). However, down-staging had no impact on survival, regardless of type of neoadjuvant therapy (Table 2).

Table 1. Demographic and clinical characteristics between patients who received neoadjuvant therapy and those who did not.

Demographic Variables	Neoadjuvant Therapy	Primary Resection Only
N	N=182	N=3115
Race (p: 0.0324)		
Caucasian	125 (69)	2425 (78)
Black or AA	56 (31)	651 (21)
Asian	0 (0)	16 (1)
AI/AN	0 (0)	2 (0)
Other/NR	1 (1)	19 (1)
Age (p: <0.001)	63 (56, 69)	68 (61, 74)
Sex (p: 0.4323)		
Male	104 (57)	1686 (54)
Female	78 (43)	1427 (46)
Insurance (p: <0.001)		
Medicare	45 (25)	1417 (45)
Medicaid	42 (23)	438 (14)
Commercial	91 (50)	1148 (37)
Self/ None	4 (2)	112 (4)
Non-Invasive Staging		
CT Scan †	135 (74)	2879 (92)
PET/CT †	106 (58[RO2])	2553 (82)
Brain Scan (p: <0.001)	98 (54)	877 (28)
Invasive staging tests (p: <0.001)		
No	144 (79)	2778 (89)
Yes	38 (21)	337 (11)
Histology (p: <0.001)		
Adenocarcinoma	65 (40)	1547 (54)
Squamous	57 (35)	985 (34)
Other including but limited to Adenosqamous, large cell, carcinomas, and other	40 (22)	339 (11)
Grade (p: <0.001)		
Well/Moderately	50 (30)	1684 (54)
Poorly/Undifferentiated	60 (33)	1040 (34)
Not Reported	66 (36)	390 (13)
Tumor Size (p: 0.50312)		
<= 3 cm	123 (68)	1984 (64)
>3-5 cm	36 (20)	733 (24)
>5-7 cm	17 (9)	255 (8)
>7 cm	6 (3)	143 (5)
8th Clinical T (p: <0.001)		
Tx	0 (0)	2 (0)
T0	14 (8)	184 (6)
Tis	1 (1)	0 (0)
T1a(mi)	0 (0)	1 (0)
T1b	25 (14)	865 (28)
T1c	24 (13)	621 (20)
T2a	27 (15)	521 (17)
T2b	18 (10)	201 (6)
T3	39 (22)	321 (10)
T4	25 (14)	228 (7)
T1a	5 (3)	156 (5)
Insufficient Records	3 (2)	11 (0)
8th Clinical N (p: <0.001)		
Nx	0 (0)	1 (0)
N0	130 (71)	2709 (87)
N1	13 (7)	196 (6)
N2	35 (19)	176 (6)
N3	1 (1)	20 (1)
Insufficient	3 (2)	9 (0)
8th Clinical M (p: <0.001)		
M0	131 (73)	2525 (87)
M1a	9 (5)	116 (4)
M1b	30 (17)	208 (7)
M1c	9 (5)	61 (2)
8th Clinical Stage (p: <0.001)		
Occult Carcinoma	0 (0)	2 (0)
Stage 0	13 (7)	167 (5)
Stage IA1	2 (1)	141 (5)
Stage IA2	15 (8)	807 (26)
Stage IA3	12 (7)	537 (17)
Stage IB	21 (12)	424 (14)
Stage IIA	10 (5)	160 (5)
Stage IIB	29 (16)	373 (12)
Stage IIIA	41 (23)	364 (12)
Stage IIIB	15 (8)	63 (2)
Stage IVA	0 (0)	3 (0)
Stage Unknown	21 (12)	59 (2)
Extent of resection (p: <0.001)		
Pneumonectomy	24 (13)	174 (6)
Bilobectomy	13 (7)	145 (5)
Lobectomy (+/-wedge)	131 (72)	2338 (75)
Segmentecto-my(+/-wedge)	4 (2)	146 (5)
Wedge	10 (5)	307 (10)
Surgical Technique (p: 0.1280)		
Open	124 (68)	1926 (62)
RATS	39 (21)	701 (23)

Demographic Variables	Neoadjuvant Therapy	Primary Resection Only
VATS	19 (10)	484 (16)
Margin Status (p: <0.001)		
Positive	15 (8)	142 (5)
Negative	152 (84)	2880 (93)
Not Reported	15 (8)	88 (3)
Peri- and Post-Operative Characteristics		
Surgery duration (in minutes, med, IQR) (p: 0.0172)	156 (109, 221)	135 (97, 186)
Estimated blood loss (CCs, med, IQR) (p: <0.001)	250 (100, 500)	150 (100, 300)
Duration of chest tube (in days, med, IQR) (p: 0.1364)	4 (2, 6.5)	4 (3, 7)
ICU duration (in days, med, IQR) (p: 0.0282)	2 (1, 3)	1 (1, 3)
Hospital duration (in days, med, IQR) (p: 0.7868)	6 (4, 9)	6 (4, 9)
Rate of blood transfusions (p: <0.001)	38 (21)	215 (7)
Rate of cardiac arrhythmias (p: 0.8513)	27 (15)	478 (15)
Rate of any post-op complications (p: 0.1323)	102 (56)	1567 (50)
Rate of ICU re-admittance prior to discharge (p: 0.0560)	14 (8)	143 (5)
Rate of hospital re-admittance within 30 days (p: 0.1285)	29 (17)	378 (13)
Clinical to pathologic T-Category Migration (<0.001)		
Down stage	76 (42)	742 (24)
No change	40 (22)	1019 (33)
Up stage	66 (36)	1354 (43)
Unknown	0 (0)	0 (0)
Clinical to pathologic N Category Change (p: <0.001)		
Down stage	48 (26)	566 (18)
No change	112 (62)	2122 (68)
Up stage	22 (12)	422 (14)
Unknown	0 (0)	1 (0)
Clinical to pathologic aggregate stage Migration (p: <0.001)		
Down stage	89 (49)	879 (28)
No change	49 (27)	953 (31)
Up stage	41 (23)	1268 (41)
Unknown	3 (2)	11 (0)
Postoperative Mortality Rates		
30 Day (p: 0.5109)	11 (6)	154 (5)
60 Day (p: 0.4222)	16 (9)	224 (7)
90 Day (p: 0.2216)	22 (12)	291 (9)
120 Day (p: 0.1850)	26 (14)	345 (11)

† CT and PET/CT scan are after neo-adjuvant therapy for neoadjuvant patients.

Table 2. Survial impact of downstaging among neo-adjuvant patients.

Prediction Variables	Hazard Ratio	95% Confidence Interval	P-value
T-category			
Up-staged vs Down-staged	1.69	0.955, 2.977	0.0715
No change vs Down-staged	1.64	0.971, 2.4757	0.0642
N Category (among all patients)			
Up-staged vs Down-staged	0.73	0.45, 1.20	0.2191
No change vs Down-staged	1.26	0.62, 2.58	0.5270
N Category (among clinical N2 disease patients)			
Up-staged vs Down-staged	NA	NA	NA
No change vs Down-staged	1.44	0.47, 4.43	0.5261

NA – not applicable due to small sample size

Conclusion: Neoadjuvant therapy was safe, but had no survival impact in this cohort, despite increased down-staging, possibly because of an inexplicably high proportion of stage I patients.

Keywords: survival, neoadjuvant, NSCLC

P1.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.17-12 COLLEAGUE PEER REVIEW OF RADICAL LUNG RADIOTHERAPY TREATMENT PLANS: THE IMPACT ON INTERVAL FROM DECISION TO TREAT TO TREATMENT DELIVERY

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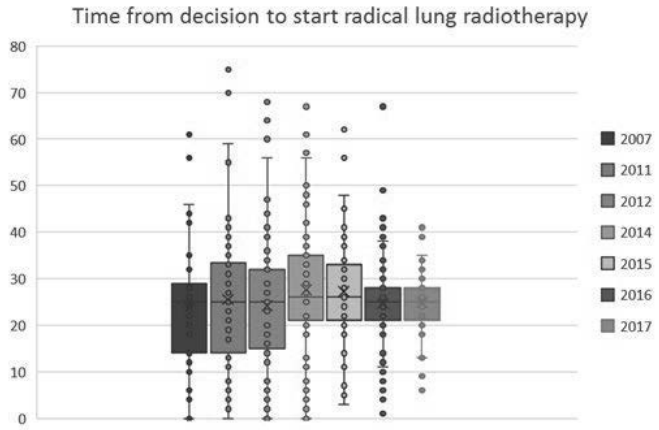
Background: Quality assurance by colleague-led peer review (CPR) is recommended in the radiotherapy treatment planning of curative intent treatments such as for lung cancer. Previous studies have demonstrated a proportion of radiotherapy plans are amended following CPR resulting in enhanced quality and uniformity of treatment approached. CPR is an extra step in the radiotherapy planning process, and it may affect the timeliness of commencing radiotherapy. CPR was initiated in our centre in 2011. This study considers the temporal impact of adding an additional step to the planning process. **Method:** Using our institutional lung radiotherapy database we recorded the timescales between decision to treat (DTT) and commencement of radical lung radiotherapy, pre-peer review and post-peer review initiation at a single institution. The data for all patients was analysed for the years 2007 to 2017. **Result:** Prior to peer review for the calendar year of 2007, 71% of the 63 patients receiving curative intent radiotherapy for lung cancer commenced treatment within 28 days of the DTT (median 26 days, range 0-61). In 2016, 80% of the 133 patients receiving curative intent radiotherapy had treatment initiated within 28 days (median 25 days, range 6-41). There was a notable reduction in the variability in planning time making booking of appointments with a reduction in extreme wait times to start treatment (figure 1). **Figure 1** Box and whisker plot of the time from the decision to treat until the commencement of radiotherapy for the representative years available for analysis.

(See next page)



Conclusion: In our institutional series, CPR does not prolong planning time with the median number of days taken to commence treatment remaining comparable, but may standardise radiotherapy start times due to enhanced team working via the CPR meetings. We recommend that peer review is performed as standard practice as it improves treatment quality without a detrimental prolongation of planning time.

Keywords: college peer review, Lung radiotherapy planning

P1.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
MONDAY, SEPTEMBER 24, 2018 - 09:45-18:00

P1.17-13 THE ROLE OF POST-OPERATIVE RADIATION THERAPY IN PATIENTS WITH LOCALLY ADVANCED NSCLC AFTER NODAL DOWN-STAGING WITH SYSTEMIC CHEMOTHERAPY

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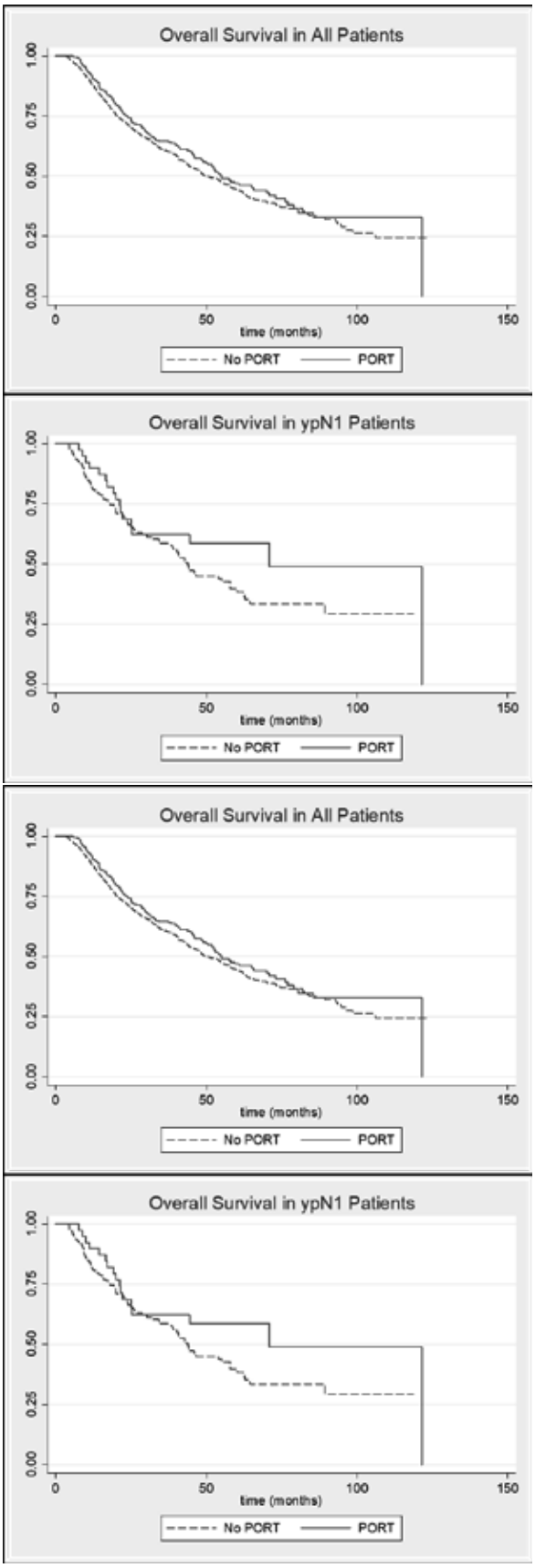
Background: Post-operative Radiation Therapy (PORT) has been shown to improve local-regional control and overall survival in patients with non-small cell lung cancer (NSCLC) undergoing surgical resection with pathologic N2 nodal involvement. It is unclear if PORT is needed in patients with clinical N2 involvement who are downstaged with neoadjuvant chemotherapy. **Method:** The National Cancer Database was queried for patients diagnosed between 2006-2015 with clinical N2, Stage IIIA NSCLC and treated with neoadjuvant chemotherapy followed by R0 surgical resection with either a lobectomy or pneumonectomy. Patients were included if they were alive for at least 3 months following their diagnosis. Kaplan Meier method was used for overall survival (OS) analysis. **Result:** A total of 1,174 patients were evaluated. The median age was 65 years (range: 33-89). Most patients were treated with lobectomy (90%). The median radiation (RT) dose was 50.4 Gy (range: 45-54 Gy). Pathologic downstaging and OS rates with and without PORT are demonstrated in Table and Figure.

Survival Rates			
ypN STAGE	PORT (N=303)	No PORT (N=871)	p-value
ypN0 (N=477) Median OS 1 yr OS 2 yr OS 5 yr OS	N=63 73.1 months 100% 89.9% 62.6%	N=414 67.5 months 93.6% 78.2% 52.6%	0.089
ypN1 (N=182) Median OS 1 yr OS 2 yr OS 5 yr OS	N=39 71.0 months 89.7% 68.6% 58.7%	N=143 43.8 months 82.4% 67.0% 38.3%	0.172
ypN2 (N=512) Median OS 1 yr OS 2 yr OS 5 yr OS	N=198 46.1 months 89.9% 71.5% 39.5%	N=314 39.8 months 84.8% 63.2% 35.9%	0.072
All patients (N=1,174) Median OS 1 yr OS 2 yr OS 5 yr OS	N=303 55.0 months 91.7% 74.8% 46.9%	N=871 50 months 88.6% 71.3% 44.3%	0.211



Conclusion: Our data demonstrate a trend for improved OS with PORT. Although this is a population-based study, this lack of statistical significance may be attributable to a small sample size as the OS curves indicate a consistent benefit with PORT.

Keywords: PORT, Adjuvant Radiation, nodal downstaging

P1.17-14 OUTCOMES OF HYPOFRACTIONATED RADIATION THERAPY (HFRT) WITH CONCURRENT CHEMOTHERAPY IN PATIENTS WITH STAGE III NON SMALL CELL LUNG CANCER (NSCLC)

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Background: Patients with unresectable locally advanced NSCLC are often treated with concurrent chemoradiation. HFRT regimens are becoming increasingly common due to convenience and healthcare costs. A database analysis was performed to evaluate the outcomes of HFRT with concurrent chemotherapy. **Method:** The National Cancer Database (NCDB) was queried for patients with stage III NSCLC who received RT (50 Gy-80 Gy) with concurrent chemotherapy without surgery from 2004-2015. Patients were defined as receiving concurrent chemotherapy if chemotherapy was started within 3 weeks of the start of radiation. Patients received conventionally fractionated RT (CFRT): 180-200 cGy/fraction (fx) or HFRT: 210-400 cGy/fx. Baseline characteristics were compared. Kaplan Meier method was used for overall survival (OS) and Cox-proportional hazards were used for uni- and multivariable analyses (UVA/MVA). **Result:** A total of 54,559 patients were evaluated: 50,938 CFRT and 3,621 HFRT. Patients treated with HFRT were more likely to receive RT at an academic center (32.6% vs. 27.2%, p<0.01), more likely to have higher T-stage (cT3/T4: 56.5 vs. 49.2%, p<0.01) but lower N-stage (cN2/3: 77.6% vs. 81.4%, p<0.01). There was no difference in age (median 66 yo), sex, race, insurance, education, Charlson-Deyo Comorbidity Score (CDCS), tumor location, or grade. For the CFRT and HFRT groups, the median RT dose, Biologic Equivalent Dose (BED) and dose/fx were 64 Gy; 76.4; 185 cGy/fx and 65 Gy; 80.5; 235 cGy/fx, respectively. The median and 2-yr rates of OS were 19.8 mos and 43.2% for CFRT vs 16 mos and 36.1% for HFRT (p<0.01). On UVA and MVA, (data shown for MVA: HR, p-value), age (1.01, <0.01), male gender (1.2, <0.01), white race (1.09, <0.01), Medicare (1.04, <0.01), urban dwelling (0.93, <0.01), distance from treatment center (0.999, <0.01), treatment at an academic center (0.91, <0.01), CDCS (1: 1.11, <0.01, 2: 1.21, <0.01, 3: 1.29, <0.01), diagnosed 2010-2014 (0.85, <0.01), upper lobe location (0.89, <0.01), T3/T4 stage (1.15, <0.01), N2/N3 stage (1.12, <0.01), stage IIIB (1.11, <0.01), HFRT (1.26, <0.01) and BED (0.99, 0.01) were associated with OS. **Conclusion:** Patients who received HFRT had slightly inferior OS rates, which may be due to toxicity (not captured in the NCDB) or unaccounted confounders such as baseline performance status and aggressiveness of disease.

Keywords: hypofractionated radiation therapy

P1.17-15 PERIOPERATIVE PROGNOSTIC NUTRITION INDEX FOR INDUCTION CHEMORADIOTHERAPY FOLLOWED BY SURGERY IN LOCALLY ADVANCED NON-SMALL LUNG CANCERS

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Background: The perioperative nutritional and immunological statuses significantly associated the clinical outcome of the surgery, especially for the extended surgery. Induction chemoradiotherapy (iCRT) followed by surgery is one of treatment options for locally advanced (LA) non-small cell lung cancers (NSCLCs) although there is a risk for increasing postoperative complications. A prognostic nutritional index (PNI), calculated using serum albumin levels and peripheral lymphocyte count, has been used to predict the clinical outcome of various cancers including early stage NSCLCs but not LA-NSCLC after iCRT. In this study, we investigated the impact of PNI on clinical outcome of iCRT followed by surgery in the patients with LA-NSCLCs. **Method:** During 1999 to 2016, 173 patients underwent iCRT followed by surgery in Okayama University Hospital. Among them, 128 patients who matched to inclusion criteria were studied. We retrospectively calculated the PNI at (1) pre-iCRT (median 5 days before administration), (2) pre-operation (Ope) (median 5 day before surgery), and (3) post-Ope (median 30 days after surgery) and reviewed the medical records. **Result:** The median age was 62 years old (range 31 – 79) and 100 patients were male. Seventy patients were adenocarcinomas and 46 were squamous cell carcinomas. Clinical stages were IIA / IIB (n = 15), IIIA (n = 87), IIIB (n = 25), and IV (n = 1). Main regimen of iCRT was CDDP / DOC with concurrent radiotherapy (46 gray). Treatment responses were CR/PR (n = 99), SD (n = 27), and PD (n = 2). Lung resections were lobectomy (n = 109), bi-lobectomy (n = 14), and pneumonectomy (n = 5) and additional procedures were performed in 93 patients. Based on the invasiveness of surgery, we categorized into three groups: 1) highly invasive group (n = 60), 2) intermediate group (n = 33), and 3) standard group (n = 35). Pathological complete responses were present in 37 patients. The PNI were significantly decreased during treatment course [49 (24 – 71) in pre-ICRT, 44 (30 – 58) in pre-Ope, and 41 (22 – 58) in post-Ope]. Among the entire cohort, the perioperative PNI values showed some effect on overall survival. However, among the highly invasive group, the poor preoperative PNI values significantly correlated with worse overall survival. **Conclusion:** Peri-treatment nutritional evaluation using PNI is important to predict clinical outcome of the patients who received the iCRT followed by surgery with LA-NSCLCs especially when highly invasive surgery is required.

Keywords: locally advanced non-small cell lung cancer, Prognostic Nutrition Index, induction chemoradiotherapy

P1.17-16 CORRELATION OF TUMOR VOLUME REDUCTION DURING NEOADJUVANT CHEMORADIOTHERAPY WITH PATHOLOGICAL COMPLETE RESPONSE OF LUNG CANCER

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Background: A study has reported that tumor volume (TV) reduction after neoadjuvant chemoradiotherapy (NACRT) was associated with pathological complete response (pCR) in patients with non-small cell lung cancer (NSCLC). We think that the prediction of pCR during NACRT may be able to assist clinical decisions. Therefore, we retrospectively investigated the relationship between TV reduction during NACRT and pCR. **Method:** We evaluated patients who received NACRT followed by surgery between 2007 and 2017. The eligibility criteria of this study were as follows: NACRT was performed with a dose of 50 Gy in 25 fractions with the platinum-doublet regimen, and contrast enhanced computed tomography (CECT) was obtained before and during NACRT. TVs before and during NACRT (TVpre and TVduring, respectively) were measured with the sums of the primary tumor and clinically involved lymph node volumes. Relative changes in the TVs were calculated as %(TVduring – TVpre)/TVpre. The factors affecting pCR were evaluated in a univariate analysis, by Fisher's exact test or Wilcoxon rank-sum test, and in a multivariate analysis using the multiple logistic regression test. **Result:** In total, 31 patients met the eligibility criteria: 52%, 42%, and 52% of patients had squamous cell carcinoma, cT3, and cN2 disease, respectively. CECT during NACRT (CECTduring) was obtained at a median dose of 40 Gy (range, 24-50 Gy). The median TVpre and TVduring were 45.1 cc (range, 11.4-584.2 cc) and 27.0 cc (range, 5.9-195.0 cc), respectively. The median relative change in the TVs was –49% (range, –83 to –10%), and after surgery, pCR was confirmed in 11 patients (35%). Relative change in the TVs (p = 0.002) and TVpre (p = 0.039) were significant factors affecting pCR in the univariate analysis. No significances were observed in histology, cT, cN, RT dose at the time of CECTduring, and TVduring factors (p = 0.458, 0.449, 1.000, 0.547, and 0.984, respectively). In the multivariate analysis, relative change in the TVs remained an independent predictor of pCR (p = 0.003). The cut-off value for the relative change in the TVs affecting pCR was –64%, which was determined by a receiver operating characteristic curve (area under the curve = 0.841): 8 of 9 patients (89%) whose tumors shrunk more than this cut-off value achieved pCR. **Conclusion:** TV reduction during NACRT seems to be associated with pCR in patients with NSCLC. A cut-off value of –64% in relative change in the TVs at a dose of around 40 Gy may be promising to predict pCR.

Keywords: Prediction, pathological complete response, chemoradiation

P1.17-17 THE IMPACT OF INDUCTION CHEMORADIOTHERAPY FOLLOWED BY SURGERY FOR N1 INVOLVED NON-SMALL CELL LUNG CANCER

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Background: Induction chemoradiotherapy (iCRT) followed by surgery is usually selected for locally advanced non-small cell lung cancer (NSCLC) patients with mediastinal lymph node (LN) metastasis or invasion to adjacent organs, whereas it is occasionally performed for clinical N1 (cN1) NSCLC patients harboring such as a centrally located primary tumor or a bulky LN to improve local control rate and secure a cancer-free surgical margin. However, the survival benefit of iCRT followed by surgery for NSCLC patients with N1 LN involvement remains controversial. Furthermore, the accuracy of the radiological examination for N1 metastasis is unsatisfactory. In this study, we investigated the clinical outcomes of surgery with or without iCRT based on the estimation of the pretreatment LN metastatic status from fibrotic or necrotic changes of resected LNs in the cN1 NSCLC patients. **Method:** cN1 NSCLC patients who underwent complete resection with or without iCRT at our institution between January 1999 and December 2016 were subjected. We divided the enrolled patients into two groups as the primary surgery (PS) group and the iCRT followed by surgery (IC) group. As for IC group, we determined the pretreatment LN metastatic status based on the pathological features of resected LNs. We compared the clinical outcomes of pretreatment N1 involved patients with or without iCRT. **Result:** Among 127 cN1 NSCLC patients, 40 patients were considered as pretreatment N1 involvement, consisting of 26 and 14 patients in the PS and IC groups, respectively. The central type tumor and the continuous type of LN, which frequently required the extended surgical procedures, were significantly more frequent in the IC group than in the PS group ($P < 0.01$). Although there was no significant difference in the recurrence pattern between the two groups, none of patients developed local recurrence in the IC group. Regarding the patients with a centrally located tumor or a bulky LN (> 2.0cm), the 5-year recurrence-free survival was significantly better in the IC group than in the PS group (74.1% vs, 36.4%; $P = 0.03$). **Conclusion:** Our study demonstrated that iCRT followed by surgery could suppress the disease recurrence in the N1-involved NSCLC patients especially for the patients harboring a centrally located tumor or bulky LNs at N1 level, suggesting that these patients may be good candidates for iCRT followed by surgery to avoid extended resections and to suppress the local recurrence.

Keywords: induction chemoradiotherapy, non-small cell lung cancer, N1 lymph node metastasis

P1.17-18 TREATMENT FOR PATIENTS WITH T4 SUPERIOR SULCUS NON-SMALL CELL LUNG CANCER: A PROPENSITY-MATCHED ANALYSIS OF SEER DATABASE

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Background: Superior sulcus tumors (SSTs), a unique subgroup of locally advanced non–small-cell lung carcinoma (NSCLC), remain a great challenge for clinicians. T4 SSTs used to be a contraindication for operations, and the optimal treatment modality for T4 SS NSCLCs remains uncertain. The aim of our study is to evaluate the roles of surgical treatment and radiotherapy for patients with T4 SSTs. **Method:** We used the SEER database [1973-2015] to identify patients diagnosed with T4 stage SS NSCLC (according to 7th edition AJCC staging system) between 2004 and 2015, those with M1 disease were excluded. Propensity score matching with Kaplan-Meier and Cox proportional hazards model were performed to estimate prognosis. **Result:** A total of 384 patients were included (mean 66.4±11.71 years-of-age). Among them, the majority was male (59.4%) with lesions located in the left lung (52.3%) and diagnosed with IIIB stage (56.6%). 47 patients underwent cancer-directed surgery, and radiotherapy was received by 66.9% of patients. Median overall survival (OS) and lung cancer specific survival (LCSS) was 12 and 17 months, and 5-year OS, LCSS was 15.8%, 25.4%, respectively. In the matched population, the median survival outcomes were better with receipt of surgery (OS: 51.3 vs 35.1 months; p=0.049 LCSS: 67.1 vs 36.3 months; p=0.003). Multivariate Cox analysis showed that age ≧ 66 years (hazard ratio [HR] = 1.639, 95% confidence interval [CI] 1.214-2.213, p=0.001), unmarried status (HR = 1.356, 95% CI 1.023-1.798, p=0.034), tumor sized ≧ 6.0 cm (HR = 1.694, 95% CI 1.263-2.273, p<0.001) were associated with inferior OS. Cancer-directed surgery (HR = 0.537, 95% CI 0.337-0.855, p=0.009) and radiotherapy (HR = 0.644, 95% CI 0.472-0.878, p=0.006) were independent protective factors for patients with T4 superior sulcus NSCLC. However, neither adjuvant nor neoadjuvant radiotherapy was independent prognostic factor for those received surgery (p>0.05). Conversely, in the subgroup analysis, favorable impacts of radiotherapy were observed for non-surgery patients (OS: HR = 0.58, 95% CI 0.42-0.79, p<0.001; LCSS: HR = 0.55, 95% CI 0.37-0.75, p<0.001). **Conclusion:** Our study shows superior sulcus NSCLC patients with T4 stage have dismal prognosis. Surgical resection remains the optimal option for those with resectable disease. Moreover, for non-surgery tumors, the use of radiotherapy should be considered.

Keywords: propensity score matching, Superior Sulcus Tumors, non-small cell lung cancer

P1.17-19 CORRELATION OF DOSIMETRIC AND CLINICAL FACTORS WITH RADIATION PNEUMONITIS IN LUNG CANCER PATIENTS RECEIVED INVOLVED-FIELD IMRT

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Background: Radiation pneumonitis is a potentially fatal complication in lung cancer patients treated with definitive radiotherapy. The ability to identify patients at risk for this complication would be of value to clinicians. The objective of this study was to identify significant predictors of grade 2 or higher radiation pneumonitis. Previous reported studies mostly focused on extended-field three-dimensional conformal radiotherapy without image guided. The purpose of the study was to correlate clinical and dosimetric factors with the development of radiation pneumonitis in patients with lung cancer treated with involved-field image guided intensity modulated radiation therapy (IMRT). **Method:** 149 lung cancer patients treated with involved-field image guided IMRT were recruited. Potential predictive factors examined included age, gender, histology, stage, pulmonary function, KPS, radiation dose, surgery history, usage of chemotherapy. RP events were prospectively scored using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Kaplan-Meier analysis was used to determine the cumulative probability of RP of grade ≥ 2. Univariate and mutivariate analysis was used to determine predictors of grade 2 or higher pneumonitis. **Result:** Of the 149 patients, Median prescription dose was 60Gy. With a median follow-up of 9 months, 10 cases (6.7%) developed RP of grade 3 or higher level, 57 (38.3%) developed RP of grade ≥ 2 RP, and 90 (62.7%) of grade 1 or lower level. The median time of grade ≥ 2 RP was 2.6 months (range from 1 to 6 months). Grade ≥ 2 RP pneumonitis was correlated with age and volume of lung receiving 20 Gy (V20). Surgery had a bordline significant association with risk of grade≥ 2 RP pneumonitis. **Conclusion:** Age and V20 were significant predictors of grade≥2RP radiation pneumonitis in lung cancer patient treated with involved-field image guided IMRT, Surgery also had a bordline significant predictive value.

Keywords: Radiotherapy, Radiation pneumonitis, lung cancer

P1.17-20 EXCLUDING PTV FROM LUNG VOLUME MAY BETTER PREDICT RADIATION PNEUMONITIS FOR IMRT TREATED LUNG CANCER PATIENTS

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Background: Lung dose-volume histogram(DVH) could be calculated from multiple normal lung definitions. These dose differences have a direct impact on lung cancer radiotherapy treatment planning. Earlier study from 3D conformal radiation therapy suggested dose computation from total normal lung excluding gross tumor volume (GTV) may be

more accurate than that of excluding planning target volume (PTV). It is unclear which definition should be used to more accurately predict radiation pneumonitis (RP) in lung cancer patients treated with intensity-modulated radiation therapy (IMRT). We aim to determine a superior normal lung volume to more accurately predict symptomatic RP in lung cancer patients treated with IMRT. **Method:** This is a retrospective study. All patients treated with IMRT with at least 3 months follow-up are eligible. The normal lungs are defined by total lung volume excluding GTV, PTV or directly using the total lung volume. V5, V20, and MLD have been extracted for all three definitions. RP was diagnosed and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03. The primary endpoint was grade 2 or higher RP (RP2). Correlation between RP2 and dose parameters were analyzed by logistic regression. We compared RP prediction performance of each lung volume using area under the receiver operating characteristic curve (AUC). **Result:** A total of 184 consecutive patients treated between January 2014 and October 2017 were eligible, 26 patients (14%) developed RP2 within 3 months after treatment. Significant dosimetric difference was found between any 2-paired lung volumes (Ps<0.0001). All dose parameters from Lung-PTV method had significant correlation with RP2, with greater AUCs than the other two definitions. The best RP prediction performance was found in Lung-PTV volume MLD (AUC=0.649), which is significantly better than Lung-GTV volume MLD (AUC=0.611, P=0.006). **Conclusion:** There were significant dosimetric differences from various normal lung definitions. Excluding PTV method may accurately predict acute symptomatic radiation pneumonitis for IMRT treated lung cancer patients.

Keywords: Radiation pneumonitis (RP), Normal lung definitions, intensity-modulated radiation therapy (IMRT)

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-01 THE IMPACT OF ANLOTINIB ON BRAIN METASTASES OF NSCLC: POST-HOC ANALYSIS OF A PHASE III RANDOMIZED CONTROL TRIAL (ALTER0303)

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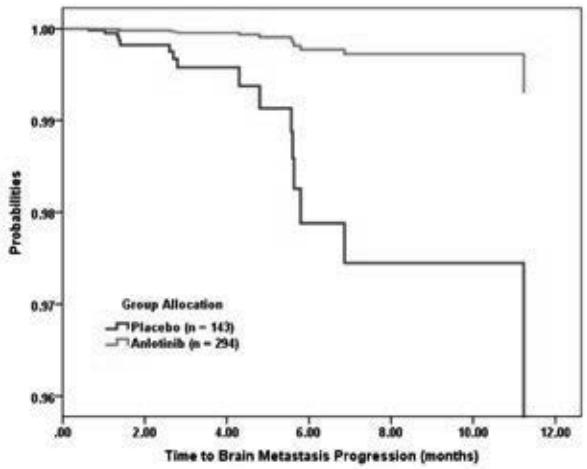
Background: Few evidence has measured the intracranial impact of multitargeted VEGFR-TKIs. Anlotinib hydrochloride, which targets VEGFR, PDGFR, FGFR and c-Kit, has been shown to significantly prolong PFS and OS compared with placebo as second/third-line treatment for NSCLC in a randomized, double-blind, phase III trial (NCT02388919). Herein we sought to analyze anlotinib's effect in managing brain metastases (BM) and its brain-associated toxicities. **Method:** The PFS/OS of anlotinib versus placebo in those with and without BM records at baseline were calculated and compared respectively. In addition, time to brain progression (TTBP), a direct indicator of intracranial control, was also compared between anlotinib and placebo. All calculations were adjusted for confounding factors, including stage, histology, driver mutation type, etc. **Result:** A total of 437 patients (294 receiving anlotinib; 143 receiving placebo) were included. 97 cases (22.2%) were recorded to have BM at baseline. There were more BM cases among younger patients and those with adenocarcinoma. Both of the benefit magnitude from anlotinib over placebo were similar between BM and non-BM group in terms of PFS (BM: HR 0.19, 0.11-0.34; non-BM: HR 0.29, 0.22-0.37; interaction P=0.691) and OS (BM: HR 0.71, 0.44-1.16; non-BM: HR 0.67, 0.51-0.89: interaction P=0.789). More specifically, anlotinib was associated with significantly longer TTBP (HR 0.11, 95% CI 0.03-0.41, P=0.001; Figure1) despite all confounders, indicating a 90% reduction of brain progression risk from anlotinib. Interestingly, anlotinib was also associated with more neural toxicities (18.4% vs. 8.4%, P=0.007) and psychological symptoms (49.3% vs. 35.7%, P=0.008) compared with placebo, especially headache (P=0.01), brain edema (P=0.04) but not infarction or cerebral hemorrhage. The above results were all confirmed both in intention-to-treat and per-protocol population.



Conclusion: Anlotinib can benefit NSCLC patients with brain metastases and is highly potent in managing intracranial lesions. Its special effect on brain metastases and cerebral tissues merits further investigation.

Keywords: advanced NSCLC, Anlotinib, Brain metastasis

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-02 OSIMERTINIB FOR EGFR-POSITIVE ADVANCED NSCLC WITH BRAIN METASTASES: PRELIMINARY ANALYSIS OF AN OPEN-LABEL, TWO-ARM, PHASE 2 STUDY

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Background: Osimertinib is an *EGFR* tyrosine-kinase inhibitor (TKI) selective for both *EGFR* TKI sensitizing and Thr790Met resistance mutations. While intracranial activity of osimertinib was observed in *EGFR*-mutant NSCLC in larger trials, a study focusing on patients with brain metastases was not reported yet. **Method:** This phase 2, open-label, two-arm study enrolled patients with *EGFR*-mutant, advanced NSCLC and at least one asymptomatic brain metastasis. Treatment-naïve (arm A) and Thr790Met-positive patients who progressed on *EGFR*-TKI therapy (arm B) received osimertinib 80 mg QD. Dose escalation (160 mg QD) was performed in cases of intracranial progression without symptomatic systemic progression. The primary endpoint was intracranial metastasis response. The trial is ongoing (NCT02736513 at ClinicalTrials.gov) and here we present a preliminary analysis. **Result:** Between May 31, 2016, and November 30, 2017 (data cutoff), 20 patients started osimertinib (arm A=15, arm B=5). Median duration of follow-up was 43 weeks. Intracranial response was achieved in 11 (73%; 95% CI 45%-92%) of 15 arm A and in four (80%; 95% CI 28%-99%) of five arm B patients. Dose escalation was performed in four cases (arm A=2, arm B=2), with one continuous response (25%, 95% CI 5%-70%). Ten of 15 patients (67%) in arm A and one of five patients (20%) in arm B continue responding to osimertinib 80 mg at data cutoff. Median intracranial PFS (80 mg) was not available for arm A (95% CI 232 days–NA), and was 510 days in arm B (95% CI 161–not available). Toxic effects were similar to previous reported data. **Conclusion:** Osimertinib shows equal intracranial and systemic activity with minor side-effects in *EGFR*-mutant NSCLC as first-line, as well as in previously treated Thr790Met-positive patients. It might therefore be a reasonable treatment for these patient populations and defer brain radiotherapy.

Keywords: NSCLC, osimertinib, brain metastases

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-03 QUALITY OF LIFE OUTCOMES FOR FDA-APPROVED AGENTS IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Symptom control and quality of life (QoL) improvement are among the most important goals of systemic therapy in advanced NSCLC, but they are not required for regulatory approval. We reviewed published QoL data for agents approved for use in advanced NSCLC by the United States Food and Drug Administration (FDA) and explore their potential uses in the era of precision medicine. **Method:** Through systematic review, we identified 19 agents approved by the FDA for the treatment of advanced NSCLC between 1999 and 2017. Clinical trials associated with regulatory approval of these agents were identified. QoL results were abstracted from study publications, in addition to trial characteristics (phase, sponsor). **Result:** 46 trials were identified supporting the FDA approval of the 19 agents. Of these, 33 (72%) were phase 3 randomized trials (including 3 cooperative group studies) and 13 (28%) were early phase (I/II) trials. QoL data were reported for 27 trials (59%), including all cooperative group trials. Another 5 (11%) measured QoL but results were not published. The remaining 13 (24%) trials did not measure QoL, 8/13 are phase III, 3/13 phase II and 2 phase I. In trials that reported QoL outcomes, better global QoL and cancer-related symptoms were identified in 17/33 (51%) and 18/33 (55%), respectively. Time to symptom deterioration was reported in 18 (55%) studies, with all but one showing benefit for the approved agent. The remaining studies reported no significant difference in QoL between study treatment arms. All studies reporting improved QoL parameters also reported improved response rates. In trials demonstrating OS and PFS improvement, 3/14 and 10/21 reported better QoL outcomes, respectively. ORR was higher in 26 trials, and it was associated with improvement in QoL in 12/26. Of 12 early phase trials leading to drug approval based on response rate and duration, 6 reported improved QoL outcomes. Three have not yet

reported QoL data and 3 did not measure QoL. **Conclusion:** QoL is clearly associated with response rate but improved QoL or symptom control was only demonstrated in17/33 (51%) and 18/33 (55%) of studies supporting regulatory approval. QoL may be a clinically relevant endpoint for drug approval based on early phase trials of agents with high response rates and should be given further consideration by pharmaceutical sponsors and regulators in this era of precision medicine.

Keywords: Quality of life, Lung cancer, Drug approval

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-04 REDUCING TIME TO MOLECULAR DIAGNOSIS FOR ADVANCED NSCLC IN THE CONTEXT OF A REFERENCE TESTING CENTER

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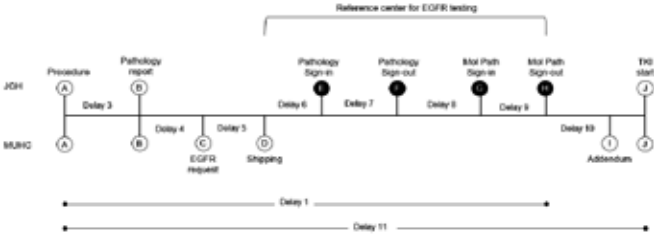
Background: Testing for mutation of the epidermal growth factor receptor (EGFR) gene is required for treatment of patients with advanced non-small cell lung cancer (NSCLC). First-line treatment with an EGFR tyrosine kinase inhibitor (TKI) in NSCLC patients with an activating EGFR mutation significantly impacts survival. Within the Rossy Cancer Network, the McGill University Health Centre (MUHC) has a supra-regional designation to perform all thoracic surgeries, while the Jewish General Hospital (JGH) is the reference testing center for specialized molecular pathology services. Significant differences in time to TKI therapy were noted between these centers. Our objective was to identify contributing factors to reduce network-wide delays. **Method:** We used the JGH molecular pathology database to identify all specimens tested for EGFR between 2015 and 2016 and mapped the process steps from diagnostic procedure to start of TKI therapy. We identified process differences and initiated reflex testing at the MUHC; EGFR testing was ordered reflexively by pathologists for all non-squamous NSCLC biopsies and other specimens from known or suspected advanced stage NSCLC. **Result:** Implementation of reflex testing led to a 13-day reduction from pathology report to EGFR request (Figure 1, BàC). We subsequently identified that MUHC time from molecular results to start of TKI therapy was twice that of the JGH (24 vs 12 mean days). This was due to an additional step requiring integration of faxed molecular results into the patients' electronic health record.



Conclusion: We applied lean strategies to reduce time to initiation of targeted therapy. Within our network and in the context of a reference testing center, we identified two critical components that significantly contributed to delays in treatment planning: (i) absence of reflex testing and (ii) unlinked information technology systems. As Quebec moves towards specialized testing centers, it is important to be cognisant of their impact on timely treatment.

Keywords: Reflex testing, advanced NSCLC, EGFR

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-05 ADENOCARCINOMA OF THE LUNG: THE WOMAN'S CANCER?

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Background: We previously observed a significant interaction between sex and age-standardized incidence rates of Non-small cell lung cancer (NSCLC) patients showing higher rates of Adenocarcinoma (ADC) in women, from the systematic review of published studies within the last 20 years. Our analysis showed disparities across gender over time, and the main effect of gender on incidence rates is significant (p= 0.01). This study aimed to replicate observed sex-related disparities in published records using a 15-year retrospective analysis of a local large-scale database of NSCLC patients diagnosed in Southern Alberta, Canada. **Method:** We extracted data from the Glans-Look Lung Cancer Database, a comprehensive clinical and demographic database of all lung cancer patients diagnosed in southern Alberta from 1999-2015. We assessed the impacts of gender on NSCLC risks and mortality. Clinical data e.g. smoking history, histology and NSCLC stage were collected and analyzed using chi-square test, and smoking history and tumor stage were stratified for the analysis. The Kaplan-Meier analysis was conducted to compare gender-based post diagnosis survival and disease progression. Statistical significance was 95% confidence level ($p < 0.05$). **Result:** Among 7738 lung cancer patients, 95.6% (3743/7738) were NSCLC: 52% male and 48% female. Significant gender-based differences were observed in histology (p=0.00). SCC and ADC were the most frequent histology in both genders. However, ADC was commoner in women (49% vs 41%), while SCC was commoner in men (27% vs 17%). Relative changes of ADC rate over 15 years have increased significantly among women compared to men (58% vs 32%, $P<0.02$). The risk of developing NSCLC was greatly elevated with cigarette consumption in both genders; however, ADC in never smokers was higher in women (18%) compared to men (8%). Among ADC, smoking history and gender both showed a significant effect on survival, where mOS for never-smokers females exceeded that of never-smokers males [20 months vs 14 months, 95%CI, $P=0.00$]. The same trend was also seen in smokers [13 months vs 7 months, 95%CI, $P=0.021$]. In addition, the OS among male ADC cases was significantly lower than women of all tumor stages ($P=0.00$), but these disparities were insignificant across genders with SCC ($P=0.46$). **Conclusion:** Similar to what we observed in our systematic review, gender influences the clinical course of NSCLC regardless of smoking history or stage in Southern Alberta. Identifying the cause of the increase in ADC rate over 15 years in women and higher prevalence of NSCLC in never smoking women warrants aggressive research strategies.

Keywords: NSCLC, Gender, Adenocarcinoma

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-06 HSP72 EXPRESSION ASSOCIATES WITH SURVIVAL IN EGFR MUTATED NSCLC

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Background: Heat shock protein 72 (HSP72) was observed to be important for editing DNA replication errors and repairing base damage. EGFR mediates HSP72 Y41 stability via phosphorylation. EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy inhibited phosphorylation of HSP72 leads to its degradation with suppression of polymerase α (Polα) and a resultant increase in overall mutation rate in EGFR mutant lung cancer cells. Our primary objective was to determine if baseline HSP72 expression is a prognostic biomarker for NSCLC patients with *EGFR* mutant NSCLC. **Method:** A retrospective cohort of patients was identified with known *EGFR* mutation positive NSCLC and available tissue from the City of Hope Comprehensive Cancer Center seen between 2008 and 2016. Immunohistochemical (IHC) analysis was performed to analyze HSP72 levels. A chi-square test for categorical data and multivariate logistic regression analyses was used to study the relation between HSP72 expression and the other clinical and demographic data. **Result:** 48 patients with *EGFR* mutated NSCLC and available tissue were identified. The median age was 64 range (39-84) with 50% Asian (n = 24), Caucasian 38% (n = 18), and African American 8% (n = 4) and other 4% (n = 2). Most patients were Stage IV at initial diagnosis (n = 41, 85%), other were Stage IB (n = 2), Stage IIB (n = 1), Stage IIIA (n = 1) and Stage IIIB (n = 3). HSP72

expression was 0 in 16 patients, 1 in 15 patients, 2 in 9 patients and 3 in 8 patients. Median survival of HSP72 0, 1, 2,3 were 28.3, 42.4, 41.2, and 107.7 months respectively ($p < 0.02$, log-rank test). In univariate Cox regression analysis, HSP72 expression of 3 compared to others correlated with an HR of 0.23 (95% CI 0.07-0.77). When stratifying by stage (Stage IV vs all others), the HR associated with an HSP72 expression of 3 was 0.22 (95% CI 0.05-0.97), and the signal for HSP72 was also significant when stratifying by stage and considering HSP72 score as either a continuous marker or as the four categories (0,1,2,3). There was no relationship noted in the change in HSP72 values as tumors transformed from T790M- to T790M+, and no relationship related to L858R or exon 19 deletions. **Conclusion:** In *EGFR* mutated NSCLC, high levels of HSP72 expression are associated with improved survival. Further investigations are evaluating mechanisms of increased DNA damage following EGFR TKI therapy and association with the development of resistance.

Keywords: EGFR, HSP72, non-small cell lung cancer

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-07 SAFETY AND EFFICACY OF LATTICE RADIOTHERAPY IN VOLUMINOUS NON-SMALL CELL LUNG CANCER: A RETROSPECTIVE STUDY OF 10 PATIENTS OVER 7 YEAR PERIOD

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Background: Lattice radiotherapy (LRT) is a novel technique of delivering heterogeneous doses of radiation for the management of voluminous tumors which are not amenable to surgical resection. Built from the conventional 2-dimensional GRID, LRT utilizes the power of new technology in the field of radiation therapy to implement 3-dimensional dosimetry plans. LRT allows delivery of higher doses of radiation to small spheres, also called vertices, in the interior of the bulky tumors limiting the exposure of surrounding healthy tissue to unacceptably high doses of radiation. **Method:** Ten patients with non-small cell lung cancer (NSCLC): Nine males and 1 female, with ages from 49 to 87 with a median of 70 who presented with bulky, unresectable primary tumors were treated with LRT during a 7-year period. Follow-up ranged from 4 to 73 months with a median of 10 months. All patients received one initial LRT fraction of 18 Gy in the lattice vertices and 3 Gy in the tumor periphery. All patients continued treatment with conventional radiation given in 25 to 33 daily fractions of 1.8 Gy to 2 Gy each. Image guided radiation therapy IGRT with CBCT and Volumetric Arc Therapy technique were used in all patients. **Result:** There was no associated morbidity or mortality to the addition of LRT in these patients. There was a significant decrease in tumor volume from the time of planning CT to the last f treatment imaging. **Conclusion:** In this early experience, LRT appears to be a safe and effective modality of treatment for bulky NSCLC. LRT should be considered for non-surgical patients presenting with voluminous tumors. It is postulated that this technique induces changes in the tumor microenvironment leading to a more effective tumor control. More research is needed to elucidate the mechanisms by which LRT is effective in the reduction of tumor size.

Keywords: Voluminous Tumors, Lattice Radiotherapy, GRID Therapy

P2.01 ADVANCED NSCLC
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P2.01-08 CONVERSION SURGERY FOR LOCALLY ADVANCED LUNG ADENOCARCINOMA HARBORING DRIVER GENE MUTATION AFTER TKI FOLLOWED BY CYTOTOXIC AGENT

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Background: The optimal treatment of locally advanced non-small cell lung cancer including stage IIIA still remains controversial. For lung adenocarcinoma harboring driver gene mutation, it has been reported that tyrosine kinase inhibitor (TKI) shows great tumor response and downstaging. Moreover, some reports showed its usefulness of salvage surgery after TKI treatment. **Method:** Between January 2016 and April 2017, we performed surgical resection for five non-small cell lung cancer patients who underwent TKI followed by platinum agent and pemetrexed treatment at Kagoshima University Hospital. All patients were diagnosed as having c-stageIIIA (three patients with c-T2aN2M0 and each one patient with c-T4N1M0 and c-T3N2M0) lung adenocarcinoma harboring driver gene mutation (four patients with EGFR mutation and one patient with EML4-ALK rearrangement) by preoperative examinations (Computed Tomography, 18F-fluorodeoxyglucose Positron Emission Tomography, brain Magnetic Resonance Imaging and bronchoscopic examination). Because these patients initially had locally advanced tumor burden or mediastinal lymph nodes metastasis, one-stage radical surgery would not have been feasible. Therefore, these patients received TKI administration for less than six months, followed by two cycles of platinum agent and pemetrexed treatment before the operation. After the operation, three patients received two or four cycles platinum agent and pemetrexed treatment, however, the other two patients did not receive additional treatment. We obtained informed consent from all the patients before the beginning of treatment. **Result:** In all patients, the effect on tumor response of TKI followed by platinum agent and pemetrexed treatment was shown. In addition, the complete resection was confirmed microscopically. None of these patients experienced disease flare after stopping TKI administration. The exon 20 T790M mutation gene was not found in all resected specimens with EGFR mutation. There were no postoperative major complications and mortality. Brain metastasis appeared in one patient who did not receive postoperative chemotherapy six months after the operation. This patient was managed successfully with gamma knife radiotherapy. All the five patients are now under follow-up treatment with no local recurrence. **Conclusion:** Conversion Surgery after TKI followed by platinum agent and pemetrexed treatment can become feasible and useful strategy for locally advanced lung adenocarcinoma harboring driver gene mutation.

Keywords: Conversion Surgery, locally advanced lung adenocarcinoma, driver gene mutation

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-09 TARGETABLE GENOMIC ALTERATIONS IN KRAS MUTANT LUNG ADENOCARCINOMA BY TARGETED NEXT GENERATION SEQUENCING

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Background: *KRAS* mutant (m) non-small cell lung cancer (NSCLC) represents 25% of cases. Despite the common mutation, biological and clinical behaviour of this disease is diverse. The aim of our study was to analyze co-occurring genomic alterations in advanced *KRAS*m lung by next-generation sequencing (NGS) and compare them to a *KRAS* wild-type (WT) population. **Method:** Advanced lung adenocarcinoma patients treated with a platinum doublet with *KRAS* mutation by Sanger were submitted to targeted NGS with the Oncomine Solid Tumor kit (DNA) and compared to a KRAS WT population of clinically similar patients. Association with outcome of the genomic alterations was evaluated. **Result:** 32 *KRAS*m patients and 18 WT patients were analyzed. The most frequent *KRAS* mutation was p.Gly12Cys (45%), followed by p.Gly12Val (24%). *TP53* mutation was observed in 55% of *KRAS*m tumors and 60% of WT cases (Table 1). Mutations in *STK11* were found in 10% of cases in the *KRAS* mutant cohort while none in the WT. 3 out of the 4 cases of *STK11* mutations coexisted with *TP53* mutations. *FGFR3, SMAD4* and *DDR2* mutations were more frequently found in cases with *KRAS* mutations, although at low frequencies. Neither *KRAS* nor *TP53* mutations had an impact in OS. We then selected the *KRAS* mutant cohort and evaluated the impact of co-mutations. *TP53* or *STK11* did not significantly affect OS of *KRAS* mutant patients. **Table 1. Co-ocurring alterations in KRAS mutant and WT tumors**

Mutations/CNG	KRAS mutant % (N: 38)	KRAS WT % (N: 15)
TP53 mut	55%*	60%*
STK11 mut	10%**	0%
FGFR3 mut	13%	6%
SMAD4 mut	8%	0%
DDR2 mut	5%	0%
MYC mut	5%	6%
KRAS CNG	8%	6%

Conclusion: *KRAS*m lung adenocarcinoma is genomically diverse. NGS provides biologically relevant information and druggable targets in this subset of patients.

Keywords: kras mutation, next generation sequencing, Targeted therapy

P2.01-10 PROGNOSTIC IMPACT OF LONGITUDINAL MONITORING OF RADIOMIC FEATURES IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Tumor growth dynamics varies substantially in non-small cell lung cancer (NSCLC). We aimed to develop novel biomarkers reflecting longitudinal change of radiomic features in NSCLC and evaluate prognostic power of those. **Method:** Fifty-three patients with advanced NSCLC included in this retrospective study. Measurable lesions on baseline and follow-up computed tomography (CT) were segmented and 23 radiomic features were extracted. All three variables reflecting patterns of longitudinal change were extracted: the area under the curve (AUC), beta value, and AUC2. We constructed models for predicting survival using multivariate cox regression, and identified the performance of these models. **Result:** In volume, AUC2 showed an excellent correlation with pattern of longitudinal volume change (r = 0.848, $p < 0.000$), and showed a significant difference in overall survival time ($p = 0.035$). In multivariate regression analysis, kurtosis of positive pixel values ($p < 0.000$), and surface area ($p = 0.001$) on baseline CT, and AUC2 of density ($p < 0.000$), skewness of positive pixel values ($p = 0.003$), and entropy at inner ($p = 0.001$) were found to be associated with overall survival time, and the area under the receiver operating characteristics curves were 0.922, and 0.771 at 1 year, and 3 years of follow-up. **Conclusion:** Longitudinal change of radiomic tumor features would be prognostic biomarkers in patients with advanced NSCLC.

Keywords: Prognosis, follow-up, Radiomics

P2.01-11 CHARACTERISTICS OF NON-SMALL CELL LUNG CANCER: DIFFERENCES BY SEX AND HORMONAL STATUS IN A HISPANIC POPULATION

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Background: Non-small Cell Lung Cancer (NSCLC) appears to be a different disease between women and men. Clinical features and lung cancer behavior by sex and particularly by hormonal status has been poorly approached. We describe the differences in NSCLC by sex and by hormonal status among women in a Hispanic population. **Method:** We performed a retrospective study among NSCLC patients from the National Cancer Institute of Mexico. We assessed clinic-pathological (tobacco, wood smoke and asbestos exposure, histology, disease stage, ECOG, Body Index Mass, Metastases sites) and molecular characteristics (EGFR and KRAS mutation profile). Overall survival (OS) according to sex and hormonal status were estimated using the Kaplan-Meier method and compared using the Log-rank test. Multivariate cox-proportional analysis was performed adjusting for clinical and statistically relevant features. **Result:** Among the 1,104 patients 52.7% were men and 47.3% were women. **C**ompared to men, women were more likely to be non-smokers (68% vs. 23%, p<0.001), reported higher frequencies of wood-smoke exposure (50% vs 28.2%, p<0.001), and of EGFR-sensitizing mutations (38.8% vs 18.7%, p<0.001), had a better ECOG performance (<2) (76.2% vs 69.9%, p=0.020) and showed a higher frequency of BMI ³25 (48.4% vs 41.5% p=0.003). Likewise, women, showed better OS (p=0.021) compared to men as well as overweight patients (vs. normal or obese patients) (p=0.045), non-smokers (p=0.002) and patients with lower ECOG status (p=0.006). Differences were found also when considering hormonal status. Postmenopausal women showed higher wood-smoke exposure (52.5% vs 41.7%, p=0.037) and wood-smoke exposure index (113.2% vs 50.6%, p=0.006) as well as tobacco smoking exposure index (19.8 vs 10.2, p=0.017) compared to premenopausal younger women who exhibited higher frequencies of exposure to asbestos (16.7% vs 7.0%, p=0.001) compared to postmenopausal. OS was better in postmenopausal women compared to premenopausal (31.1 vs 19.4 months, p=0.046). No differences were found between premenopausal and postmenopausal women stratified by EGFR mutation status regarding their clinic-pathological and molecular characteristics, neither in the OS. **Conclusion:** Our results support the differences in lung cancer presentation by sex and also by hormonal status. It is important to highlight that wood-smoke exposure and tobacco consumption were associated with hormonal status. Furthermore, premenopausal women (which showed a younger age at diagnosis) showed a worse OS regardless of other molecular features (e.g. EGFR, KRAS) which highlights the need of investigating in detail hormonal profiles when considering the clinical approach of NSCLC diagnosis and treatment.

Keywords: postmenopausal, premenopausal, Women

P2.01-12 RAMUCIRUMAB+DOCETAXEL USAGE FOLLOWING RAPID DISEASE PROGRESSION IN REAL WORLD ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: In the Phase III REVEL study, the overall treatment effect of ramucirumab+docetaxel (ram+doc) in patients with rapid disease progression (RDP), defined as disease progression ≤ 12 weeks after start of prior platinum-based chemotherapy, was consistent with that observed in the intent-to-treat population. This real-world, retrospective study described baseline characteristics, treatment patterns, and clinical outcomes among RDP patients subsequently treated with ram+doc in the United States. **Method:** Advanced non-small cell lung cancer (aNSCLC) patients receiving ram+doc as 2nd line or 3rd line therapy between March 2015 - May 2017 after platinum-based chemotherapy, with ≥ 3 months of potential follow-up, were identified in the Flatiron Health EHR-derived database. Analyses were conducted for RDP and non-RDP patients. Overall survival (OS) was measured from start of 1st line therapy. Real-world progression-free survival (rwPFS) and time-to-progression (rwTTP) were measured from start of ram+doc. OS, rwPFS, and rwTTP were estimated using Kaplan-Meier method. **Result:** Baseline characteristics were generally similar across RDP (n=49) and non-RDP (n=123) patients with respect to age, gender, and race. Non-RDP patients more often had stage IV disease at diagnosis and non-squamous histology. Among patients with ECOG performance status (PS) reported (n=101, 58.7%), a higher proportion of RDP patients had ECOG PS ≥ 2 (18.4%) than non-RDP patients (9.8%). The majority of patients received ram+doc as 3rd line therapy and the median duration of ram+doc treatment was similar for RDP and non-RDP patients. The most frequently administered chemotherapy regimen prior to ram+doc was carboplatin+pemetrexed for RDP patients and carboplatin+pemetrexed+bevacizumab for non-RDP patients. RDP was associated with shorter median OS (13.2 [95% CI: 10.3 - 15.8] vs. 21.6 [95% CI: 17.1-24.1] months, log-rank $P < 0.01$) whereas median rwPFS (3.0 [1.8 - 4.1] vs. 3.6 [2.9 - 4.1] months, log-rank $P = 0.74$) and median rwTTP (4.6 [95% CI: 3.5 - 7.9] vs. 5.5 [95% CI: 4.1 - 7.4] months, log-rank $P = 0.81$) on ram+doc were similar between the RDP vs. non-RDP groups, respectively. **Conclusion:** While this real-world cohort shows that RDP correlates with poorer OS, similar rwPFS and rwTTP were observed with ram+doc among aNSCLC patients with RDP vs. non-RDP. This study did not assess the effects of ram+doc vs. other subsequent treatments in patients with RDP. Further research is needed to identify RDP risk factors and to aid in development of optimal treatments for aNSCLC patients with the most aggressive disease.

Keywords: ramucirumab, NSCLC, rapid progression

P2.01-13 NUMBER, RATHER THAN LOCATION OF METASTASES, DICTATES OUTCOME IN STAGE IV, M1B, NON-SMALL CELL LUNG CANCER

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Background: To assess the impact of location versus number of extra-pulmonary metastatic sites (EPMS) on survival in stage IV non-small cell lung cancer (NSCLC). **Method:** A large scale, multi-year retrospective

analysis was conducted on patients with a new diagnosis of stage IV, M1b (AJCC 7th edition) NSCLC between 1999-2013. Demographic, clinical, histopathological, treatment and outcome data was extracted from the Canadian institutional Glans-Look Lung Cancer Database. We assessed the impact of location and number of EPMS and identified correlates of overall survival using the Kaplan-Meier method and Cox regression. **Result:** A total of 2,065 NSCLC patients with EPMS were identified. Median age was 67 (IQR 58-75) years, 52% were male, and 78% reported a history of smoking. 60% had one EPMS, and 40% had two or more EPMS. Among those with only one EMPS, most frequent organ involvement included bone (40%), brain (32%), liver (13%) and adrenal (10%). Median overall survival (mOS) was worst in those with liver metastasis and best in those with adrenal metastasis (2.0 vs. 5.2 months, p=0.015). However, outcomes based on organ site involvement did not retain prognostic significance in multivariable analysis after controlling for other measured confounders. Compared to patients with one EPMS, individuals with ≥ 2 EPMS experienced worse outcomes (mOS 3.9 vs 2.9 months, p<0.001), and were associated with worse prognosis in Cox regression analysis (HR 1.5, 95%CI 1.3-1.7, p<0.001). A statistically and clinically significant inverse relationship persisted between increasing number of EMPS sites and mOS. Those patients who received systemic anti-cancer therapy or surgical resection of metastatic disease (received by 25% and 3% of total cohort respectively) demonstrated the most improved mOS, regardless of number or location of EMPS (10.0 vs 2.0 months, p<0.001, and 9.0 vs 3.0 months, p<0.001, respectively). **Conclusion:** We conclude that number, rather than location of EPMS is a prognostic factor in patients with stage IV M1b NSCLC. A simple count of metastatic sites at diagnosis may be of clinical value in in the management and advanced care planning for patients with metastatic NSCLC. Of note, this could assist in identification of patients who would benefit from either more aggressive treatment or best supportive care, and may be an important consideration in future clinical trial design. Overall, this study reinforces the need to advance efforts to determine and mitigate the factors predisposing patients to develop metastatic disease, and develop initiatives to reduce the number of patients presenting with advanced disease.

Keywords: number and location of metastases, extra-pulmonary metastases, Survival outcomes

P2.01 ADVANCED NSCLC
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P2.01-14 PREFERRED AND ACHIEVED GOALS OF PATIENTS WITH METASTATIC LUNG CANCER AND THEIR ONCOLOGISTS IN END-OF-LIFE THERAPY

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Background: Systemic therapy with chemotherapy, immunotherapy or targeted therapy are possible treatments for patients with metastatic lung cancer (stage IV NSCLC). This palliative treatment might prolong survival and reduce symptoms but frequently causes side-effects which may decrease their quality of life (QOL). Little is known about patients' and oncologists' goals before starting a new therapy. Therefore, we studied the goals patients and their oncologists have before starting a new treatment for stage IV NSCLC and to what extent these goals are achieved. **Method:** Patients with stage IV NSCLC were prospectively studied in three hospitals between November 2016 and April 2018. At the start of systemic therapy patients and their oncologists were asked to complete a questionnaire about their treatment goals. These open questions were coded by the investigators. After treatment patients and oncologists were asked to what extent the goals they mentioned before were achieved. The data collection has not been finished yet. Now we report the preliminary results of 240 patients and their oncologists on predefined goals and of 90 patients (whose treatment was finished) and oncologists on achieved goals. **Result:** Patients and oncologists most often mentioned improvement in QOL (49%;74%), a decrease in tumor size (44%;68%) and life prolongation (43%;50%) as treatment goals. 19% of the patients mentioned cure as a treatment goal. According to patients life prolongation and improvement in QOL were achieved in 56% and 51% respectively. According to oncologists this was only 35% and 32% respectively. **Conclusion:** Patients and oncologists mention improvement in QOL, decrease in tumor growth and life prolongation most often as treatment goals. It can be questioned whether the 19% of the patients who mentioned cure as a treatment goal think this is a realistic goal or that it is more a sign of hope. After treatment, patients were more optimistic about the treatment effects than their oncologists.

Keywords: quality of life, goals, achievement

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-15 A RADIOLOGIST-LED TRAINING WORKSHOP FOR MR BASED NORMAL TISSUE AND TUMOUR DELINEATION FOR LUNG CANCER RADIOTHERAPY.

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Background: A potential benefit of MR-image guided radiotherapy (MRIgRT) in lung cancer is the reduction of treatment related uncertainties through improved soft tissue contrast. However, this benefit may be obscured by inter-observer variation in gross tumour volume (GTV) and organ at risk (OAR) contouring. A radiologist led workshop was organised to provide training in such contouring on MR. **Method:** Planning CT, PET-CT and MRI were acquired in four lung cancer patients. MR sequences included 3D radial gradient echo, T2 DIXON Turbo Spin Echo (TSE), and T2 TSE with and without fat-sat. Data sets were local rigidly registered and imported into the so-called "Big Brother" contouring software. The radiologist led teaching on OAR and GTV contouring used an MR lung atlas (produced by this group). Seven radiation oncologists contoured the brachial plexus (BP), heart, proximal bronchial tree, oesophagus and GTV. This was followed by a multi-disciplinary group discussion (oncologists, radiologists and physicists) on the contouring challenges and subsequently contours were reviewed and the atlas adjusted. **Result:** The BP and heart were the most difficult OARs to contour and showed the largest inter-observer variation. Following contour review and discussion between radiologist and oncologists updates to atlas and protocols were made. The GTV was found to be most challenging at the soft tissue interfaces and requires further work (Figure 1).

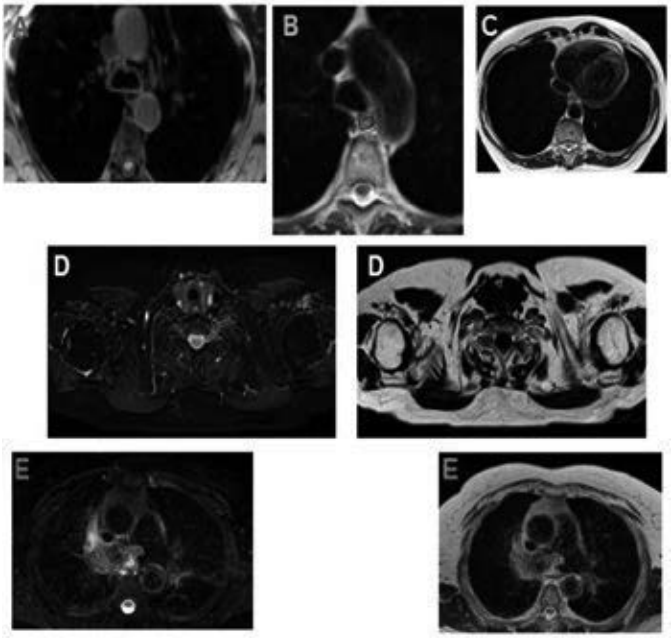

Figure 1. *'Big-Brother' evaluation of inter-observer variation of OAR and GTV delineations in lung cancer;* (A) **Proximal bronchial tree** on 3D Radial GE; (B) **Oesophagus** on T2 TSE without fat sat; (C) **Heart and pericardium** on T2 TSE with fat sat; (D) **Brachial plexus** on DIXON TSE; (E) **GTV 'technically challenging case'** delineated on T2 TSE with and without fat sat.

Conclusion: This early work demonstrates the need for radiologist-led training in OAR and GTV contouring in lung cancer patients using MR images. This will be especially important for the integration of MR into treatment planning and an MRIgRT adaptive workflow. We have arranged future workshops in order to provide further training and to assess inter-observer variation in OAR and GTV contouring using MR on more cases.

Keywords: MRI, Image Guided Radiotherapy, contouring

P2.01-16 DYNAMIC CTDNA MONITORING REVEALED NOVEL RESISTANCE MECHANISMS AND RESPONSE PREDICTORS OF OSIMERTINIB TREATMENT IN EAST ASIAN NSCLC PATIENTS

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Background: Advanced NSCLC patients, harboring *EGFR* T790M, exhibit marked diversity in tumor behavior and response to AZD9291, yet a discriminable molecular profile remains elusive. In addition, although *EGFR*C797S was involved in 30% of AZD9291 resistance cases in Western patients, mechanisms for the rest patients remain unclear, especially for the East Asian population. We utilized circulating tumor DNA (ctDNA) profiling to conduct dynamic monitoring in patients undergoing AZD9291, thus characterizing mutational heterogeneity and genomic evolution. **Method:** Longitudinal plasma samples were collected before, during and post of the AZD9291 treatment in Chinese NSCLC patients with acquired T790M mutation. A ctDNA panel, spanning 160KB of human genome, was used to perform capture-based targeted sequencing that comprises critical exons and introns of 168 genes. The EGFR mutation abundance and dynamic changes of allele fraction (AF) were analyzed with progression-free survival (PFS) after AZD9291 treatment. **Result:** A total of 61 samples were collected longitudinally from 14 patients, of which 9 have experienced progressive disease (PD). Six patients exhibited a rebound of ctDNA prior to radiographic PD, suggesting the potential of ctDNA in early detection of PD. Several acquired mutations were detected with the AZD9291 resistance, including newly identified EGFR G796S, L792H/F/R/V, V802F, V843I mutations, expect for the previously reported RB1 and EGFR C797S, L718Q mutations. Patients with a higher ratio of T790M and *EGFR*activating mutation at baseline had a significantly longer PFS (9.6m vs 4.5m, p=0.008). A lower ratio of *EGFR*activating mutation AF compared to baseline at first follow-up was significantly correlated with a longer PFS (8.5m vs 5.0m, p=0.027). Furthermore, patients harboring other known driver mutations in addition to T790M at baseline had an inferior PFS (4.9m vs 7.8m, P=0.039). **Conclusion:** Several novel resistance mechanisms were identified by ctDNA monitoring in the East Asian patients treated with AZD9291. Relative AF of T790M, changes of AF after treatment and the presence of concurrent driver mutations at baseline could predict clinical benefit of AZD9291 treatment.

Keywords: circulation tumor DNA, Acquired resistance, EGFR TKI

P2.01-17 MALAT1-MIR-101-SOX9 FEEDBACK LOOP MODULATES THE CHEMO-RESISTANCE OF LUNG CANCER CELL TO DDP VIA WNT SIGNALING PATHWAY

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Background: Cisplatin (DDP)-based chemotherapy is a standard strategy for lung cancer, while chemo-resistance remains a major therapeutic challenge. Recent evidence highlights the crucial regulatory roles of long non-coding RNAs (lncRNA) in tumor biology. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) has important roles in regulating the proliferation, invasion and migration of lung cancer cell. **Method:** 1. Tissue samples, cell lines and reagents 2. RNA extraction and SYBR green quantitative PCR analysis 3. MTT assay and BrdU incorporation assay 4. Western blot analysis 5. RNA immunoprecipitation 6. Chromatin immunoprecipitation (ChIP) 7. Luciferase reporter assay 8. Statistical analysis **Result:** High MALAT1 expression in lung cancer was related to poorer clinicopathologic features in this study. MALAT1 knockdown alone was sufficient to amplify DDP-induced repression of cell viability. MALAT1 knockdown could also sensitized DDP-resistant lung cancer cells (A549/DDP and H1299/DDP) to DDP. Further assays indicated that MALAT1 acted as a competing endogenous RNA to upregulate SOX9 expression by sponging miR-101 in DDP-resistant cancer cells, through Wnt signaling pathway. Moreover, SOX9 could bind to the promoter of MALAT1 to activate its transcription. **Conclusion:** Taken together, MALAT1, miR-101 and SOX9 form a feedback loop to enhance the chemo-resistance of lung cancer cell to DDP; this MALAT1-miR-101-SOX9 feedback loop plays an important role in the chemo-resistance of lung cancer cell to DDP and may serve as a potential target for cancer treatment.

Keywords: Chemo-resistance, MALAT1, NSCLC

P2.01-18 DIFFERENTIAL MOLECULAR MECHANISMS ASSOCIATED WITH DRAMATIC AND GRADUAL PROGRESSION IN NSCLC PATIENTS WITH INTRATHORACIC DISSEMINATION

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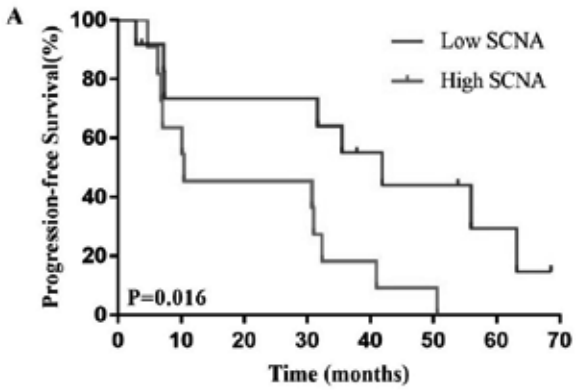
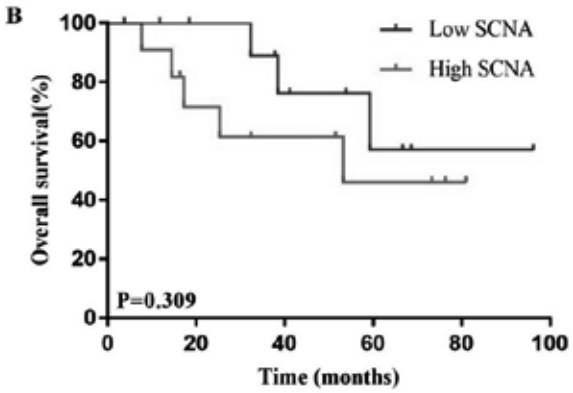
Background: Lung cancer is a highly heterogeneous disease with diverse clinical outcomes. The pleural cavity is a frequent metastasis site of proximal lung cancer. Better understanding of its underlining molecular mechanisms associated with dramatic and gradual progression of pleural metastasis in patients with non-small cell lung cancer (NSCLC) is essential for prognosis, intervention and new therapy development. **Method:** We performed whole-exome sequencing (WES) of matched primary lung adenocarcinoma and pleural metastatic tumors from 26 lung cancer patients with dramatic progression (DP, n=13) or gradual progression (GP, n=13). Somatic alterations at both genome-wide level and gene level were detected. Kaplan-Meier survival analysis and multivariate Cox regression models were applied to analyze the association between different somatic alterations and clinical parameters. **Result:** We first analyzed the differences in somatic alterations between AP and RP group in the primary tumors, and identified higher somatic copy number alteration (SCNA) level in DP group compared to GP group, which is significantly (p=0.016) associated with poorer progression-free survival (PFS). More specifically, patients with chromosome 18q loss in the primary tumor showed a trend (p=0.107) towards poorer PFS. *PTEN* (p=0.002) and *GNAS* (p=0.002) mutations are enriched in the primary tumors of DP group, and are associated with poorer PFS. Furthermore, pleural metastatic tumors harbor a relatively higher level of mutation burden (p=0.105) and significantly increased SCNA (p=0.035) compared to the primary tumors. **Conclusion:** NSCLC patients in the attenuated progression group have more stable genomes. High level of genomic instability, *GNAS* and *PTEN* mutations, as well as chromosome 18q loss are associated with rapid progression.





Keywords: NSCLC, genome instability, prognosis biomarker

P2.01-19 RADIOMICS FEATURES OF CONTRAST ENHANCED CT AS PROGNOSTIC FACTORS IN RESECTABLE ADENOCARCINOMA OF LUNG

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Background: To identify radiomics features as prognostic factors in patients with adenocarcinoma of lung and assess its incremental value to the traditional staging system and clinical-pathologic risk factors. **Method:** Total 1085 patients who underwent surgery for lung adenocarcinoma were enrolled in this study (from March 2010 to December 2014, training cohort: n = 749; from January 2015 to February 2016, temporal validation cohort: n = 336). A subset of 80/94 reproducible radiomics features including shape, first order statistics and texture features were identified reproducible and selected for analysis. A radiomics signature to predict (overall survival, OS and recurrence free survival, RFS) was generated by using the least absolute shrinkage and selection operator, or LASSO in training cohort. Association between the radiomics signature and prognosis was explored. Prognostic models incorporating radiomics signature alone and combined clinical-pathologic risk factors including staging system, age, sex, smoking status and adenocarcinoma subtype were tested in the temporal validation cohort. **Result:** s: The radiomics signatures (constructed from 5 features identified from LASSO) were significantly associated with OS and RFS. Compared with traditional staging, the radiomics signature resulted in better performance for the estimation of OS (C-index for radiomic signature vs TNM staging = 0.726 vs 0.689 in training set, 0.798 vs 0.766 in validation set) and RFS (0.760 vs 0.722 in training set, 0.773 vs 0.751 in validation set) in both training and validation cohorts. The combined model of radiomic signature and clinical-pathologic risk factors showed a significant improvement of predictive performance over the TNM staging system in both training and validation cohorts (OS, C-index = 0.774 in training set and 0.857 in validation set; RFS, C-index = 0.796 in training set and 0.837 in validation set; for all, $p < 0.05$). **Conclusion:** Contrast enhanced CT-based radiomics provided improved prognostic prediction in resectable lung adenocarcinoma, which might enable a step forward precision medicine and affect personalized postoperative treatment strategies.

Keywords: Radiomics, lung cancer, Prognosis

P2.01-20 FLT-PET FOR DETECTION OF RELAPSE FOLLOWING RADIOTHERAPY FOR LUNG CANCER. PRELIMINARY RESULTS

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Background: Differentiation of relapse from radiation induced changes of the normal lung tissue following radiotherapy for lung cancer is challenging. CT and ^{18}F-fluorodeoxyglucose (FDG) PET/CT has low specificity due to radiation induced changes; and invasive procedures might be unfeasible due to small size, difficult location, or poor lung function. ^{18}F-fluorothymidine (FLT) is a PET tracer that correlates with proliferation. FLT-PET is more specific than FDG-PET and does not accumulate in inflammatory tissue. The aim of this study is to investigate if FLT-PET is a key to better diagnosis of relapse in this difficult situation. **Method:** Patients who had received definitive radiotherapy for lung cancer and who were suspected for having a relapse were included in this prospective clinical study. Patients underwent FDG-PET/CT and FLT-PET/low dose CT within 3 weeks. PET scans were evaluated visually on a 5-level scale, and the worst graded lung lesion in each patient was selected for semi-quantitative measurements. Reference standard was a retrospective expert analysis based on histology, subsequent imaging, conference decisions, and treatment within 6 months after inclusion. Descriptive statistics and diagnostic accuracy tests were conducted. **Result:** We present the results from the first 18 patients. All patients had been treated with definitive radiotherapy (66 Gy in 24 or 33 fractions), and 17 patients had concomitant or sequential chemotherapy. FLT-PET was performed 34-541 days after radiotherapy. 7 patients had no evidence of relapse during the follow up period. 11 patients were diagnosed with relapse based on positive biopsy (3), further progression on CT within 6 months (4), further metabolic progression on FDG-PET/CT and cytology suspicious for malignancy (1), progression on the initial FDG-PET/CT and treatment with response (1), or disseminated disease/bone metastases (2). Maximum standardized uptake value (SUV_{max}) of FDG and FLT were higher in the lesions with relapse. Mean FDG SUV_{max} in lesions with relapse vs benign lesions was 13.7 vs 4.9 (range: 4.0-18.0 vs 3.3-6.7). Mean FLT SUV_{max} in lesions with relapse vs benign lesions was 4.1 vs 2.7 (range: 1.8-6.3 vs 1.7-3.3). Sensitivity; specificity; positive predictive value (PPV); and negative predictive value of FDG-PET/CT vs FLT-PET were100%;57%;85%;100% vs 73%;100%;100%;78%. **Conclusion:** With a PPV of 100% FLT-PET is a promising non-invasive tool for diagnosing relapse after radiotherapy with the potential to obviate invasive procedures in some patients. Further validation is needed.

Keywords: Radiotherapy, relapse, FLT-PET

P2.01-21 ANTIGEN CASCADE TRIGGERING CORRELATES WITH PROLONGED SURVIVAL IN ADVANCED NSCLC PATIENTS UNDERGONE PD-1 BLOCKADE WITH NIVOLUMAB.

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Background: Programmed-cell-death receptor-1 (PD-1) blockade by Nivolumab mAb is a promising treatment for metastatic (m) NSCLC patients, which may yield dramatic improvement in benefit and survival. It acts by rescuing the antitumor activity of PD-1-inactivated tumor-infiltrating-lymphocytes, residual of a pre-existing immune-reaction naturally occurring or consequential to prior radio/chemo-therapy. T-cell rescue is indispensable for the immediate response to the treatment, however, in order to obtain a prolonged effect on patients' survival continuous immune-priming able to supply fresh immune-effectors with antitumor activity, appears to be indispensable. We have thus investigated, whether Nivolumab treatment is also able to promote antigen cascade and cross-priming measured as occurrence of auto-antibody and auto-immunity and whether these effects are predictive of positive outcome in mNSCLC patients **Method:** This is a multi-institutional retrospective study including ninety-eight mNSCLC patients who received Nivolumab therapy (3mg/kg every 15 days) between September 2015 and March 2018. These patients had received at least a previous line of platinum-based doublet +/- bevacizumab. Log-rank test and Mantel-Cox analysis were carried-out to correlate patients' PFS and OS with different parameters including baseline and post-treatment levels of inflammatory markers (CPR, ESR, LDH); ANA, ENA, ASMA auto-antibodies (AAbs); hormone-profiling; Th1, Th2, Th17 cytokines; regulatory-T-cells, different CTL subsets, and natural killers. **Result:** We recorded a PFS and OS of 12.5 [95%CI:9.9-15.0] and 15.3 [95%CI:12.8-17.9] months, respectively, not correlated to histology, number of previous chemotherapy lines, radiotherapy, or TKI use. A better outcome was found in males (OS, HR=2.3, 95%CI: 1.1-4.8, P=0.028), in those who presented autoimmunity signs (PFS: 17.2 vs. 6.7 months; HR=0.30, 95% CI: 0.15-0.57, p<0.001; OS:20.8 vs. 9.7 days; HR=0.24, 95% CI: 0.11-0.50, p<0.001) and those who showed early rise (within thirty days) of one (score 1, HR=0.235, 95% CI: 0.084-0.654. P=0.018) or more AAbs (score 2 HR= 0.22, 95% CI: 0.081-0.624, P= 0.001). Finally, Cox analysis revealed a predictive role for treatment-related early increase in eosinophil cell counts (OS, HR: 0.68, 95% CI: 0.57-0.81, P=0.031). **Conclusion:** Antigen cascade triggering measured as early occurrence of ANA ENA, ASMA AABs and subsequently, self-limiting autoimmunity is strongly predictive of longer survival in mNSCLC patients receiving treatment with Nivolumab. Additionally, the occurrence of AAbs strongly supports the occurrence of Nivolumab- dependent antigen cascade and cross-priming. These results offers a strong rationale to design future perspective trials in NSCLC patients.

Keywords: autoantibodies, PDL1 blockade, Biomarkers

P2.01-22 INCREASED INCIDENCE, MORBIDITY AND MORTALITY RATES FOR LUNG CANCER IN WOMEN IN BRAZIL BETWEEN 2000 AND 2014

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Background: *Introduction:* Lung cancer is the principal cause of death from cancer worldwide. However, little is known of its epidemiological and histological profile and of the incidence and mortality rates in Brazil according to sex. *Objectives:* To evaluate the incidence, morbidity and mortality rates of lung cancer in Brazil from 2000 to 2014, as well as the epidemiological and histological profile of the disease. **Method:** An analytical, cross-sectional study was conducted using three types of sources of secondary data: population-based cancer registries, hospital-based cancer registries and the national mortality database. **Result:** The incidence rate in women increased from 7.92/100,000 in 2000 to 9.12/100,000 in 2012, while mortality increased from 6.02/100,000 in 2000 to 8.29/100,000 in 2014. In men, the incidence decreased from 23.40/100,000 in 2000 to 18.47/100,000 in 2012 and mortality also fell from 16.12/100,000 to 15.11/100,000 in 2014. There was a reduction in the male-to-female ratio from 2.54 in 2000 to 1.46 in 2014. Women tended to be younger (p<0.001), black (p<0.001), non-smokers (p<0.001), to have adenocarcinoma or small-cell lung cancer (p<0.001), and to have metastatic disease (p<0.001). In addition, the time between diagnosis and the start of cancer treatment was longer in women (p<0.001). In relation to treatment, women were more likely to have undergone chemotherapy, surgery or surgery in combination with chemotherapy (p<0.001) and to have response to the initial treatment (p<0.001). **Conclusion:** An increase was found in the incidence and mortality rates of lung cancer in women in Brazil.

Keywords: Incidence, lung cancer, Women

P2.01-23 BASELINE PLASMA BIOMARKERS PREDICT LONG-TERM RESPONSES TO ALK-TKIS IN ALK+ ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Median progression free survival (PFS) for ALK tyrosine kinase inhibitors (ALK-TKIs) range from 10.9-25.7 months (mos)[1],[2],[3],[4]. While most ALK+ NSCLC patients develop resistance to ALK-TKIs within 1-2 years, a subset of patients experience a response >2 years. Given the lack of proteogenomic markers predicting long-term responses to ALK-TKIs, we conducted whole-exome sequencing (WES) and proteomic profiling to define molecular determinants that could predict a long-term ALK-TKI response, help guide the sequentiality of therapies and optimize treatment strategies. [1]Soria, J.C. et al. *Lancet***389,**917–929 (2017) [2] Peters, S. *et al. N. Engl. J. Med.***377**, 829-838(2017) [3]Kim, D.-W. *et al.J. Clin. Oncol.***35,**2490–2498 (2017) [4]Solomon, B. J. *et al.N. Engl. J. Med.***371,**2167–2177 (2014). **Method:** Twenty-four patients with advanced ALK+ NSCLC were enrolled in our study. WES was performed on primary and post-treatment metastatic tissue to identify genomic aberrations and ALK fusions. MRM-MS was used to analyze 327 protein candidates in plasma collected from patients at baseline. **Result:** Patients were categorized into 3 groups based on duration of response: long-term responders [LR; PFS ≥24 mos (n=8)], normal responders [R; 3 < PFS < 24 mos (n=10)] and non-responders [NR;PFS <3 mos (n=6)]. At data cutoff (30 April 2018), median PFS was 1.6 mos for NR, 11.7 mos for R and 37.1 mos for LR. Two LR remain on treatment and have experienced a PFS > 37.4 mos. Despite detecting novel ALK fusion partners, multiple somatic mutations and copy number aberrations by WES, we could not define a genomic signature predictive of a long-term response to ALK-TKIs from our small cohort. However, MRM-MS identified 15 proteins differentially regulated between LR and NR, including SODE, F13A, LYAM1, FCGBP, PGBM and LUM. Differences in protein levels were further pronounced between LR and NR. To determine whether our protein signature can discriminate according to response groups, we performed principal component and hierarchical clustering analyses. Both analyses successfully segregated LR from R and NR. Moreover, we used our set of 15 proteins to generate single-sample Gene Set Enrichment Analysis scores which distinguished LR from R and NR as distinct groups. **Conclusion:** Targeted proteomic profiling of baseline plasma from ALK+ NSCLC patients identified a protein signature that may predict a long-term response or resistance to ALK-TKIs. A collaboration is in development to confirm the validity of this protein signature in a larger cohort, and with next-generation ALK-TKIs.

Keywords: ALK+, long-term response, Proteomic

P2.01-24 MLPH ACTIVATES CDC42/PAK1 SIGNALING TO PROMOTE EPITHELIAL–MESENCHYMAL TRANSITION VIA TGF-β IN NON-SMALL CELL LUNG CANCER

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Background: Brain metastasis (BM) is associated with poor prognosis, recurrence, and death in patients with non-small cell lung cancer (NSCLC). Therefore, a better understanding of molecularmechanisms underlying NSCLC development and progression could provide helpful insights for NSCLC prevention and effective treatment. Melanophilin (MLPH) is a protein coding gene encoding a member of the exophilin subfamily of Rab effector proteins. Recently, MLPH was reported to be associated with cancers, however, to date, the role of MLPH in lung cancer has never been studied. **Method:** RNA-Sequencing was performed to identify differentially expressed genes- MLPH in lung tissues of NSCLC patients with and without BM, then the expression of MLPH was further examined in the serum of BM+ and BM- patients. To study the role of MLPH in the initiation and progression of NSCLC, we examined MLPH levels in NSCLC cells and tissues and analyzed the relationship between MLPH levels and patient survival. Then we knocked down MLPH in NSCLC cells. We used cell counting kit-8 assay, wound healing assay, transwell assay, flow cytometry analysis, Phalloidin staining, xenografted tumor model and brain metastasis model to determine the effects of MLPH on the proliferation, migration, invasion, EMT, tumorigenesis and brain metastasis of NSCLC. Western blot analysis was used to explore the underlying mechanism. **Result:** In this study, we found that MLPH was up-regulated in NSCLC tissues and cells. Patients with high levels of MLPH expression had significantly shorter survival than those with low MLPH expression. In NSCLC cell lines, shRNA-mediated depletion of MLPH inhibited the proliferation, lead to apoptosis, induced G0/G1 arrest and suppressed cell migration, invasion, EMT, tumorigenesis and brain metastasis. Mechanistically, we identified TGF-β as a key downstream effector of MLPH. More importantly, MLPH silencing attenuated CDC42/PAK1 signaling activation at least in part through the downregulation of TGF-β. **Conclusion:** Together, our findings demonstrated that MLPH positively modulated the CDC42/PAK1 signaling pathway via TGF-β to promote EMT and metastasis, suggesting MLPH as a potential oncogenic biomarker and a promising therapeutic target in the treatment of NSCLC and brain metastasis.

Keywords: MLPH, NSCLC brain metastasis, epithelial–mesenchymal transition

P2.01-25 MICRORNA-330-3P PROMOTES BRAIN METASTASIS OF NON-SMALL CELL LUNG CANCER BY ACTIVATING MAPK/MEK/ERK SIGNALING THROUGH GRIA3

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Background: Brain metastasis (BM) is associated with poor prognosis, recurrence, and death in patients with NSCLC. Discovery and development of biomarkers and elucidation of the mechanism underlying BM in NSCLC is critical for effective prophylactic interventions. MicroRNAs (miRNAs) play an essential role in the development of NSCLC. We investigated miRNAs that serve as biomarkers to differentiate NSCLC patients with and without BM, and explored the underlying mechanism. **Method:** Logistic regression was conducted in 122 NSCLC patients (60 without BM, 62 with BM) to examine the association between miRNAs

and BM. Stable over-expression and knock-down of miR-330-3p in NSCLC cells was constructed with lentivirus. Expression levels of miR-330-3p in NSCLC cells were quantified by quantitive real-time PCR (qRT-PCR). The effects of miR-330-3p on NSCLC cells were investigated using assays of cell viability, migration, invasion, cell cycle, apoptosis, western blotting, immunohistochemical and immunofluorescence staining. A xenograft nude mouse model and in situ brain metastasis model were used to observe tumor growth and brain metastasis. The potential target of miR-330-3p in NSCLC cells was explored using the luciferase reporter assay, qRT-PCR, and western blotting. The miR-330-3p targets were identified using bioinformatics analysis and verified by luciferase reporter assay. **Result:** High serum miR-330-3p was an independent risk for BM. Tissue miR-330-3p was also higher in subjects with BM (P=0.003). Migration and invasiveness were increased by over-expressing miR-330-3p using a lentivirus, and decreased by miR-330-3p knockdown in both cell lines. In nude mice receiving NSCLC cells, either subcutaneously or into the brain, tumor growth was faster in mice receiving cells permanently expressing exogenous miR-330-3p, and slower in cells expressing the anti-miR-330-3p sequence. Bioinformatics analysis, followed by microarray analysis of A549 cells over-expressing miR-330-3p and luciferase reporter assay suggested the glutamate receptor GRIA3 as a target of miR-330-3p. Experiments using selective kinase inhibitors suggested that GRIA3 is regulated by miR-330-3p via MAPK/MEK/ERK signaling pathway. **Conclusion:** miR-330-3p promotes NSCLC brain metastasis possibly in part via the MAPK/MEK/ERK pathway and GRIA3, and might be a potential target for the further research of NSCLC brain metastasis.

Keywords: metastasis, miR-330-3p, MAPK/ERK signaling

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-26 ASSOCIATION OF BASE EXCISION REPAIR GENE POLYMORPHISMS WITH RESPONSE TO CHEMOTHERAPY OF ADVANCED NON SMALL-CELL LUNG CANCER

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Background: Base excision repair (BER) plays an important role in the maintenance of genome integrity and anti-cancer drug resistance. This study aims to explore the role of BER genes polymorphisms in response to chemotherapy of advanced non small-cell lung cancer (NSCLC) patients treated with platinum-based chemotherapy. **Method:** During the period from November 2009 to January 2016, a total of 152 patients diagnosed with IIIB or IV stage NSCLC in the First Hospital of Jilin University were admitted into our study. The XRCC1 G28152A, MUTYH G972C, HOGG1 C1245G, PARP1 T2444C polymorphisms of all the patients were detected by the mass spectrometry. And the relationship between BER genes polymorphisms and the response of platinum-based chemotherapy is analyzed by Logistic regression. **Result:** Logistic regression model shows that the response rate of chemotherapy of the PARP1 T2444C polymorphisms, CC genotype (OR: 5.216, 95%CI: 1.568-17.352, *P*= 0.007) and TC genotype (OR: 2.692, 95%CI: 1.007-7.198, *P*=0.048) is significantly higher than that of TT wild type, as well as the genotype of TC together with CC (OR: 3.178, 95%CI:1.229-8.219, *P* = 0.017). There is no relationship between G28152A, MUTYH G972C, XRCC1 HOGG1 C1245G gene polymorphism and chemosensitivity. **Conclusion:** PARP1 2444 mutation allele C might be associated with the decreased sensitivity to platinum based chemotherapy in advanced NSCLC. Our findings may be helpful towards designing individualized cancer treatment.

Keywords: gene polymorphism, Platinum, non-small cell lung cancer

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-27 MR, CT AND CONE-BEAM CT FOR LYMPH NODE VISUALISATION IN LOCALLY-ADVANCED LUNG CANCER

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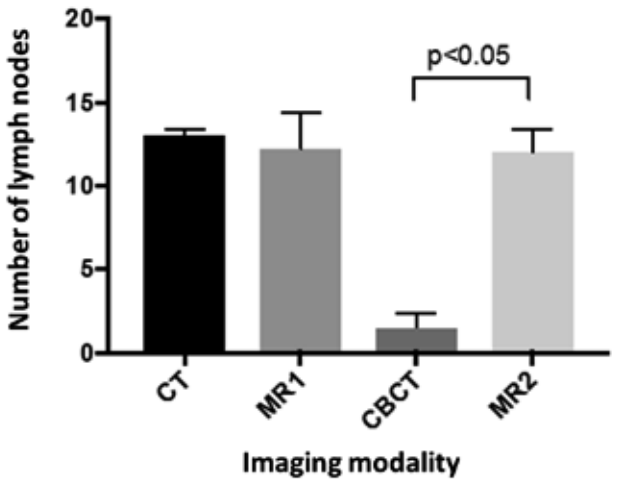
Background: The largest benefit of MR-guided radiotherapy in lung cancer may be on-board visualisation of malignant lymph nodes (LNs). In this study, we assessed whether MR images were suitable for LN visualisation for treatment adaptation. We hypothesised that MR would outperform CT and Cone-Beam-CT (CBCT). **Method:** CT, CBCT and MR images were acquired in four lung cancer patients with malignant LNs, confirmed using PET-CT and/or endobronchial ultrasound-guided biopsies. A total of 15 LNs from mediastinal and hilar nodal stations were assessed. Imaging datasets included: (1) CT planning scan with IV contrast; (2) MR1 (within 1 week of CT); (3) Mid-treatment CBCT (without contrast); and (4) MR2 (day of CBCT). MR sequences included: Turbo Spin Echo (TSE), TSE with fat-sat and 3D radial gradient echo. The images were randomised and independently scored by four thoracic radiation oncologists according to whether the malignant LN in each nodal station was visualised well enough to permit contouring. Scores were: not visible (1), unclear (2), clear (3) and very clear (4). Scores 3 and 4 were designated as '*suitable for contouring*'. **Result:** As shown in figure 1, there was no significant difference in the number of LNs deemed suitable for contouring on CT (87%) compared to MR1 (82%). A significant difference was found between CBCT (10%) and MR2 (80%).



Conclusion: MR did not out-perform CT with contrast for malignant LN visualisation, possibly due to greater observer familiarity with CT. MR was significantly better than CBCT, likely due to superior soft tissue contrast. These findings support the use of MR-guided radiotherapy in locally-advanced lung cancer for adaptive planning or treatment verification. The greater variation in MR scores between oncologists (especially between sequences) could be due to lack of experience with thoracic MR. Future research will optimise MR for this task and assess LN localisation on a larger dataset.

Keywords: MRI, Radiotherapy, lymph node

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-28 GENDER AND SYSTEMIC TREATMENT PATTERNS: IMPACTS ON THE OVERALL SURVIVAL OF STAGE IV NSCLC 2010 – 2014 DIAGNOSES

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Background: Our previous work reports only ~25% systemic treatment uptake in stage IV non-small cell lung cancer (NSCLC) patients and proposed the availability of more tolerable regimen as one way of improving survival for NSCLC patients. The current study followed-up with the systemic treatment trend in stage IV NSCLC patients from 2010 to 2014, the era where effective and tolerable targeted agents such as EGFR- tyrosine kinase inhibitors (TKIs) and ALK inhibitors are available, to determine changes in clinical and treatment patterns impacting NSCLC survival over time. **Method:** Using the Glans-Look Lung Research (GLR) database, we defined the clinical features of stage IV NSCLC patients from 2010 to 2014, determined the impact of systemic treatment patterns and uptake rates on overall survival (OS).The findings were summarized with descriptive statistics (Fisher's Exact tests) and Kaplan Meier survival curves using SPSS. Statistical significance was set at p value < 0.05 and 95% confidence intervals. **Result:** Among the 470

patients diagnosed between the year 2010 – 2011, and 724 in 2012 – 2014, 26% and 33% received 1st line systemic treatment respectively. Overall, there was increased use of EGFR and ALK targets (18% in 2010 – 2011 versus 34% in 2012 – 2014 of all 1st line therapy) and a 13% decrease in platinum-based doublet (PBD) uptake over the years, (p = 0.001). This pattern of change was similar for patients ≤70 years versus >70 (p < 0.001). However, for female patients, PBD use remain constant despite the increased targeted agents uptake, (p = 0.001). The median OS was slightly better for female in the subsequent years, 7 (95% CI: 6 – 8) versus 4 (95% CI: 3 – 5) months, p = 0.036. In EGFR/ALK mutation positive patients who received 1st line TKIs, a non-statistically significant lower OS was observed in 2012 – 2014 compared to the previous years (p = 0.188). No significant difference in the OS between the year groups for patients with no actionable mutation treated with 1st line PBD (p = 0.393). **Conclusion:** In stage IV NSCLC, systemic treatment uptakes slightly increased with targeted agents, however this may not add up to overall survival benefits for the disease. Targeted agents may confer more benefits to female patients. Outcome results from multivariate analysis will be presented and discussed.

Keywords: Advanced NSCLC, Systemic therapy, Sex

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-29 ECONOMIC ANALYSIS OF OSIMERTINIB IN PREVIOUSLY UNTREATED EGFR-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Osimertinib doubles progression-free survival (PFS) in previously untreated *EGFR*-positive advanced non-small cell lung cancer (NSCLC) patients, with remarkable intracranial response rates. However, its cost-effectiveness has not been established. We assessed the cost-effectiveness of first-line osimertinib from the perspective of the Canadian public health care payer. **Method:** A remaining lifetime Markov model was used to project the outcomes and costs of 2 treatment pathways, osimertinib or current standard-of-care (SoC) first-line *EGFR* TKI gefinitib or afatinib, in previously untreated *EGFR*-mutant advanced NSCLC patients from the health care system perspective. Clinical, health preference and cost input estimates were informed from the available literature, including second-line osimertinib after SoC failure in those with *EGFR T790M* mutant cancer. Model outcomes included costs (in 2017 Canadian dollars), quality-adjusted life-years (QALYs), and the incremental cost per QALY gained. The model was fully probabilistic to assess parameter uncertainty. **Result:** Osimertinib was associated with a gain of 0.70 quality-adjusted life-years (QALYs) at an incremental cost of $58,619 vs SoC (incremental cost-effectiveness ratio [ICER]: $83,164/QALY gained). Unadjusted LY gain was 0.95. Osimertinib had a 7% probability of being cost-effective at a willingness-to-pay threshold of $50,000/QALY, and a 77% probability at a threshold of $100,000/QALY. Deterministic sensitivity analysis showed that health utilities and cost of osimertinib had the largest impact on ICER results. **Conclusion:** First-line osimertinib use in patients with advanced *EGFR* mutant lung cancer was found to involve a trade-off between improved PFS, QALYs and LYs versus increased cost.

Keywords: economic evaluation, Osimertinib

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-30 APPLICABILITY OF LUNG-MOLGPA INDEX IN NON-SMALL CELL LUNG CANCER PATIENTS WITH DIFFERENT GENE ALTERATIONS AND BRAIN METASTASES

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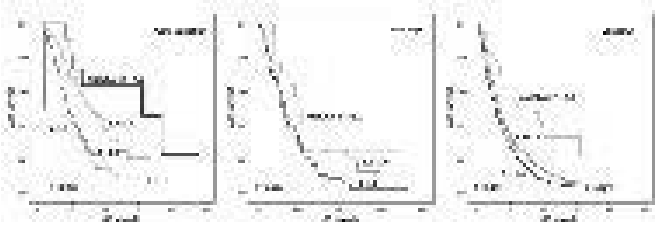
Background: The Lung-molGPA was based on the original Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) by incorporating recently reported gene alteration data for non-small cell lung cancer (NSCLC) patients with brain metastases (BM). However, the prognostic prediction value of DS-GPA and Lung-molGPA models remains undetermined, especially in patients with different molecule types. **Method:** A total of 1184 NSCLC patients with BM analyses for clinical factors and outcomes were identified at Zhejiang Cancer Hospital, China. All prognostic factors were weighted for significance by hazard ratios. The applicability of DS-GPA and Lung-molGPA were reappraised in NSCLC patients with BM and various genetic profiles. Additionally, a modified Lung-molGPA, was newly developed for mutant NSCLC patients. **Result:**



The NSCLC patients in the present study had a median survival of 14.0 months from the time of BM diagnosis. Both DS-GPA and Lung-molGPA models could predict the outcomes (P<0.001), while Lung-molGPA model appeared to exhibit better accurate prediction. Furthermore, Lung-molGPA scores performed a discrimination capability in patients with gene variations (3.5-4.0 vs 2.5-3.0 vs 1.5-2.0 vs 0-1.0=62.0 vs 32.0 vs 17.7 vs 3.2 months, P<0.001). However, no significant difference was reached in wild-type patients (P=0.133). Regarding to the oncogene-positive NSCLC patients with BM, a modified Lung-molGPA index had been established derived from the prognostic factors with the C-index of 0.73 (95% CI: 0.73-0.80) to accurately calculate the survival probability (P<0.001). **Conclusion:** In an era of precision medicine, Lung-molGPA could precisely predict the prognosis of mutant NSCLC patients with BM, while not work in wild-type patients.

Keywords: non-small cell lung cancer, Lung-molGPA, brain metastases

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-31 UPDATED EGFR MUTATION FREQUENCY IN 1,689 NSCLC BRAZILIAN PATIENTS – A NATIONAL-WIDE STUDY

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Background: EGFR mutation status is crucial to improving therapeutic results in advanced NSCLC, due to the development of highly effective EGFR-TKIs. Recent local data suggest that EGFR mutation frequency is lower in Brazil (22%-33%) than in Asia and higher than in North America and Europe. We intended to describe the EGFR mutation frequency in a large national-wide Brazilian population. **Method:** This retrospective analysis evaluated a database composed of samples collected between January and August 2017, from all Brazilian regions. Tumor tissue samples of patients with advanced NSCLC were submitted, at discretion of attending physicians, for EGFR mutation testing. EGFR exons 18 to 21 were analyzed by cobas®, NGS, or other non-specified test. Unfortunately, smoking status data was not available and was not included in this analysis. **Result:** 1,689 tests were included. Table-1 demonstrates EGFR mutation rates according to test used. Mean age (±SD) was 64.5 (±11.3) for female and 66.0 (±11.1) for male population. From all detected mutations, exon 19 deletion was the most frequent (49.2%), followed by L858R (25.6%), exon 20 insertion (8.4%), T790M (4,7%), and G719X (3.0%). Patients with multiple EGFR variants (more than one EGFR mutation) corresponded to 10.3% of cases. Among different Brazilian geographic macro-regions, EGFRm rate was 33.3% in North (36 tests only), 25.1% in Northeast (307 tests), 30.9% in Central-West (175 tests), 25.8% in Southeast (841 tests), and 20.6% in the South (330 tests) region. Table1 – EGFR mutation rate divided by gender and EGFR mutation detection method.

	cobas®	NGS	Other	Overall
Female	58/183 (31.7%)	223/586 (38.1%)	25/159 (15.7%)	306/928 (33.0%)
Male	25/167 (15.0%)	89/447 (19.9%)	9/147 (6.1%)	123/761 (16.2%)

Overall	83/350 (23.7%)	312/1,033 (30.2%)	34/306 (11.1%)	429/1689 (25.4%)

Conclusion: Our findings confirm that EGFR mutation rate among Brazilian is higher than observed in Western countries, women have a higher EGFR mutation rate than men, and detection rate using NGS is higher than cobas®. Frequency of EGFR mutation was lower in South region, what could be explained by a higher smoking rate (not evaluated in this study) and a larger Caucasian population.

Keywords: EGFR mutation, Mutation frequency, advanced NSCLC

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-32 ECONOMIC EVALUATION OF DIAGNOSTIC PLATFORMS FOR T790M DETECTION IN POST EGFR-TKI NSCLC IN BRAZIL

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Background: 50% of acquired resistance to first or second-generation EGFR-TKIs NSCLC treatment is attributed to T790M mutation. Clinical trials demonstrated superior efficacy of osimertinib versus chemotherapy in second line setting. Nevertheless, the required molecular testing to identify T790M mutation is a challenge considering difficulties related to tissue re-biopsies. Nowadays, availability of noninvasive ctDNA techniques permits safer and faster molecular diagnostic. In Brazil, there are some commercially available tests presenting different accuracy rates. Our objective was to compare current T790M ctDNA tests cost-effectiveness, under local perspective. **Method:** The population is NSCLC post first-line EGFR-TKI progression. Decision tree model started with cfDNA evaluation (RT-PCR based kit, Digital Droplet PCR, or NGS). Due to ctDNA methods intermediate sensitivity, tumor sample analysis is recommended if plasma result is negative. Strategies were a combination of cfDNA tests and RT-PCR based kit or NGS for tumors re-biopsies. Prevalence of T790M mutation, test accuracy, proportion of unknown or unfeasible samples were used to calculate each branch. Tissue re-biopsies complications and costs were also considered. The model was analyzed from a healthcare-payer perspective based on Brazilian private sector. **Result:** Plasma ddPCR then tissue biopsy NGS (if plasma negative) was the most effective, with cost-effective ratio of US$ 3,855.43 per positive T790M detected. Its cost was higher than the second most effective strategy (plasma-NGS + tissue NGS). Incremental cost-effectiveness ratio between both was US$ 21,193.66 per additional positive case detected. All strategies using RT-PCR based kit for plasma and/or tissue were dominated.

Strategies (re-biopsy if T790M was negative in cfDNA)	Σ Costs	Σ T790M Positive	Status
6. Liq bx ddPCR+ re-bx NGS	$ 2,106.28	0.546	
5. Liq bx ddPCR + re-bx RT-PCR (Cobas®)	$ 2,177.66	0.544	Dominated*
4. Liq bx NGS + re-bx NGS	$ 1,055.98	0.497	
3. Liq bx NGS + re-bx RT-PCR (Cobas®)	$ 1,139.03	0.492	Dominated*
2. Liq bx RT-PCR (Cobas®) + re-bx NGS	$ 1,220.97	0.473	Dominated*
1. Liq bx RT-PCR (Cobas®) + re-bx RT-PCR (Cobas®)	$ 1,307.86	0.468	Dominated*

Conclusion: In terms of costs and effectiveness, the best algorithms to detect more T790M positive cases are combination of ctDNA (ddPCR or NGS) and NGS test for tumor re-biopsy. ddPCR use followed by NGS permits identification of 5% more T790M mutations than the dominated methods. This study is an effort to optimize expenditures and integrate diagnostics discussions in Brazilian health system.

Keywords: economic evaluation, ctDNA, T790M

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-33 OPEN-LABEL, BIOMARKER-DIRECTED PLATFORM STUDY IN NSCLC PATIENTS WHO PROGRESSED ON AN ANTI-PD-(L)1 CONTAINING THERAPY (HUDSON)

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Background: Immune checkpoint inhibitor (ICI)-containing regimens have significantly improved survival outcomes in first- and second-line NSCLC. However, the majority of patients do not respond or have non-durable responses to anti-programmed cell death-1/programmed cell death-ligand 1 (anti-PD-1/PD-L1) containing therapy (primary resistance) or progress during anti-PD-1/PD-L1 containing therapy (acquired resistance). HUDSON addresses the urgent need to identify treatments and understand ICI resistance for this emerging ICI-resistant population. **Method:** HUDSON is a multi-centre, international multi-arm umbrella study that will 1) evaluate therapies to reverse ICI resistance and 2) define mechanisms of ICI resistance in NSCLC patients who have progressed following standard-of-care platinum and ICI-based therapies. HUDSON is a platform study that consists of two groups; a biomarker matched and a biomarker non-matched group. Within the biomarker matched group, different cohorts will test 1) homologous recombination repair (HRR) defects and 2) LKB1 aberration for response to durvalumab and olaparib (PARP inhibitor), 3) ATM deficiency for response to durvalumab and AZD6738 (ATR inhibitor) and 4) RICTOR amplification for response to durvalumab and vistusertib (mTORC1/2 inhibitor). In the biomarker non-matched group, cohorts will test durvalumab in combination with either i) olaparib, ii) AZD9150 (STAT3 inhibitor) or iii) AZD6738, in patients with primary and acquired resistance to a prior ICI. Allocation to a cohort is informed by the tumour molecular profile according to a pre-specified assignment algorithm. New cohorts will be added as new translational hypotheses are established. Translational research will be performed on serial peripheral blood samples (including ctDNA) and tumour biopsies. HUDSON enrols ICI-resistant patients in a signal searching manner. Biomarker matched and non-matched groups will be opened simultaneously, and all eligible patients can be allocated a treatment option irrespective of their tumour profile. Enrolment is ongoing, clinical trial information: NCT03334617. **Result:** Section not applicable
Conclusion: Section not applicable

Keywords: Metastatic NSCLC, Biomarkers, Immunotherapy resistance

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-34 PROGNOSTIC VALUE OF NEUTROPHIL TO LYMPHOCYTE RATIO FOR METASTATIC NSCLC PATIENTS TREATED WITH IMMUNOTHERAPY AND RAMUCIRUMAB PLUS DOCETAXEL.

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Background: High NLR has been associated with inferior OS in metastatic NSCLC patients. We previously demonstrated a significant relationship between a high NLR at baseline and at follow-up and poorer OS in patients with metastatic NSCLC. Case series suggest potentially improved benefits of cytotoxic chemotherapy administration post immunotherapy but little is known about whether high NLR is associated with inferior outcomes in patients receiving salvage ramucirumab plus docetaxel (RD). We evaluated the potential predictive value of NLR in pts with metastatic NSCLC who received at least one cycle of immunotherapy and treated with RD regimen. **Method:** Retrospective analysis of patients with metastatic NSCLC who received at least one cycle of nivolumab or pembrolizumab and treated with RD regimen between April 2015 and May 2017. Patient demographics including NLR, RD and immunotherapy starting dates, and date of progression were recorded. Associations between NLR and both PFS and OS were assessed using Mann-Whitney-Wilcoxon tests. Cutoffs of NLR of 5.0 (based on published data) were analyzed for differences in median OS and PFS. **Result:** Of 62 patients analyzed, 47% were male, 81% former smoker, 76% Caucasian and 76% patients who were treated with RD regimen also received immunotherapy during their treatment course. For entire cohort, baseline NLR $\leq$ 5 was associated with superior survival (median OS 20.86 mos for NLR $\leq$ 5 vs 5.78 mos for NLR >5, p=0.01) and superior PFS (median PFS 6.01 mos for NLR $\leq$ 5 vs 2.76 mos for NLR >5, p=0.03). Another significant predictor of OS was albumin at baseline (HR= 0.44, p = 0.01) and at 6 weeks (HR= 0.38, (p = 0.01). Patients who received immunotherapy had significantly superior OS than those who did not receive immunotherapy (median not reached vs 7.43 mos, p =0.03) within one-year follow-up. **Conclusion:** Low NLRs and higher albumins at baseline & 6 weeks were associated

with a prolonged PFS and OS in patients with metastatic NSCLC who were treated with RD regimen. In this small retrospective study, longer OS was observed in pts treated with RD regimen and immunotherapy. Pts who did not receive immunotherapy had shorter OS. Additional data are needed to evaluate the impact of treatment sequence.

Keywords: Neutrophil-to-lymphocyte ratio, Metastatic NSCLC, Immunotherapy

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-35 PREDICTING RISK OF CHEMOTHERAPY-INDUCED SEVERE NEUTROPENIA IN PATIENTS WITH ADVANCED LUNG CANCER

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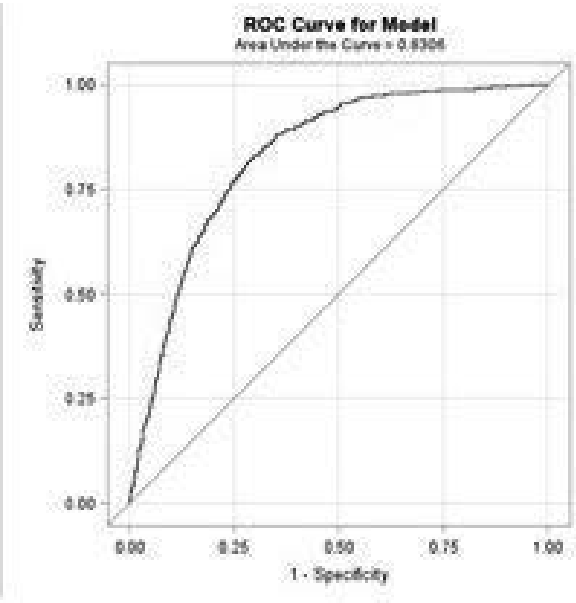
Background: Neutropenia is associated with the risk of life-threatening infections, chemotherapy dose reductions and delays that may compromise treatment outcomes. The goal of this study was to develop simple prediction model for severe neutropenia in lung cancer. **Method:** A lung cancer dataset was assembled using data from existing national cooperative group phase II/III trials conducted between 1991-2010. Chemotherapy trials in patients with stages III and IV non-small cell lung cancer (NSCLC) or extensive small-cell lung cancer (SCLC) were included. We randomly selected 2/3 patients to derive the model, and the remaining were used for validation. Models were built with stepwise logistic regression and lasso regression on imputed data sets. We fitted the model on the imputed training data sets individually to get 10 models with 10 sets of selected predictors. Next we picked the union set and the intersection set of predictors from the models. The variables in the final model were selected by lasso regression, and then fitted into a logistic model. The performance of the model was evaluated by receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC). **Result:** The dataset was randomly separated into training [n=7606 (67%)] and testing sets [n=3746 (33%)]. The final predictive model included: Age (>65 years), gender (male), weight (kg), BMI, insurance status (yes/unknown), stage (IIIB/IV/ESSCLC), number of metastatic sites (1, 2 or ≥3), individual chemotherapy agents (gemcitabine, taxanes), number of chemotherapy agents (2 or ≥3), planned use of growth factors, associated radiation therapy, previous therapy (chemotherapy, radiation, surgery), duration of planned treatment, pleural effusion (yes/unknown), performance status (1, ≥2) and presence of symptoms (yes/unknown). Figure: ROC Curve for Final model AUC=0.8306 **Conclusion:** We have developed a relatively simple model with variables that are routinely available prior to treatment, to predict for neutropenia. This model should be validated prospectively.



Keywords: non small cell lung cancer, Neutropenia, Predictive model

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-36 REAL-WORLD TREATMENT PATTERNS IN TREATMENT-NAÏVE ADVANCED NSCLC PATIENTS IN NORTH AMERICA: A SYSTEMATIC LITERATURE REVIEW

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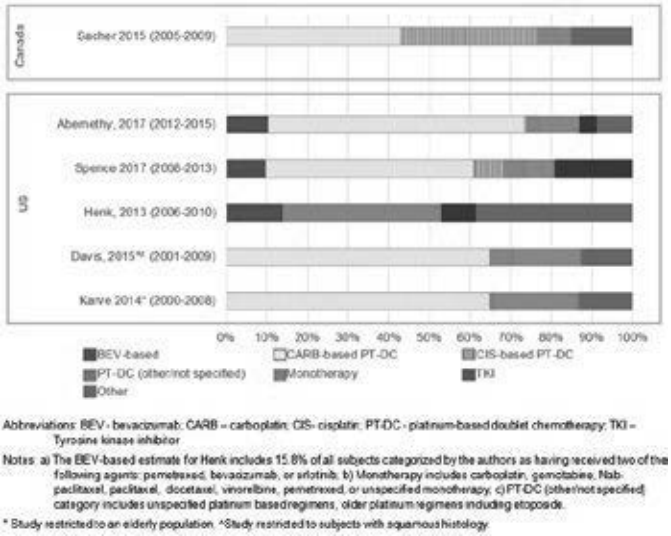
Background: Clinical practice guidelines in North America for first-line (1L) treatment of advanced NSCLC (aNSCLC) include a range of systemic therapy combinations, with consideration given to patient and disease characteristics. As the aNSCLC treatment landscape evolves, it is relevant to understand which combinations are routine in clinical practice. We aimed to characterize treatment patterns in real-world (RW) practice in the US and Canada. **Method:** A systematic literature review of RW observational studies was conducted using EMBASE and MEDLINE (January 2012 to March 2018), alongside searches of conference proceedings (2015 to 2018). Two reviewers assessed eligibility and included studies that described treatment patterns among treatment-naïve patients with aNSCLC. Studies focusing exclusively on sub-populations, e.g. EGFR+ or ALK+ were excluded. Data regarding the study's sampling frame and the frequency and type of therapies received (1L systemic regimens, other 1L treatment modalities, maintenance therapy, subsequent lines of systemic therapy) were extracted and validated. **Result:** From 4600 abstracts, 18 studies met inclusion criteria (n=14 US; n=4 Canada). All studies used a retrospective design; patient sample sizes ranged from 147 to 55,189 and study periods ranged from 2000 to 2015. Six studies (n=5 US; n=1 Canada) applied a sampling frame that captured all regimens available in 1L and provided breakdowns by 1L regimen (Figure 1). Eight studies (n=8 US) applied a sampling frame restricted to a pre-defined subset of 1L regimens. Among these, five were restricted to those receiving bevacizumab-based regimens; the remaining three restricted to those on specific platinum doublet regimens. Four studies (n=1 US; n=3 Canada) provided breakdowns only by treatment modality (surgery, radiation, best supportive care or no systemic therapy).



Conclusion: The identified studies capture treatment patterns primarily in an era when immunotherapy was unavailable in the 1L setting and reflect the prevalent use of platinum doublets as the mainstay of 1L treatment.

Keywords: systematic literature review, Real-world treatment patterns, NSCLC

P2.01-37 A PH 1/2 STUDY OF ORAL SELECTIVE AXL INHIBITOR BEMCENTINIB (BGB324) WITH DOCETAXEL IN PTS WITH PREVIOUSLY TREATED NSCLC

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Background: AXL is a receptor tyrosine kinase expressed on tumor as well as innate immune cells. AXL regulates multiple cellular processes including tumour cell survival, therapy resistance as well as immunosuppression in the tumour microenvironment. AXL overexpression is an independent negative prognostic factor in NSCLC. Bemcentinib (BGB324) is a phase 2, highly selective, orally bioavailable small molecule AXL kinase inhibitor shown to increase efficacy of chemo-, targeted- and immuno-therapies in NSCLC *in vivo* models. Preclinically, the combination of bemcentinib with docetaxel was shown to be additive in *in vivo* models of NSCLC. In pts with advanced, pre-treated NSCLC, bemcentinib monotherapy led to disease stabilization in 2 out of 8 pts including evidence of tumor reduction. Clinical benefit including partial responses and disease stabilization in excess of 2 years has been observed in a subset of EGFR therapy resistant previously treated NSCLC pts when treated with bemcentinib in combination with erlotinib. In a study combining bemcentinib with pembrolizumab, objective responses have been reported in pts with previously treated NSCLC. The BGBIL005 trial (NCT02922777) is an open label, investigator-initiated dose escalation and expansion trial designed to assess the safety, tolerability, preliminary efficacy and biomarkers of bemcentinib in combination with docetaxel in previously treated NSCLC. **Method:** Dose escalation of daily bemcentinib in combination with 60 or 75 mg/m^2 q3wks followed a standard 3+3 design in pts with at least one line of prior Pt-based doublet therapy and appropriate targeted therapy if indicated. Tumor responses were assessed per investigator using RECIST v1.1. Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM) in pts pre-dose and at C2D1. **Result:** As of 30th April, 12 patients have been enrolled. The starting dose of 75 mg/m^2 docetaxel and 100 mg daily of bemcentinib led to 2 hematological DLTs, thus recruitment is currently ongoing at 60 mg/m^2 docetaxel and 100 mg bemcentinib. Confirmed objective responses have been reported at both dose levels. All pts benefitting had received prior immune checkpoint inhibitor (CPI) therapy and some had been refractory to this treatment. Candidate predictive and pharmacodynamic biomarkers have been identified. **Conclusion:** The combination of bemcentinib and docetaxel is active in pts with advanced NSCLC who progressed on chemotherapy, targeted therapy (where applicable) as well as CPIs.

Keywords: bemcentinib, chemotherapy, Axl

P2.01-38 SARCOPENIA IS ASSOCIATED WITH METASTATIC BURDEN AND IS A NEGATIVE PROGNOSTIC FACTOR IN METASTATIC NON-SMALL CELL LUNG CANCER

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Background: Sarcopenia is associated with poor outcomes in patients with solid tumors. Factors affecting sarcopenia in metastatic NSCLC (mNSCLC) are not well defined. We utilized a novel computerized tomography (CT) method to measure muscle composition and evaluate its impact on metastatic disease burden and survival in mNSCLC patients. **Method:** We conducted a retrospective study of consecutive adults diagnosed with mNSCLC. Demographic features, clinicopathologic variables, radiologic imaging, and outcomes data were collected and analyzed. Total, healthy, and unhealthy muscle were identified at the L3 psoas level using a previously validated novel CT method. Blinded outcomes assessments were conducted. The primary outcome was correlation between healthy muscle percentage and number of metastases. The secondary outcome was the impact of healthy muscle on overall survival. We hypothesized less total healthy psoas muscle would be associated with greater metastatic burden and worse overall survival. Analyses were adjusted for sex, age, BMI, Charlson comorbidity index, ECOG score, total psoas cross-sectional area, and weight-loss. The survival analysis was also adjusted for presence of a targetable mutation. **Result:** We identified 242 patients with mNSCLC. Mean age was 65 years. Forty-seven percent were females. Two hundred thirteen (88%) were current or former smokers. Adenocarcinoma was the most common histological subtype (162,67%) followed by squamous (49,20%) and undifferentiated (18,7%). One hundred thirteen (44%) patients had oligometastatic disease, defined as 1-3 lesions, and 142 (56%) had 4 or more lesions. Eighty (33%) had brain metastases and 69 (29%) visceral. Mean ECOG was 1. Mean percentage of healthy psoas was 74% (SD: 14). Multivariate analysis demonstrated that for every 10% increase in healthy muscle, metastatic lesions decreased by 12% (RR=0.88, 95% CI 0.78-0.98, p=0.02). The odds of oligometastatic disease increased by 39% for each 10% increase in healthy muscle (OR=1.39, 95% CI: 1.06-1.79, p=0.014). Reduced percentage of healthy muscle was associated with reduced survival (median OS 8.9, 19.1, 16.3 months for <70%, 70-80%, >80% of healthy muscle, respectively, log-rank test p=0.038). This effect was preserved in the adjusted analysis, with 13% decrease in the hazard of death for every 10% increase in percent healthy muscle (HR=0.87, 95% CI: 0.75-1.0, p=0.05). **Conclusion:** Greater healthy muscle at mNSCLC diagnosis is associated with lower metastatic burden and improved survival. Our novel CT method to identify sarcopenia may be useful in mNSCLC prognostication.

Keywords: sarcopenia, metastatic non-small cell lung cancer, prognostication

P2.01-39 CAN BENEFIT OR FUTILITY IN TREATING ADVANCED NSCLC BE DETERMINED EARLY USING THE LCSS 3-ITEM GLOBAL INDEX (3-IGI) PRO?

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Background: Early assessment of the effect of treatment for advanced NSCLC can prevent unnecessary exposure to toxic and costly therapy while aiding in decision making to continue or change treatment. In a prior analysis in patients with mesothelioma (Symanowski *JCO* 2014), a 20% decline from baseline after 2 cycles of chemotherapy in the 3-Item Global Index of the LCSS identified patients unlikely to benefit. The 3-IGI (which evaluates: 1) global distress, 2) patient rated activities, and 3) quality of life, all in single VAS scales) takes less than 2 minutes to assess. **Method:** s: 164 patients with NSCLC receiving chemotherapy or checkpoint inhibitors were prospectively evaluated with the LCSS at baseline and every 3 weeks using electronic media. Patients were also randomized 1:1 so that their physicians knew the results of the LCSS immediately in half of the patients. **Result:** s: Patients: Stage IV 92%; first line 73%; female 43%; median PS 1; mean age 63. The LCSS was completed after 2 cycles of treatment and prior to planning for the next cycle (generally 6 weeks after baseline; representing 91% of the 148 patients living). Patients with a 20% decline in the 3-IGI compared with baseline had a median survival of 7.6 months, contrasted to 15.8 months for those without this degree of 3-IGI decline (p = 0.01); 1 year survivals = 26% versus 62%. Even with the marked PRO decline after 2 treatment cycles, patients in the 20% decline group received a median of 2.3 more cycles of the same chemotherapy (median cost = $10,712 per patient). In the 50% of patients for which their physicians knew the ongoing LCSS results, fewer chemotherapy and imaging studies were performed, but the differences were not significant (p = 0.8). **Conclusion:** s: Assessing change from baseline with the 3-IGI of the LCSS identifies after only 2 cycles of treatment those patients who have poor response and survival outcomes if continued on the same therapy. This PRO assessment is rapid, easy, and inexpensive. Physicians need to consider the impact of decline on decision options given that even when physicians were aware of the worsening PRO they often did not act on the findings. Patient responses to this validated PRO questionnaire provide valuable information that is not otherwise attainable. Responding to 3-IGI changes can result in better decisions concerning continuing or changing treatment, lessening toxicity, and savings in cost of unhelpful treatment.
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Keywords: LCSS, PRO, 3-IGI

P2.01-40 PROGNOSTIC IMPORTANCE OF SARCOPENI AND INFLAMMATORY STATEMENTS IN STAGE III NON SMALL CELL LUNG CARCINOMA

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Background: Sarcopenia is characterized by progressive loss of skeletal muscle mass, muscle strength and physical performance. Systemic inflammation is thought to contribute to sarcopenia. Current retrospective evidence suggests that sarcopenia is an independent prognostic value on overall survival(OS). In this study, we aimed to investigate the prognostic significance of sarcopenia and inflammatory markers in stage III small cell lung cancer (NSCLC). **Method:** Eighty-three patients with stage III NSCLC undergoing definitive chemoradiotherapy in our clinic between April 2014 and August 2017 were evaluated. The cross-sectional area of muscle at the level of the third lumbar vertebra (L3) was measured using of radiotherapy planning CT images. Sarcopenia was defined as a L3 muscle index of less than 55 cm2/m2 for men and of less than 39 cm2/m2 for women as proposed by international consensus of cancer cachexia. Systemic inflammatory markers investigated included serum lactate dehydrogenase (LDH), neutrophil: lymphocyte ratio (NLR), C-reactive protein (CRP), and albumin(alb) . Relations between variables were determined by Pearson Chi Square and FischerExact Test. Risk factors affecting dependent variables were determined by CoxRegresson Analysis. **Result:** Seventy-five (90%) of the patients were male and 8 (10%) were female. The number of sarcopenic patients was 52 (62.6%). The mean age was higher in sarcopenic patients (68.3 ± 9.7 vs 63.7 ± 9.4, p = 0.037). There was no statistically significant difference between the groups with and without sarcopenia in the ratio of low albumin level, LDH height, N / L ratio. Mean survival was 18.14 months (2-48 months). In sarcopenic patients, OS was 17.2 months, while non-sarcopenic patients were 19.58 months (p = 0.310). When the effects on general survival were examined, it was found statistically significant that the presence of sarcopenia (p = 0.016), age (p = 0,001), low alb level (p = 0,009), N / L ratio is higher than 4 (p = 0,003). Multivarible Cox regression analyzes showed independent prognostic significance in survival with RT dose (HR (95% CI) = 1,2; p = 0.001), low albumin level (HR (95% CI) = 2.42; p = 0.007) and age (HR(95%CI)=1,03; p=0,044). **Conclusion:** In our study, the presence of sarcopenia in patients with stage III definitive KTRT NSCLC, as well as the LOW alb ratio and N / L ratio of inflammatory markers was found to be a significant prognostic factor for OS. We aim to investigate the prognostic significance of sarcopenia 'cutoff' value for Turkey with a prospective, multicenter, larger group of patients.

Keywords: Sarcopenia, Non small Cell Lung Cancer, İnflammation statements, Albumin, Neutrophil/lymphocyte, prognostic factor

P2.01-41 THE ROLE AND MECHANISM OF FBW7 DEFICIENCY IN ADVANCED NON-SMALL CELL LUNG CANCER WITH DOCETAXEL RESISTANCE

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Background: Lung cancer is one of the most common malignant tumors of human. NSCLC accounts for about 80%-85% of all lung cancer, and 65%-80% of NSCLC patients have been diagnosed at the advanced stage[1]. Because of the existence of drug resistance, many patients have relapsed or progressed soon after chemotherapy, and the resistance always lead to unsuccessful effect. Docetaxel is an anti-microtubule chemotherapeutic agent that acts on cellular tubulin, which can prevent the normal physiological accumulation of intracellular microtubules , resulting in the withering of cells[2]. Like other chemotherapeutic drugs, the drug resistance of docetaxel reduces its efficacy. **Method:** RT-PCR and Western-blot were used to detect the differences of FBW7 expression in docetaxel-resistant cell line SPC-A1/DTX and parental SPC-A1 cells, and the overexpression and interference sequences of FBW7 were constructed. The SPC-A1/DTX and parental SPC-A1 cells were transfected with lentiviral packaging, and the SPC-A1/DTX FBW7 O/E cell line and SPC-A1 FBW7 D/R cell line were screened by monoclonal screening method. RT-PCR and Western-blot were also used to detect the differences of FBW7 expression among SPC-A1/DTX, SPC-A1/DTX FBW7 O/E, SPC-A1 and SPC-A1 FBW7 D/R cell lines. Finally, MTT colorimetric assay and colony formation assay were used to research the effects of regulation of FBW7 on the sensitivity to docetaxel. **Result:** RT-PCR and Western-blot proved that the expression of FBW7 in NSCLC docetaxel-resistant cell line SPC-A1/DTX was significantly lower than that of parental cell line SPC-A1. With lentiviral transfection and monoclonal screening, a SPC-A1 FBW7 D/R cell line with down-regulated FBW7 expression and an SPC-A1/DTX FBW7 O/E cell line with up-regulated FBW7 expression were constructed. The expression of FBW7 in SPC-A1 cell line and SPC-A1/DTX FBW7 O/E cell line was higher than that of SPC-A1/DTX FBW7 O/E cell line and SPC-A1 by RT-PCR and Western-blot. /DTX cell line. Finally, MTT colorimetric assay and colony formation assay showed that SPC-A1 cell line and SPC-A1/DTX FBW7 O/E cell line were more sensitive to docetaxel than SPC-A1 FBW7 D/R cell line and SPC-A1 / DTX cell line. **Conclusion:** For non-small cell lung cancer, the sensitivity to docetaxel was higher in cells with high expression of FBW7 than the cells with low expression of FBW7; the loss of FBW7 gene was associated with drug resistance of NSCLC to docetaxel. However, the specific mechanism of FBW7 deletion causing non-small cell lung cancer resistance to docetaxel still needs further study.

Keywords: FBW7(F-box and WD repeat domain -containing7), non-small cell lung cancer, docetaxel

P2.01-42 IMPACT OF TOBACCO SMOKING ON OUTCOMES IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER IN THE ERA OF TARGETED THERAPY

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Background: Prior epidemiological studies have noted differences in the demographic and clinical characteristics among patients with metastatic non-small cell lung cancer (NSCLC) between those with and without exposure to tobacco smoke. Most notably never smokers are more likely to harbor genomic driver mutations and (in the era of targeted therapy) improved survival. Observational databases, capturing real world diagnostic and treatment patterns, can provide insights on outcomes of NSCLC based on smoking history. **Method:** The electronic health records (EHR) of patients with de novo stage IV NSCLC diagnosed between January 2013 and December 2016 from 30 cancer centers, contributing to the Cota Observational Cancer Database, from 184 oncologists were reviewed. **Result:** 1716 NSCLC pts were identified including 243 (14.2%) never tobacco smokers, 405 (23.6%) active smokers, 1026 (59.8%) former smokers, 7 (0.4%) passive smokers, and 29 (1.7%) not reporting. Never Smokers (NS) were more likely than smokers (S=active and former smokers combined) to be female (NS: 67.4%; S: 47.2%; p<0.0001) with similar ages (NS: 66 yrs; S: 67 yrs), but included more Asians pts (7.4% vs 1%, p<0.0001). Histologic subtypes differed: Squamous NS: 9%; S: 17.8%: (p<0.0001), AdenoCA NS: 73.2%; S: 68% (p=0.1), NOS N: 5.3%; S: 6.1% (p=0.8). Genomic profiling for EGFR/ALK was more common and identified more mutations in the NS cohort. In the non-squamous histologies EGFR testing was NS: 87% with 45.9% mutated; S: 70% with 10.4% mutated (tested p<0.0001; mutated p<0.0001). In the non-squamous histologies ALK testing was NS: 74% with 5.4% translocated ; S: 67% with 1.4% translocated (tested p=0.04; translocated p<0.001). As first line therapy 40% of NS received targeted therapy (11% receiving targeted 2nd line) whereas 4.8% S received 1st line and 1.5% 2nd line targeted therapy. The median overall survival for the NS cohort was 21 months compared to 11 months among S (log-rank p<0.05); with PFS of 9 vs 6 months (p<0.05). Excluding use of targeted therapy in 1st or 2nd line, the median OS for NS was 17 mo; for S was 10 mo (p<0.05). **Conclusion:** This real world observational study confirms a higher rate of targetable genomic driver mutations among never smoker NSCLC. Despite guidelines recommending universal genomic testing, never smokers are tested at a higher frequency. In the era of targeted therapy (but before the widespread use of immunotherapy) never smoker NSCLC patients experienced improved overall survival with and without targeted treatment compared to individuals with tobacco exposure.

Keywords: smokers, Real world data, non-small cell lung cancer

P2.01-43 ADSCAN: A RANDOMISED PHASE II STUDY OF ACCELERATED, DOSE ESCALATED, SEQUENTIAL CHEMO-RADIOTHERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC)

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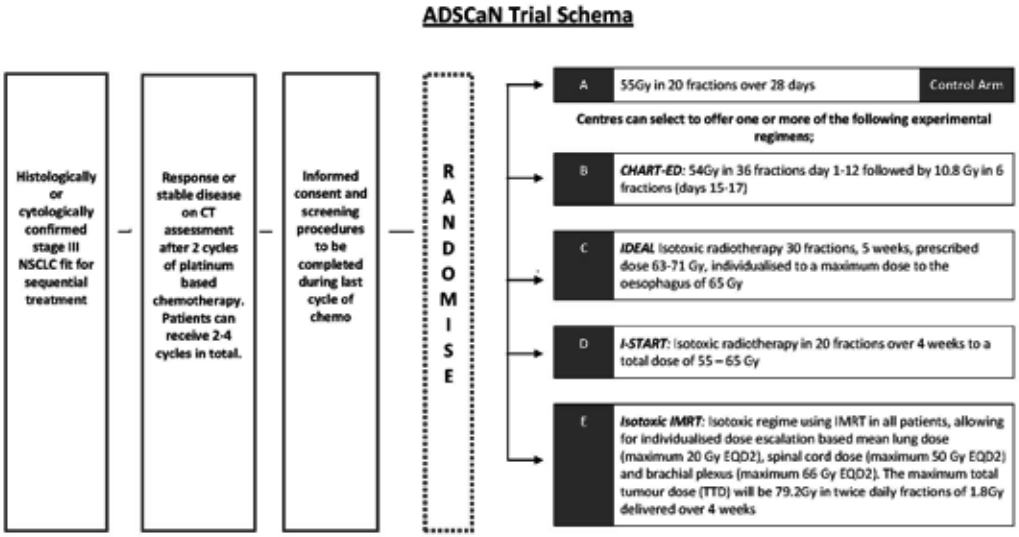
Background: Lung cancer is the most common cause of cancer mortality in the UK, and NSCLC accounts for approximately 85% of all lung cancers. Most patients present with inoperable disease therefore radiotherapy plays a major role in treatment. However, the majority of patients are not suitable for gold standard treatment (concurrent chemo-radiotherapy) due to performance status and comorbidities. Novel strategies integrating radiotherapy advances and radiobiological knowledge need to be evaluated in patients treated with sequential chemo-radiotherapy. Four separate accelerated dose escalated radiotherapy schedules have been completed in UK (CHART-ED[(1)], IDEAL-CRT[(2)], I-START[(3)] and Isotoxic IMRT[(4)]). ADSCaN will compare these schedules with a UK standard sequential chemo-radiotherapy schedule. A combined randomized phase II screening / 'pick the winner' approach will identify the best schedule to take into a randomised phase III study against conventionally fractionated radiotherapy. **Method:** Suitable patients will have histologically / cytologically confirmed, stage III NSCLC and be able to undergo chemo-radiotherapy treatment. The study will recruit 360 patients; 130 on the standard arm and 60 on each experimental arm. Patients will complete 2-4 cycles of platinum based chemotherapy before being randomised to one of the radiotherapy schedules. Logistic / capacity challenges make it impractical for sites to open all experimental trial arms; a novel trial design allows centres to select upfront the experimental arms they are able to participate in and all will offer the standard arm.



Result: CURRENT STATUS CRUK is funding this multicentre study which is being co-ordinated by the CRUK CTU Glasgow. The study opened to recruitment on 22/08/2017 with planned recruitment lasting 3 years 8 months. The study includes a tailored QA programme through the UK RTTQA Group. 20 of the 36 sites expressing interest have started the QA process, 12 have completed with a further 8 expected to complete in the next few months. **Conclusion:** Section Not Applicable

Keywords: Chemo-radiotherapy, non-small cell lung cancer, Sequential

P2.01-44 PROGNOSTIC VALUE OF TP53 HOT EXON MUTATION IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Numerous studies have revealed either very marginal or no prognostic value of *TP53* mutation NSCLC patients. Currently, in clinical settings, all *TP53* mutations have been considered equally, without any differentiation between the various types and positions of mutations. However, increasing evidence has triggered us to challenge such practice. **Method:** We retrospectively investigated the correlation between mutations occurring at hot exons (5-8) and overall survival (OS) in 214 previously tyrosine kinase inhibitor (TKI) treated advanced NSCLC patients. Among them, 184 had 1 line of TKI-treatment and the remaining 30 patients had more than 1 line of TKI-treatment. 115 harbored *TP53* mutation; among them 105 patients had concurrent *EGFR* mutation; 5 had *ALK* rearrangements; 1 had *ROS1* rearrangements; 1 had *KRAS* and 2 had *ERBB2* mutations. 99 patients had wild type (WT) *TP53*; among them, 92 had *EGFR* mutation, 4 with *ALK*-rearrangements, 1 with *MET* and 1 with *BRAF* mutation. Fisher's exact test and the Mann-Whitney test were used to determine if categorical and continuous variables, respectively, differed between *TP53* WT and mutant groups. **Result:** The prevalence of *TP53* mutation in our cohort is 53.7% (115/214); 28 had mutation on exon 5, 18 on exon 6, 22 on exon 7 and 32 on exon 8. 32 patients had loss of function mutation and 51 patients had disruptive mutation. Our data revealed a positive correlation with N and M stage. Patients harboring *TP53* mutation are more likely to diagnose with more advanced N (p=0.018) and M stage (p=0.001). Furthermore, patients with *TP53* mutation are more likely to have liver (p<0.001) and bone metastasis (p=0.012). In patients treated with only 1 line of TKI-treatment, although *TP53* status had no effect on PFS (p=0.241) and OS (p=0.49) when they were considered collectively, we observed patients with mutation in exon 5 had shorter OS (p=0.029) and mutation in exon 8 had shorter PFS (P=0.003) after controlling for age, gender, stage and histology.

Furthermore, within the osimertinib subgroup (N=101), patients harboring mutation in exon 8 had significantly shorter PFS (P=0.007). In patients treated with more than 1 line of treatment, neither *TP53* mutation considered collectively, nor hot exon mutations had correlation with PFS or OS. **Conclusion:** Our study revealed unfavorable prognostic value of mutations in exon 5 and no prognostic value of *TP53* if all mutations were considered collectively. Our study adds new dimension to the emerging picture that not all *TP53* mutants are equal.

Keywords: NSCLC, Prognosis, TP53

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-45 MUTATIONAL AND INFLAMMATORY BIOMARKERS FOR LUNG CANCER PATIENTS WITH PLEURAL EFFUSIONS

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Background: Pleural effusion is often associated with the progression of lung cancer and the treatment options for patients with malignant pleural effusions are rather limited. The estimation of prognosis remains to be challenging and personalized therapeutic strategies require a set of validated biomarkers. **Method:** 87 lung adenocarcinoma, 27 squamous cell carcinoma and 8 neuroendocrine carcinoma patients with pleural effusions were treated in our department between July 2016 and April 2018. Preoperative C-reactive protein and white blood cell count was collected and their association with clinicopathological parameters and overall survival was calculated. KRAS, EGFR and ALK mutational status was available in advanced lung adenocarcinoma cases. The association of oncogenic mutations with the malignancy of effusion was also analyzed. **Result:** 39 of the 122 patients had malignant pleural effusions (32%). 64 patients had TNM stage IV disease. Importantly, high CRP (>5 mg/dl, HR: 14.7, CI95% 2.9-73, p=0.0011) but not high WBC (>9000 cells per microliter) was a strong predictor of shorter survival in lung cancer patients with pleural effusions. High CRP remained a significant prognosticator in lung cancer patients with benign effusions (HR: 21.5, CI95% 1.9-242, p=0.013). KRAS mutation was identified in 28% of the lung adenocarcinoma cases. There was a tendency for lower KRAS mutation incidence in the MPE subcohort when compared to BPE cases (16.6% vs 34.6%, p=0.15). Interestingly, 22% of patients had EGFR mutation and EGFR mutations were more frequent in lung cancer patients with malignant effusions when compared to benign effusions (OR 4.8, CI95% 1.2-19.9, p=0.029). **Conclusion:** Oncogenic driver mutations may impact the development of malignant effusions in lung adenocarcinoma patients. Furthermore, our study indicates that the routinely available, circulating preoperative C-reactive protein level carries prognostic information. These findings suggest that oncogenic mutations and inflammatory biomarkers can further personalize therapeutic decisions and can contribute to the risk stratification of lung cancer patients with pleural effusions.

Keywords: pleural effusion, kras mutation, EGFR mutation

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-46 INVESTIGATING THE EFFECTS OF PRIOR MALIGNANCY ON NSCLC TRIAL ELIGIBILITY

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Background: Up to 18% of patients with non-small cell lung cancer (NSCLC) who are candidates for participation in a clinical trial are excluded due to a prior malignancy. Common reasons include the need for another anti-cancer therapy and potential impact on clinical trial endpoints. We evaluated the proportion of trials that exclude patients with a prior history of malignancy, and estimate the potential impact of the prior malignancy from a cohort of NSCLC patients treated with first line systemic therapy. **Method:** Clinical trials of palliative systemic therapy for NSCLC registered on or after January 1st 2014 from clinical trials.gov were reviewed to determine the proportion of trials that included a prior malignancy as an exclusion criterion. Patients with NSCLC and a prior malignancy, treated with first line palliative systemic treatment between January 1st 2010 and January 1st 2016 at the Princess Margaret Cancer Centre (PMCC), Toronto, Canada were identified from a cancer registry. A list of prespecified criteria of ways in which a prior malignancy may impact safety or a clinical trial endpoint was defined. These included: requirement for non-NSCLC anticancer therapies, other cancer detected on imaging, biopsy or tumour markers, disease progression or death from other malignancy, clinician uncertainty as to presence of synchronous other cancers. The proportions of patients with one or more of these criteria were assessed. **Result:** 66% of 359 clinical trial protocols contained an exclusion criterion for prior malignancy. 112 patients with advanced NSCLC and a prior malignancy were identified at PMCC, the median age was 71, 49% were male, the median time between prior cancer and NSCLC diagnosis was 74 months. 21% of patients were enrolled on a clinical trial. 52(59%) of the 88 patients not enrolled on a clinical trial did not meet any of our predetermined criteria, which may impact safety or a clinical trial endpoint due to other malignancy. **Conclusion:** A prior history of a malignancy is a common exclusion in NSCLC clinical trials. Preliminary results suggest the majority of patients in our study did not appear to have a complication that would have impacted safety or clinical trial endpoints. Further analyses to explore appropriate exclusion criteria for prior malignancies, which may minimize need to exclude patients from clinical trials, are underway.

Keywords: NSCLC, Prior Malignancy, clinical trial eligibility

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-47 CLINICAL OUTCOME AFTER SURGICAL RESECTION OF CLINICAL SINGLE-STATION N2 NON-SMALL CELL LUNG CANCER

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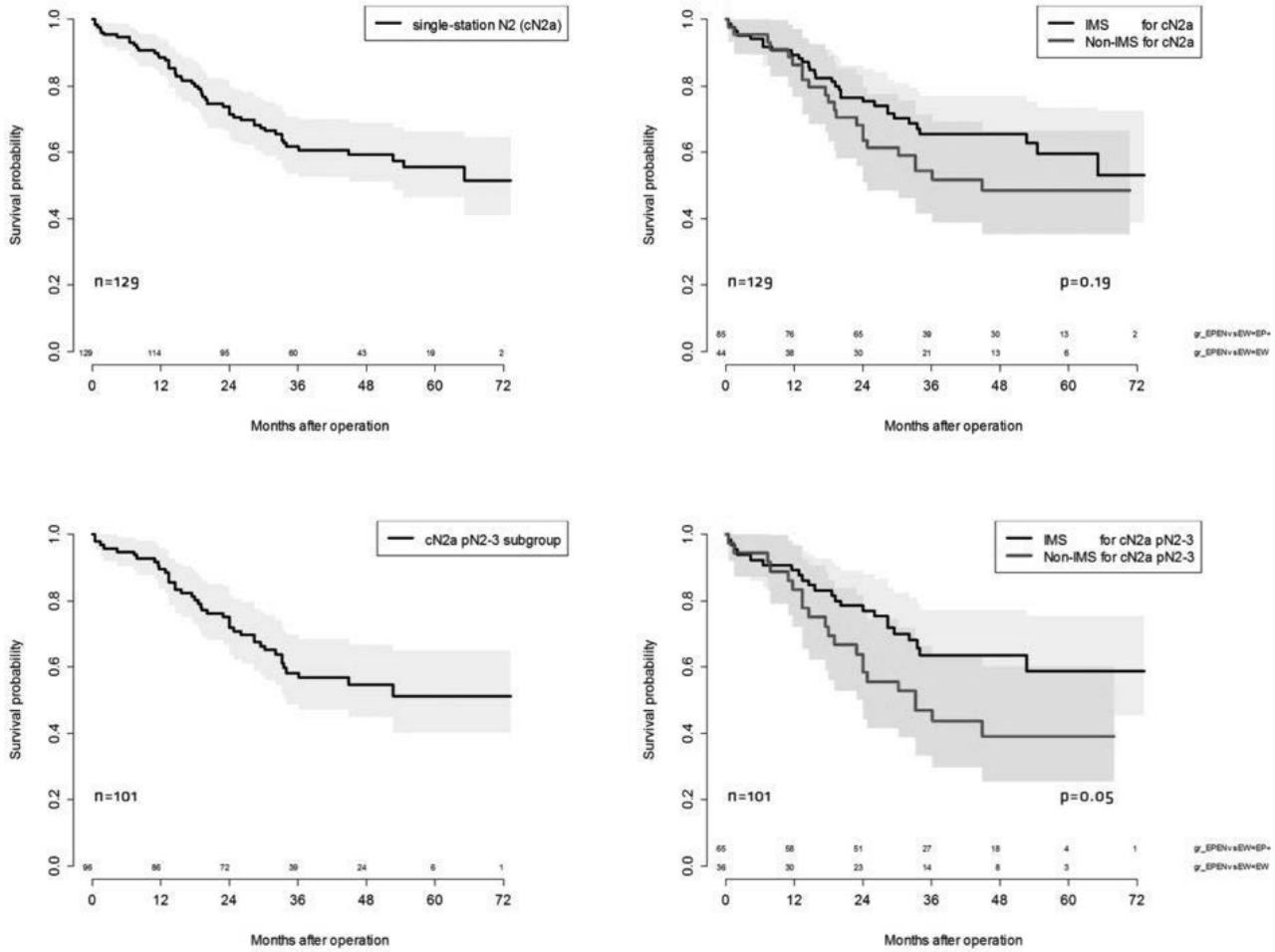
Background: We set up our treatment protocol performing upfront surgery for non-bulky, single-station clinical N2 (cN2a) patients. **Method:** Between 2012 and 2016, 129 patients underwent upfront surgery for cN2a disease diagnosed on CT and PET-CT findings. 85 patients underwent preoperative invasive mediastinal staging (IMS group), whereas, in 44, IMS was not performed (Non-IMS group). Survivals were compared with log-rank test. Subgroup analysis for pN2-3 is performed to identify prognostic factors using Cox-regression. **Result:** Pathologic N stages were pN0-1 in 26 patients (20%: 18 IMS, 8 non-IMS), pN2a in 51 (40%: 33 IMS, 18 non-IMS), pN2b in 47 (36%: 29 IMS, 18 non-IMS) and pN3 in 5 (4%: all IMS). The overall 5-year survival was 55.4% with no difference between groups (p=0.19). In pN2-3 patients, 5-year survival was 51.0% and IMS group was better (p=0.05). In a Cox's regression, non-IMS (HR 1.89, p=0.04), no adjuvant chemotherapy (HR 3.55, p<0.001), extensive burden of metastatic lymph nodes (number of metastatic LN≥13, HR 3.32, p=0.002) were independent risk factors for survival.

Univariate and multivariate analysis of overall survival in the subgroup of stage IIIA cN2-pN23

	Univariate analysis				Multivariate analysis	
Predictor Variable	HR	lcl	ucl	p value	HR (95% CI)	p value
Age at operation (≥ 70)	2.33	1.25	4.31	0.007	1.76 (0.83-3.75)	0.14
Gender (male)	1.54	0.76	3.11	0.23		
VATS	1.27	0.70	2.30	0.43		
Laterality (right)	1.12	0.62	2.03	0.72		
Cell type						
adenoca	1					
Others (SqCC, miscellaneous)	1.08	0.59	1.99	0.80		
pT3-4 (vs. pT1-2)	1.36	0.71	2.61	0.35		
pN2a (vs. pN2b+pN3)	0.94	0.52	1.70	0.83		
LN burden						
# of positive LN (cont.)	1.01	0.97	1.06	0.57		
# of positive LN (≥13)	1.77	0.90	3.52	0.10	3.32 (1.55-7.12)	0.002
Total harvested LN (cont.)	0.98	0.96	1.01	0.14		
Invasive mediastinal staging (IMS)						
IMS	1					
Non-IMS	1.83	1.01	3.30	0.05	1.89 (1.04-3.45)	0.04
No adjuvant chemotherapy	3.68	2.01	6.71	0.00	3.55 (1.71-7.35)	<0.001
Incomplete resection	3.58	1.1	11.64	0.03		

VATS, video-assisted thoracoscopic surgery; adenoca., adenocarcinoma; SqCC, squamous cell carcinoma; LN, lymph node; cont., continous variable;

HR is the hazard ratio and 95% CI is the confidence interval of the HR, estimated by Cox's proportional hazard regression model with backward elimination method



Conclusion: We found significant number of cN2a patients were pN2b-3 even after IMS, but surgery resulted in reasonable survival. This suggests upfront surgery for cN2a disease is a valid option if preoperative IMS and adjuvant chemotherapy are warranted.

Keywords: Single station N2, Upfront surgery, Invasive mediastinal staging

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-48 PREDICTIVE FACTORS IN NSCLC PATIENTS WITH STAGE IIIB/IV TREATED WITH FIRST LINE PLATINUM-DOUBLET CHEMOTHERAPY

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Background: Predictive factors for response to chemotherapy in non-small cell lung cancer (NSCLC) are deficient. We investigate the associations between mutation status and treatment outcome of first line platinum-doublet chemotherapy in a 1.5 years population-based cohort of stage IIIB/IV patients. Furthermore, we will investigate the usefulness of gene expression signatures in predicting chemotherapy response in patients with advanced NSCLC. **Method:** In the region of Skåne, Sweden, n= 600 (preliminary) patients with NSCLC stage I-IV (TNM 7th edition) had conclusive results from reflex NGS testing with Illumina TruSightTumor 26-gene panel between January 2015 – June 2016. From this cohort, we include all patients with stage IIIB/IV with first line platinum-doublet treatment not interrupted by other cause than progressive disease (PD) and evaluate their extra-cranial response to treatment by using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 with slight modifications. Patients who received radiotherapy against the primary tumor and/or mediastinum before or concomitant with chemotherapy are excluded. **Result:** So far, 91 patients have been included, 10 (11%) with stage IIIB and 81 (89%) with stage IV. First-line chemotherapy included carboplatin/cisplatin in combination with gemcitabine/pemetrexed/vinorelbine. Bevacizumab were given in addition to chemotherapy in 3 patients. 25 (28%) responded with progressive disease (PD), 27 (30%) with stable disease (SD) and 39 (43%) with partial response (PR). *TP53+/KRAS+* tumors were detected in 22 (24%) patients, *TP53+/KRAS-* in 34 (37%), *TP53-/KRAS+* in 21 (23%) and *TP53-/KRAS-* in 14 (15%). No difference in response to treatment (p=0.6, Fisher's exact test) or progression-free survival (PFS) (log rank test, p=0.6) according to mutation status was seen, although we observed a weak tendency of worse PFS in *TP53+* patients with or without *KRAS* mutation compared to *TP53-/KRAS-* patients. **Conclusion:** In this population-based Swedish cohort, mutations in *KRAS* and/or *TP53* are not significantly associated with first line chemotherapy response. However, also subtypes of these mutations should probably be considered. Additional analyses of potential predictors of treatment response, in association with other clinicopathological variables, will be presented.

Keywords: Advanced NSCLC, chemotherapy response

P2.01-49 COMPARISION OF RADIOTHERAPHY CONCURRENT WEEKLY TREATMENT IN LOCALLY ADVANCED UNRESECTABLE NON SMALL CELL LUNG CANCER

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Background: Despite concurrent chemoradiotheraphy is standard treatment of unresectable locally advanced non small cell lung cancer (NSCLC),optimal chemotheraphy regimen is still inconclusive. Radiotheraphy concurrent weekly chemotheraphy has been studying and due to less toxicity it is preferred. In this study, we aimed to compare two weekly different regimens in terms of outcome and toxicity . **Method:** We screened retrospectively 142 patients with stage III, locally advanced unresectable NSCLC, treated with radiotheraphy concurrent weekly platinum-paclitaxel (PP) or platinum-docetaxel (PD) between 2006 and 2017 years.Age, sex, stage, histologic subtype, response rates, survival and toxicity were analyzed. In RT concurrently PP arm 50 mg/m^2 paclitaxel and 20 mg/m^2 cisplatin or carboplatin AUC 2; in PD arm 20 mg/m^2 dosetaxel and 20 mg/m^2 cisplatin applied. Radiotheraphy applied as weekly 5 fraction/ 60-66 Gy. Treatment response classified progression and clinically responsive which consist of stable response (SR), complete response(CR) and partial response(PR). **Result:** One hundred thirty one (92,3%) patients were man and median age was 62 (25-79). Histologic subtype was squamous cell carcinoma in 77 (54.2%) patients. At diagnosis 53 patients (37,3%) were stage IIIA, 89 (62,7%) patients were stage IIIB and IIIC. There were 102 patients in DP arm whereas 40 patients were in PP arm. Age, gender, stage and histologic subtypes were similar in both groups.There were no statistically significant in clinically response rates between two group (PD 96,1% vs PP 90% , p = 0.15) . Median overall survival (OS) was higher in PP arm than PD arm (29 vs 14,4 months ,p=0,018). Progression free survival (PFS) were same in both arms (15,6 vs 15,4 months p=0,522).There were no statistically significant in mucositis and eosophitis(90% vs 80 %, p=0,418) and vomiting (10% vs 8,8%, p=0,931) in both arms. In PP arm neutropenia (p=0,000) and thrombocytopenia rates were higher (p=0,021). Pulmonary toxicity (p=0,053) and nausea (p=0,056) was higher in PP arm, which is closed to statistical significance. Although deaths due to treatment toxicity were not detected ,progression and other reason related death were more common in PD arm (p<0,001). **Conclusion:** In our study, despite clinical response and PFS were same in both radiotheraphy concurrent regimens in locally advanced unresectable NSCLC, OS was higher in PP arm. There are few study compared this two arms, which show no OS differences. Although it must be supported by prospective studies,OS is beter in PP arm than PD arm.

Keywords: lung cancer, locally advanced, weekly treatment

P2.01-50 THROMBOEMBOLISM IN ROS1 REARRANGED NON-SMALL CELL LUNG CANCER

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Background: The risk of thromboembolism (TE) is estimated to be 0.001% per year and hereditary thrombophilia present in 0.2-5% of the general adult population. It is estimated that 8-15% of patients with advanced non-small cell lung cancer (NSCLC) will develop thromboembolism throughout their disease course. In *ALK* rearranged NSCLC this incidence has been reported to be three to four fold higher at 36%. We sought to investigate the incidence in TE in a cohort of the rare *ROS1* rearranged molecular subgroup. **Method:** Electronic records were reviewed in six tertiary hospitals to identify all patients diagnosed with *ROS1* NSCLC. Predefined data were analysed in STATA15 software for Kaplan-Meier (KM) plot and Cox-regression modelling. **Result:** Forty-two patients were identified at data cut (31/1/2018). Median follow up was 10.9 months (mo); 38% had died. Median age was 53 years (31-80); 74% were female; 67% non-Asian and 88% non- smokers and 29% CNS disease during diagnosis. Median overall survival (OS) overall was estimated 28.8mo (range: 0.1-180.4mo). Thromboembolism incidence was 48% (n=20); 19 venous, 11 with pulmonary embolus (PE). One patient presented with fatal arterial TE (*ROS1* diagnosed pre-mortem). Median time to TE was 2.3mo. In four patients TE was the harbinger for their diagnosis and two had encountered unprovoked TE prior to diagnosis, one then recurrent TE throughout diagnosis. Screening for a thrombophilia (TP) was not mandatory, and tested in n=9/20 cases with TE, one without. A co-occurring TP was identified in 15% (n=3/20); two factor V Leiden; one anti-thrombin III (ATIII) deficiency. Of interest, one patient with TE had factor XII deficiency; one thalassaemia minor and one acute-promyelocytic leukaemia without evidence of disseminated intravascular coagulation. Age; race; baseline ECOG; smoking history; treatment received; brain metastases at diagnosis; hereditary thrombophilia and neutrophil to lymphocyte ratio were not predictive of TE in this small cohort. Median OS in patients with TE was 21.3mo (0.1-180.4) versus 28.83mo (1.2-63.5) with no TE; hazard ratio 1.16 (95%CI 0.43-3.15, p=0.77). The ROS-1 fusion partner was known in two cases, both CD74-ROS1, one encountering TE (PE). Twenty-five have archival tissue available to identify the fusion partner and explore an association with TE. **Conclusion:** To the best of our knowledge, this is the first report on the incidence of thrombotic events specifically in *ROS1*-rearranged NSCLC. In this small cohort intriguingly there was a high incidence of TE and a higher incidence than the general population of hereditary thrombophilia.

Keywords: ros1, thromboembolism, NSCLC

P2.01-51 STUDY OF CD26/DPP4 EXPRESSION IN A LARGE SERIES OF NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Lung cancer is a leading cause of cancer-related death worldwide and the prognosis remains poor CD26/dipeptidyl peptidase 4 (DPP4) is a transmembrane exopeptidase expressed on various hematopoietic but also somatic cells including malignancies of breast, colon, and mesothelioma. We previously found that the activity of CD26/DPP4 in human lung adenocarcinoma is four times higher than in normal lung tissue and the inhibition of CD26/DPP4 decreased the growth of lung tumors in experimental models. These data prompted us to analyze the expression of CD26/DPP4 in samples from lung cancer patients to unravel the role of CD26/DPP4 as a potential therapeutic target to reduce lung cancer burden. **Method:** To identify CD26/DPP4, we performed immunohistochemistry (IHC) on multi-organ tissue micro array (TMA) using four different antibodies. We finally selected the antibody produced by Cell Signaling Technology. For the analysis of CD26/DPP4 by IHC, TMAs constructed from the samples of non-small cell lung cancer patients were used. The cohort consisted of **1110 patients** (Adenocarcinoma (AC): 567; Squamous carcinoma (SC): 443). Three pathologists independently scored the staining intensity from zero to three in a blinded manner. Lung AC cell lines from tissue (H2347, H522, A549, and Hop62) and pleural malignant effusion (H1437, H460, Mai9, and Gon8) were employed to assess the expression of CD26/DPP4. ELISA was used to quantify CD26/DPP4 from cell lines. **Result:** Overall survival of the patients showed no difference between AC and SC groups. IHC scores revealed AC expressing significantly higher CD26/DPP4 levels vs. normal lung or SC (p=0.035, p<0.0001, respectively). In consistency with our previous findings, early stage cancer (IA) expresses significantly higher levels of CD26 than other stages IIB (p=0.0012), IIIA (p=0.0019), and IV (p=0.02) among AC samples. From our *in vitro* studies, we found that early stage derived cell line (H2347: stage I) expresses significantly more CD26/DPP4 compared to others (H522: stage II, A549 and HOP62 stage IV). In contrast, metastatic AC cell lines secrete significantly more CD26/DPP4 in culture medium compared to tissue derived cell lines, while the cellular level of CD26/DPP4 was higher in tissue derived cell lines. **Conclusion:** AC expresses significantly more CD26/DPP4 than SC. Furthermore, the expression of CD26/DPP4 was higher at early stages of AC compared to advanced stages. Human cell line data suggest that metastatic AC secretes CD26/DPP4 more actively than primary cancer. We therefore deem CD26/DPP4 to be a target for inhibition of human AC.

Keywords: NSCLC, CD26/DPP4, stage

P2.01-52 IDENTIFICATION OF LEPTOMENINGEAL METASTASIS-SPECIFIC EXOSOMAL MIRNA SIGNATURES IN CEREBROSPINAL FLUIDS OF NSCLC PATIENTS

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Background: Leptomeningeal metastasis (LM) is a devastating complication with poor prognosis in non-small-cell lung cancer (NSCLC) patients. The confirmed diagnosis of LM usually involves neurological evaluation, MRI imaging, and cytopathology analysis of limited tumor cells from cerebrospinal fluid (CSF). Exosomes are extracellular vesicles in body fluids enriched with microRNAs (miRNAs), which have been implicated to participate in brain metastasis. Here, we aimed to identify LM-specific exosomal miRNA signatures in NSCLC patients to elucidate their potential role in LM mechanism and to predict LM via liquid biopsy. **Method:** Exosomes prepared from CSF and plasma samples of 39 advanced NSCLC patients with (LM+) or without (LM-) LM as well as 12 non-cancer individuals (NC) were underwent small RNA next-generation sequencing. For patients in the LM+ group, paired plasma samples were taken before (P_{LM+pre}) and upon ($P_{LM+post}$) LM diagnosis. Exosomal miRNA profiles were subjected for differential expression analysis, pathway enrichment analysis, and signature discovery. **Result:** Unsupervised hierarchical clustering of the miRNA expression profiles clearly separated CSF samples into LM+ and LM free groups (LM- and NC). Interestingly, these samples were stratified based on their LM status only, regardless of their intraparenchymal metastasis status. In total, 247 (185 up and 62 down-regulated) miRNAs were identified differentially presented in the LM+ CSF exosome samples compared to the LM- and NC groups. Top altered miRNAs include dramatically up-regulated miR-200 family and down-regulated miR-144/451 cluster. Predicted gene targets of these top-regulated miRNAs were significantly enriched in Ras/MAPK/PI3K-AKT signaling, endocytosis pathways, and so on. Promisingly, a signature of five CSF exosomal miRNAs (let-7e-5p, miR-28-3p, miR-375, miR-200a-3p, and miR-486-5p) was identified for classification of LM+ patients with 100% sensitivity and 100% specificity. Due to the higher background complexity, we only identified one miRNA (miR-24-3p) was significantly up-regulated and one miRNA (miR-92b-5p) was significantly down-regulated in LM+ patients' plasma-derived exosomes (P_{LM+pre} and $P_{LM+post}$) compared with the LM free group (P_{LM-} and P_{NC}). However, a combined signature of seven miRNAs (miR-24-3p, miR-223-3p, miR-340-5p, miR-27a-3p, miR-423-5p, miR-2110 and miR-342-5p) from P_{LM+pre} samples was identified for the prediction of future LM with 81% sensitivity and 76% specificity. **Conclusion:** NSCLC patients with LM present a remarkably distinct CSF exosomal miRNA signature, which may involve in the progression of LM, and can be used as diagnostic biomarkers for LM. Furthermore, the identification miRNA signature in the pre-LM plasma samples suggests the potential use of liquid biopsy to predict LM for better patient care.

P2.01-53 LOCAL TREATMENT FOR OLIGOPROGRESSION/OLIGOMETASTASES AFTER FAILURE TO CRIZOTINIB FOR ALK-REARRANGED STAGE IV LUNG CANCER

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Background: Crizotinib is approved as 1st line treatment for ALK-rearranged stage IV non-small-cell lung cancer (NSCLC). We investigated if local treatment for oligoprogression/metastases (<=5 lesions) while maintaining crizotinib could prolong progression-free survival (PFS) for ALK-rearranged stage IV NSCLC. **Method:** This is a retrospective review on crizotinib for ALK-rearranged stage IV NSCLC in the real-world setting in 4 public oncology hospitals. All patients who received crizotinib outside clinical trials were reviewed. Patients who developed oligoprogression/metastases following progressive disease to crizotinib were assessed for local treatment (surgery, palliative or radical radiotherapy or combination of surgery and radiotherapy) for these sites while continuing crizotinib until further progressive disease beyond the definition of oligoprogression/metastases. The primary study endpoint is PFS after local treatment for olioprogression/metastases. Secondary endpoints are overall survival and toxicity profiles. **Result:** A total of 165 patients were recruited, of which 115 (69.7%) and 50 (30.3%) received it as 1st line treatment and at later lines respectively. Of the 161 (97.6%) patients eligible for tumour response assessment, the objective response rate was 64.5%. After a median follow up of 18.5 months (range 0.6-70.1 months), the median PFS and OS of the whole population were 10.8 and 18.5 months. There was no statistical difference in PFS and OS among those who received crizotinib as 1st line and later lines. Twenty-nine (17.6%) patients developed oligoprogression/oligometastasis following crizotinib. Eighteen (62.1%) received local treatment (surgery – 2 , stereotactic radiosurgery/radiotherapy – 7, intensity-modulated radiation therapy/tomotherapy – 3, palliative radiotherapy – 7), of whom 3 patients received 2 courses of local treatment to different oligoprogressive/oligometastatic sites at oncologists' discretion while continuing crizotinib until their next date of progressive disease. Median PFS was significantly longer in those who received local treatment (20.9 months [95% CI 11.8-30.1 months] vs. 11.4 months [95% CI 5.1-17.7 months]; p=0.004) than those who did not for their oligoprogression/oligometastases. Median OS was not different between those who received local treatment and those who did not for their oligoprogression/oligometastases (p=0.742). Seventy-one (43.0%) patients received other ALK inhibitors following progression to crizotinib (1 line – 50, 2 lines – 19, 3 lines – 1, and 4 lines – 1). Four (2.4%) patients are still receiving crizotinib without progression. Crizotinib was well-tolerated with only 7.9% grade 3/4 adverse events. No grade >=2 events were reported for local treatment. **Conclusion:** Local treatment for oligoprogressive/metastatic diseases could significantly prolong PFS in the real-world setting, which procrastinates the later use of other systemic therapies.

Keywords: oligoprogression/oligometastases, anaplastic lymphoma kinase (ALK), crizotinib

P2.01-54 PREDICTIVE FACTORS FOR THROMBOEMBOLISM IN ADVANCED LUNG CANCER PATIENTS ON PLATINUM CHEMOTHERAPY: A PROSPECTIVE STUDY

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Background: Advanced lung cancer patients are predisposed to thrombosis due to many factors related to the disease and treatment, apart from the genetic and phenotypic factors. We aimed to determine the incidence of thromboembolic events (TEs) in advanced Non-Small Cell Lung Cancer (NSCLC) patients treated with platinum chemotherapy and study the baseline and treatment attributes predicting the onset of such events. **Method:** We evaluated advanced NSCLC patients on platinum chemotherapy for predetermined risk factors for thrombosis at baseline and routine visits. Patients with prior thromboembolism were excluded. The baseline patient characteristics were noted and patients were assigned to Khorana risk group as per the Khorana scores. The duration of follow up was until 4 weeks from the last chemotherapy. TEs occurring between the first dose of chemotherapy and 4 weeks after the last dose were considered as related. Predetermined factors associated with thromboembolism were studied in univariate analysis by chi square test. **Result:** A total of 188 patients were screened, out of which 21 patients were excluded and two patients were lost to follow up. The mean age of was 57.5 years (range 30–79). Majority of the patients were male (83.2%) and either current or former smokers (62.3 %). 69.5% of patients had a normal Body mass Index (BMI) while 13.2 % were overweight (BMI 25-29.9 kg/m$^{2)}$ and 1.2 % were class I obese (BMI 30-34.9kg/m^2). Majority of the patients (78.1%) belonged to the intermediate Khorana group (Risk score 1-2) while 23.0% belonged to high risk (Khorana score of ≥3) .Of the 165 patients who completed follow up, 67.8% received carboplatin-gemcitabine, 30.3% carboplatin-pemetrexed, 1.2% cisplatin-pemetrexed and 0.6 % carboplatin-paclitaxel. Median duration on platinum was 94 days (range 1-478). TE's occurred in 4.8% of patients. Three patients developed venous pulmonary thromboembolism and 5 patients developed cerebral infarction, out of which 4 had arterial cerebral infarction and one patient had superior sagittal sinus thrombosis. The majority of events (7 out of 8) occurred within 100 days of starting chemotherapy. None of the presumed risk factors were found to be related to TEs on univariate analysis. **Conclusion:** Despite the lower incidence of TEs in our study, exclusion of patients with prior thrombosis suggests de novo thrombosis on platinum chemotherapy .None of the predetermined risk factors for thrombosis were found to be statistically related to the occurrence of TEs, possibly due to the small number of events and sample size.

Keywords: lung cancer, thromboembolism, platinum chemotherapy

P2.01-55 DUAL-ENERGY CT SCAN TO EVALUATE SARCOPENIA IN LUNG CANCER IN COMPARISON WITH CONVENTIONAL CT SCAN

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Background: Depletion of skeletal muscle mass (sarcopenia) have been associated with poor prognosis in patients with malignancy. Although CT-determined skeletal muscle index (muscle area/height^2, cm/m^2) is regarded as a reference standard to evaluate the presence of sarcopenia, it is unclear the agreement of DECT derived images on the quantification of skeletal muscle area (SMA). The purpose of this study to evaluate the agreement of SMA quantification between dual-energy CT (DECT) derived images (virtual non-contrast; VNC and post-contrast weight-average 120kVp images) and conventional non-contrast CT image. **Method:** For a total 128 lung cancer (LCA) patients who underwent DECT at the time of diagnosis, SMA were measured using non-contrast CT, and DECT images (post-processed VNC and weight-average 120kVp). Paired T-test was used to compare the quantification results, and intraclass correlation coefficients (ICC) for the agreement between three scan results. **Result:** The agreement was excellent (ICC=0.991) between three images. However, SMA was significant higher in VNC (mean±SD, 125.2±23.8cm^2, p<0.001) and weight-average 120kVP (110.4±22.0cm^2, p<0.001) in comparison with non-contrast CT (107.4±22.7cm^2). When using recently proposed L1 muscle index cutoff (46 cm/m^2 for male, 29 cm/m^2 for female) for sarcopenia, the prevalence of CT-determined sarcopenia is significantly decreased using weight-average 120kVp and VNC to 53.1% and 22.7%, compared with 58.6% using non-contrast CT. **Conclusion:** DECT derived VNC and weight-average 120kVp images slightly overestimate SMA. Same scan parameter is recommended to minimize measurement error to evaluate sarcopenia.

Keywords: skeletal muscle mass, dual energy CT, sarcopenia

P2.01-56 METASTASES IN RESIDUAL PET UPTAKE OF LYMPH NODES AFTER TREATMENT: ADDED VALUE OF CT RADIOMIC APPROACH FOR PREDICTION

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Background: Although substantial decrease of FDG uptake on positron emission tomography-computed tomography (PET-CT) holds promise metabolic response, predicting pathologic complete response of lymph nodes still remains challenging. We investigated the potential of CT radiomics features to predict pathologic complete response of lymph nodes showing residual uptake on PET-CT after neoadjuvant concurrent chemoradiotherapy (CCRT) in stage IIIa non-small cell lung cancer (NSCLC). **Method:** From 2004 through 2013, all consecutive patients who underwent neoadjuvant CCRT for stage IIIa NSCLC, post-treatment PET-CT, and curative operation were included. As for all lymph nodes which showed remaining positive FDG uptake on restaging PET-CT, 161 CT Radiomic features from physical, shape, histogram, texture, regional feature categories were extracted. Positive and negative lymph node metastases were compared with respect to clinicopathologic characteristics as well as CT radiomic features using the Pearson $\chi 2$ test or the Fisher exact test Multivariate logistic regression was used to explore the predictive model for the the detection of metastatic lymph nodes, for which receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance. **Result:** Of 237 patients undergoing neoadjuvant CCRT for stage IIIa NSCLC, 135 patients (56.9%) showed residual PET uptake on 177 lymph nodes after treatment. Among those 177 lymph nodes, 70 lymph nodes were proven to be malignant (39.5%, 70 of 177). On multivariate analysis, metastatic lymph nodes were significantly tended to be more squamous cell carcinoma than adenocarcinoma (odds ratio [OR] = 0.370, 95% confidence interval [CI] = 0.190 to 0.722; reference of adenocarcinoma, P value = 0.004) and higher entropy-GLCM (OR = 1.437, 95% CI = 1.147 to 1.802, P value = 0.002), where the predictive model for metastasis showed discrimination performance with an area under the receiver operating characteristic curve (AUC) of 0.770 (95% CI = 0.700 to 0.839, P value < 0.001). **Conclusion:** Radiomic approach allows for noninvasive detection of lymph node metastases in lymph nodes showing residual PET uptake after treatment in NSCLC patients

Keywords: quantitative imaging analysis, Radiomics, lymph node metastasis

P2.01-57 PROGNOSTIC IMPLICATION OF CLINICAL, IMAGING, AND PATHOLOGIC PARAMETERS IN N2(+) STAGE IIIA LUNG CANCER PATIENTS

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Background: As a comprehensive study of large scale and long-term clinical outcomes from a single institution, we are trying to analyze any predictive or prognostic factors for survival outcomes in N2(+) NSCLC patients. The purpose of this study is to investigate the efficacy of clinical, imaging (CT and PET-CT), and pathologic parameters, as a prognostic factor in N2(+) NSCLC patients undergoing tri-modality therapy. **Method:** We retrospectively reviewed 160 patients with N2(+) NSCLC patients between January 2008 and June 2014. All patients underwent preoperative concurrent chemoradiotherapy (CCRT) (44-45 Gy in 22-25 fractions concurrent with weekly DP chemotherapy) and surgery. Clinical, imaging (CT and PET-CT), and pathologic parameters were analyzed with respects to outcomes. **Result:** Overall pathologic down-staging and pathologic complete response following preoperative CCRT were achieved in 66 (41.3%) and 13 patients (8.1%), respectively. The median follow-up durations of all patients was 43 months (2~106 months). The 5-year rates of disease-free survival (DFS) and overall survival (OS) were 33.3% and 53.0%, respectively. Pathologic N down-staging (HR 2.604; 95% CI 1.418-4.779; p value=0.002) was a significant factor for DFS. Histopathology (HR 0.475; 95% CI 0.242-0.930; p =0.030), GTV of nodal lesion(s) on pre-RT CT (HR 1.066; 95% CI 1.029-1.104; p <0.001), type of surgery (HR 2.985; 95% CI 1.114-7.997; p =0.030), and proportion of viable tumor on cross-section area (HR 0.986; 95% CI 0.973-0.999; p =0.034) were significant factors for OS. Neither tumor volume reduction rate (TVRR) nor SUVmax was significant for DFS or OS. **Conclusion:** In patients with N2(+) NSCLC undergoing tri-modality therapy, we proved that none of the imaging parameters correlated with prognosis, except pretreatment nodal volume. We confirmed that patients with adenocarcinoma showed prominently improved survival and pathologic N down-staging was a most important pathologic parameter as a prognosticator.

Keywords: non-small cell lung cancer, Stage IIIA, prognostic factor

P2.01-58 DEMOGRAPHICS, CLINICAL CHARACTERISTICS AND TREATMENT SEQUENCING IN STAGE III UNRESECTABLE NSCLC PATIENTS: A CANCERLINQ COHORT

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Background: To describe the demographics, clinical characteristics and treatment sequencing among a real-world cohort of stage III unresectable non-small cell lung cancer (NSCLC) treated with chemoradiation therapy (CRT) in the US. **Method:** Cancerlinq Discovery Database (CLQ), launched by the American Society of Clinical Oncology (ASCO) in 2016, consists of longitudinal, demographically and geographically diverse data aggregated from oncology practice Electronic Health Record (EHR) databases in the US. This retrospective cohort comprises 324 stage III unresectable NSCLC patients who received concurrent, platinum-based chemoradiation between January 1, 2007 and December 31, 2017 (study period). A patient was considered unresectable if s/he did not have surgery within 6 months of the stage III diagnosis date (study index date). A patient's follow-up period was defined as the time from study index date until the end of the study period, patient death, or loss to follow up, whichever event occured first. **Result:** The cohort was mostly male, white, with a mean age of 66.86 years at index date. Nearly all patients of the cohort (93.57%) had an initial diagnosis of stage III (75.31% IIIA, 2.78% IIIB); 2.47% had an initial stage I diagnosis and 4.00% had an initial diagnosis of stage II. The most common histology was squamous cell carcinoma (46.61%), followed by adenocarcinoma (41.05%). Curation

related to clinical characteristics (eg ECOG status, smoking status and other comorbidities) are ongoing, so they are largely missing at this time. During the mean follow-up time of 26.64 months, the cohort received 1.60 lines of therapy (LOT). The most common treatment sequence during the follow-up period consisted of platinum therapy +CRT (82.72%); almost 10% of patients received platinum therapy +CRT, followed by immuno-oncology (IO) therapy. Approximately 38.30% of patients progressed to line of therapy 2 (LOT2) and 29.84% progressed to line of therapy 3 (LOT3), with nearly 18% of patients receiving IO therapy during LOT2 or LOT3. **Conclusion:** This exploratory analysis of a stage III unresectable NSCLC cohort is descriptive in nature and suggests that the CLQ Discovery Database can be used to construct generalizable cancer cohorts. Future analyses will focus on validation of CLQ as a real-world data source, using findings from other retrospective, observational studies conducted by AstraZeneca as a benchmark.

Keywords: non small cell lung cancer, Cancerlinq, Unresectable

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-59 THE COST OF LUNG CANCER IN THE COUNTY OF GÄVLEBORG – SWEDEN

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Background: Lung cancer is the leading cause of cancer morbidity and mortality, both of which imply that its burden may be high upon the health services and society. The purpose of this study is to present an economic analysis of the actual care costs of lung cancer which will allow comparison with, and verification of, cost estimates that were developed through modelling and opinion. **Method:** A chart review was conducted of incident cases of all patients with newly diagnosed lung cancer during 2015 in the Department of Respiratory Medicine, Gävle Hospital. Cases were censored at two years from the date of diagnosis. Data was retrospectively collected from patient charts. This data included patient characteristics, tumour characteristics, treatment details, adverse events, survival and resource use. Relevant clinical and health utilization data were collected. Health utilization data included hospital and institutional outpatient (ie, ambulatory clinic) costs. The present analysis was performed from the economic perspective of the health care institution. **Result:** A total of more than 13 000 health service events were captured. Laboratory tests, diagnostic imaging and ambulatory visits constituted 86% of the service events while patient admissions and therapy constituted 76% of the costs. The vast majority of overall costs occurred just before, or within, three months of diagnosis. The cost for imaging was 344042 USD and for diagnostic procedures was 204272 USD. The total cost for chemotherapy was 651879 USD. More data will be presented during the conference. **Conclusion:** The results agree with the literature that the majority of lung cancer case costs are realized around the date of diagnosis (ie, early phase). The present study illustrates Swedish health care system lung cancer case costs based on actual care received .The majority of the costs occurred soon after diagnosis. These results gave an assessment of all persons treated, the course of the treatment and, thus, is an accurate assessment of costs for policy-making purposes.

Keywords: Lugn cancer, cost effectiviness, health economic

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-60 CLINICAL UTILITY OF CIRCULATING TUMOR CELL (CTC) ANALYSIS USING TARGET SELECTOR™ IN METASTATIC NSCLC CHEMOTHERAPY PATIENTS

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Background: Over half of lung cancer patients present with advanced stage disease at diagnosis. Liquid biopsy is emerging as a minimally invasive and cost-effective means of cancer biomarker evaluation to select appropriate treatment and monitor disease burden. CTC enumeration may have prognostic and predictive potential for patients receiving chemotherapy. Here we describe interim results of a prospective study analyzing blood CTCs from treatment-naïve patients with histologically confirmed metastatic non-small cell lung cancer (NSCLC) who are candidates for systemic cytotoxic chemotherapy. **Method:** Venous blood samples were obtained for CTC analysis before administration of chemotherapy on treatment days (D) 1, 8, 22 and 43, and at disease progression. Blood was collected in Biocept CEE-Sure™ blood collection tubes, and samples were processed at Biocept's CLIA-certified, CAP-accredited laboratory. Biocept's Target Selector™ CTC platform uses an antibody capture cocktail and microfluidic channel for CTC capture and biomarker analysis. Study objectives include determining the proportion of patients with D1 CTC detection, and CTC correlation to time to progression and overall survival (OS). **Result:** Twenty-three patients have been enrolled so far in this ongoing study: 16 (69.5%) adenocarcinoma, 7 (30.4%) squamous cell carcinoma. Fifteen patients progressed on initial therapy to date, with a median time to progression of 110 days. Of 22 patients with blood collections at D1 (treatment start), 14 (63.6%; 10 adenocarcinoma, 4 squamous) had detectable CTCs. For patients with detectable D1 CTCs, CTC count at D8 decreased in 13/14 (92.9%; 9 adenocarcinoma, 4 squamous) subjects, and was unchanged in 1 individual (7.1%; adenocarcinoma). Patients with 1-5 CTCs at D1 had a mean time to progression of 140.75 days; patients with >5 CTCs at D1 had a mean time to progression of 101.83 days (p=0.17). Among patients with undetectable CTCs at D1, CTCs remained undetectable in 4/8 (50%; all adenocarcinoma) and increased in 2/8 (25%; one each of adenocarcinoma and squamous) of subjects; CTCs were not collected at D8 for 2 individuals. **Conclusion:** Implementation of Biocept's TargetSelector™ enables the highly sensitive detection of CTCs in the clinical setting. CTCs are detectable in the majority of patients with metastatic NSCLC. In subjects with detectable CTCs prior to chemotherapy, CTC count declines within a week after starting chemotherapy in >90% patients. Preliminary data suggest that CTC enumeration may have prognostic and predictive potential for patients receiving chemotherapy. Further data from this ongoing study may provide additional insight into the role of CTC analysis applied to clinical practice.

Keywords: Circulating tumor cells, Metastatic non-small cell lung carcinoma

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-61 BODY MASS INDEX OVER TIME IS ASSOCIATED WITH OVERALL SURVIVAL IN ADVANCED NSCLC PATIENTS TREATED WITH IMMUNOTHERAPY.

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Background: Cachexia has been associated with inferior outcomes for patients with stage III/IV NSCLC (aNSCLC). This study evaluates the potential relationship between baseline and longitudinal body mass index (BMI) with progression free survival (PFS) and overall survival (OS) in aNSCLC patients on nivolumab or pembrolizumab. **Method:** Patients with aNSCLC who received at least once cycle of nivolumab or pembrolizumab between January 2015 and January 2017 were identified in our pharmacy database. Patient demographics, longitudinal BMIs, treatment start date, date of progression, and last follow-up were recorded. OS and PFS were assessed by log-rank tests and Cox proportional hazard analysis. Time-dependent Cox model based analyses were used to assess the association between time dependent BMIs. **Result:** The study included 162 aNSCLC patients. Median age 68 yrs, male/female 40.1%/59.9%. BMI values were obtained longitudinally at baseline, 6 wks, and 12 wks. Median BMI: baseline 24.69, at 6 wks 24.75, and at 12 wks 24.89. Median change in BMI: baseline to 6 wks = -0.50 (range: -5.79 to +2.92), baseline to 12 wks = -0.33 (range: -6.52 to +3.41), and 6 wks to 12 wks = -0.21 (range: -4.56 to +2.73). Hazard ratios for change in BMI with OS: baseline to 6 wks HR 0.7198 (p=0.0010), baseline to 12 wks HR 0.8703 (p=0.0553), and 6 wks to 12 wks HR 0.8284 (p=0.0668). **Conclusion:** Change in BMI over time is associated with OS in aNSCLC patients treated with nivolumab or pembrolizumab. Although decrease in BMI may simply be a prognostic marker for treatment with immune checkpoint inhibitors, it is possible that understanding potential relationships between cachexia and the immune system may be useful in developing strategies to improve response to immunotherapy.

Keywords: advanced NSCLC, Immunotherapy, Body mass index

P2.01-62 EXTRACELLULAR VESICLE-BASED EGFR GENOTYPING IN BRONCHOALVEOLAR LAVAGE FLUID FROM NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Liquid biopsies for EGFR genotyping using plasma cell-free DNA (cfDNA) have limited value due to low sensitivity. Extracellular vesicles (EV) have been proven to contain mutant EGFR DNA in bronchoalveolar lavage fluid (BALF) from non-small cell lung cancer (NSCLC) patients. As an alternative to plasma liquid biopsies using cfDNA, we investigated the feasibility of EV-based liquid biopsy for EGFR genotyping using BALF from NSCLC patients, prospectively. **Method:** EV DNA was extracted from the BALF of NSCLC patients with confirmed tissue/cytology-based EGFR genotyping at initial diagnostic work-up stage. (N=137) The number of patients with stage I, II, III, and IV are 37 (27%), 6 (4.4%), 23 (16.8%), 71 (51.8%), respectively. The patients were selected by favorable demographic data for EGFR mutation. EGFR mutation testing was done by peptide nucleic acid (PNA) clamping-assisted fluorescence melting curve analysis. **Result:** The overall sensitivity and specificity of EGFR genotyping using BALF EV DNA were 69.5% and 83.3% and the concordance rate was 77.4%. (Kappa=0.534, *P*=0.000) The sensitivity was significantly increased along with the stage (42.1% in stage I, II, 60.0% in stage III, and 100% in stage IV). Especially, in stage IV disease, BALF EV-based EGFR typing did not miss all of tissue-proven 30 EGFR mutant cases and detected 9 additional mutant cases. Detection of EGFR mutation becomes significantly more sensitive as T stage increases. (T1 = 43.8%, T2 = 75%, T3 and T4 = 100%) Turn-around time (TAT) for EGFR genotyping using BALF EV DNA was 1-2 days, while it takes usually 2 weeks for tissue typing. **Conclusion:** BALF EV-based EGFR genotyping is a novel and highly promising method with rapid TAT and incredible accuracy in stage IV NSCLC patients. Further research in early stage disease is necessary and the matter of over-detection should be clinically validated by evaluating EGFR-TKI drug response.

Keywords: Bronchoalveolar lavage fluid, liquid biopsy, Extracellular vesicles (EV)

P2.01-63 ARE HEART DOSES ASSOCIATED WITH SURVIVAL IN NSCLC TREATED WITH POST-OPERATIVE RADIOTHERAPY? A NATIONAL POPULATION-BASED STUDY

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Background: Some early studies suggested that post-operative thoracic radiotherapy (PORT) using non-modern radiation techniques in non-small cell lung cancer (NSCLC) might cause significant treatment-related toxicities. Higher radiation doses to the heart have been recently linked to more cardiac events and worse overall survival (OS) in patients with locally-advanced NSCLC treated with thoracic irradiation. We embarked on a national population-based study to assess the association between radiation heart doses, acute myocardial infarct (AMI) rates and OS in NSCLC patients treated with PORT using contemporary radiation techniques. **Method:** Study eligibility criteria included stage I to III NSCLC treated with PORT from 2007 to 2014 in our public hospitals which comprised about 80% of national caseload. The clinical and dosimetric data were collected from the institutional electronic medical records and linked to the national death and AMI registries. Univariate Cox regression was performed using STATA version 13. **Result:** 43 eligible patients were identified. Median follow-up duration was 36.6 months. Characteristics of study population are summarized in Table 1. There were no AMI events. The 1- and 2-year OS were 74% and 65%. Univariate Cox regression analysis showed that age (hazard ratio, 1.06; 95% confidence interval, 1.01 to 1.10; P= 0.008) was the only significant factor associated with OS. Radiation heart doses, including mean heart dose, volume of heart receiving at least 5, 25, 30, 40, 50 Gy and dose to 30% of heart volume, were not associated with OS.

Table 1: Characteristics of Study Population

Characteristics	N= 43
Sociodemographic and Clinical Characteristics	
Age at lung cancer diagnosis, year, median (IQR)	63.6 (54.2-67.0)
Gender	
Male	18 (41.9%)
Female	25 (58.1%)
Eastern Cooperative Oncology Group performance status	
0 and 1	41 (95.4%)
2	2 (4.6%)
Smoking status	
Current and former smoker	14 (32.6%)
Never smoker	29 (67.4%)
Diabetes mellitus	
Yes	7 (16.3%)
No	36 (83.7%)
Pre-existing ischaemic heart disease	
Yes	6 (14.0%)
No	37 (86.0%)
Chronic obstructive pulmonary disease	
Yes	1 (2.3%)
No	41 (97.7%)
Use of positron emission tomography-computed tomography for staging	
Yes	19 (44.2%)
No	24 (55.8%)
Use of brain magnetic resonance or contrast computed tomography for staging	
Yes	35 (81.4%)
No	8 (18.6%)
Tumour Characteristics	
Histology	
Adenocarcinoma	31 (72.1%)
Squamous cell carcinoma	5 (11.6%)
Non-small-cell lung cancer, not otherwise specified	7 (16.3%)
Tumour laterality	
Left	16 (37.2%)
Right	27 (62.8%)
Lobar location of tumour	
Upper	25 (58.1%)
Middle	5 (11.6%)
Lower	13 (30.2%)
Pathological T stage	
T1	15 (34.9%)
T2	19 (44.2%)
T3	6 (13.9%)
T4	3 (7.0%)
Pathological N stage	
N0	10 (23.3%)
N1	4 (9.3%)
N2	29 (67.4%)
Overall pathological stage	
Stage I	3 (7.0%)
Stage II	9 (20.9%)
Stage III	31 (72.1%)
Resection margin status	
R0	28 (65.1%)
R1	13 (30.2%)
R2	2 (4.7%)
Treatment Characteristics	
Type of surgery	
Lobectomy	36 (83.7%)
Pneumonectomy	7 (16.3%)
Use of concurrent or sequential chemotherapy	
Yes	31 (72.1%)
No	11 (25.6%)
Unknown	1 (2.3%)

Table 1: Characteristics of Study Population	
Characteristics	N= 43
Type of chemotherapy used Cisplatin + vinorelbine Cisplatin + gemcitabine Cisplatin + pemetrexed Carboplatin + vinorelbine Carboplatin + gemcitabine Carboplatin + pemetrexed Carboplatin + paclitaxel	 13 (30.2%) 6 (14.0%) 4 (9.3%) 2 (4.7%) 2 (4.7%) 2 (4.7%) 2 (4.7%)
Thoracic radiation technique 3D-conformal Intensity-modulated radiation therapy or Arc therapy	 30 (69.8%) 13 (30.2%)
Prescribed thoracic radiation dose, Gy, median (IQR)*	60.0 (50.0-60.0)
Dosimetric Characteristics	
Mean heart dose, Gy, median (IQR)	9.4 (2.3-14.6)
Heart volume received at least 5 Gy (heart V5), percentage, median (IQR)	34.0 (9.7-46.0)
Heart volume received at least 25 Gy (heart V5), percentage, median (IQR)	15.0 (2.0-24.0)
Heart volume received at least 30 Gy (heart V5), percentage, median (IQR)	12.3 (1.0-20.0)
Heart volume received at least 40 Gy (heart V5), percentage, median (IQR)	4.6 (0.0-14.5)
Heart volume received at least 50 Gy (heart V5), percentage, median (IQR)	2.0 (0.0-6.0)
Dose to 30% of heart volume (heart D30), Gy, median (IQR)	7.4 (1.5-17.5)
Mean lung dose, Gy, median (IQR)	11.2 (10.1-13.6)
Lung volume received at least 5 Gy (lung V5), percentage, median (IQR)	48.0 (40.0-56.0)
Lung volume received at least 20 Gy (lung V20), percentage, median (IQR)	20.4 (16.0-26.0)
Planning target volume in 10 cc, median (IQR)	20.8 (15.1-38.8)

Abbreviation:
1. IQR, interquartile range
*All doses are in equivalent dose in 2-Gy fraction

Conclusion: This study found that various radiation heart doses were not significantly associated with OS in patients with NSCLC treated with PORT. Studies with larger sample size and longer term follow-up are needed to assess cardiac outcome, given the possibility of late occurrence of AMI events.

Keywords: Post-operative radiotherapy, Non-small-cell lung cancer, Radiation heart doses

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-64 PROGNOSTIC VALUE OF PET-CT AFTER INDUCTION CHEMORADIOTHERAPY AND CURATIVE SURGERY IN IIIA-N2 NSCLC: A MULTI-INSTITUTIONAL ANALYSIS

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Background: We evaluate the correlation of clinical staging on positron emission tomography-computed tomography (PET-CT) and pathologic staging and the prognostic value of PET-CT after induction chemotherapy in patients with locally advanced Non-Small Cell Lung Cancer (NSCLC). **Method:** We analyzed 42 cases of clinical stage IIIA-N2 NSCLC who receive 2 to 4 cycles of pre-operative chemotherapy with or without radiation followed by curative resection. The maximum standard uptake value (SUVmax) of the suspected lesion on PET-CT was recorded. PET-CT findings after induction chemotherapy were compared with those of initial PET-CT and pathology after surgery. **Result:** The accuracy of PET-CT in restaging of the primary tumor after induction chemotherapy was 50.0%. 18 (42.8%) of 42 patients were underestimated ycT stage, and 3 (7.1%) of 42 patients was overestimated ycT stage by PET-CT scan. The accuracy of PET-CT in restaging of the nodal disease was 71.4%. 6 (14.3%) of 42 patients were underestimated ycN stage, and 6 (14.3%) of 42 patients were overestimated ycN stage as compared with pathologic staging. The 2-year overall survival (OS) and relapse-free survival (RFS) rate were 68.5% and 40.9%, respectively. Complete responders (ycT0N0M0) on PET-CT after induction chemotherapy had a significantly longer RFS time than did incomplete responders (28.3 months versus 9.1 months, P = 0.021). **Conclusion:** Complete response on PET-CT after induction chemotherapy with or without radiation was a good prognosticator for RFS in stage IIIA-N2 NSCLC patients who received surgery. However, response evaluation on PET-CT after induction chemotherapy should be interpreted with caution due to its unacceptable accuracy.

Keywords: chemotherapy, NSCLC, Radiotherapy

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-65 ASSESSMENT OF INDIVIDUAL AND COMBINED OF FIVE SERUM TUMOR MARKERS FOR LUNG CANCER

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Background: Tumor markers were often used to help in diagnosis lung cancer, The best known tumor markers in lung cancer were SCC, CEA,CYFRA21-1,NSE,and ProGRP. The roles of these tumor markers in diagnosis remain to be determined. **Method:** This retrospective study conducted between January 2015 and April 2017 at the First Affiliated Hospital of Wenzhou Medical University in China. A total of 2569 patients sought medical attention for a pulmonary mass presence to either confirm or exclude the disease.SCC,CEA,Cyfra21-1,NSE and ProGRP were examied with suspicious lung cancer. SPSS 20.0 used for all statistical analyses. **Result:** Finally,1135 patients were excluded,1434 patients were selected.Lung cancer was established in 1095 patients(737 males and 358 females), average age of(65.3±10.8)years and excluded in 339 patients (229 males, 117 females),average age of (55.7±13.4).Abnormal CEA were represented in 65.6% of adenocarcinoma. SCC-Ag and CYFRA21-1 significantly higher in 59.8% and 79.0% of squamous cell carcinoma respectively. Abnormal values of NSE and ProGRP were associated with 93.3% and 80.2% of SCLC.CEA and CYFRA 21-1 recorded sensitivity of 65.6% and 65.3% respectively in adenocarcinoma. In squamous cell carcinoma, SCC-Ag and CYFRA21-1 displayed sensitivity of 59.8% and 79% respectively. In SCLC, NSE and ProGRP showed sensitivities of 93.5% and 80.8%.The combination of different tumor markers yielded sensitivity values (>90%) and specificity values (>57%). The combination of five tumor markers recorded the highest sensitivity of 95.6%. The CYFRA 21-1 combine with CEA recorded the highest specificity 79.9%. ROC curves were plotted to explore the diagnostic role of these tumor markers individually and in combination. CYFRA 21-1 with AUC of 0.84[95%CI 0.820-0.863]performed better than CEA and the other remaining individual tumor markers. The combination of five tumor markers, with an AUC of 0.904[95%CI 0.888-0.920] is the highest. showed as figure 1.

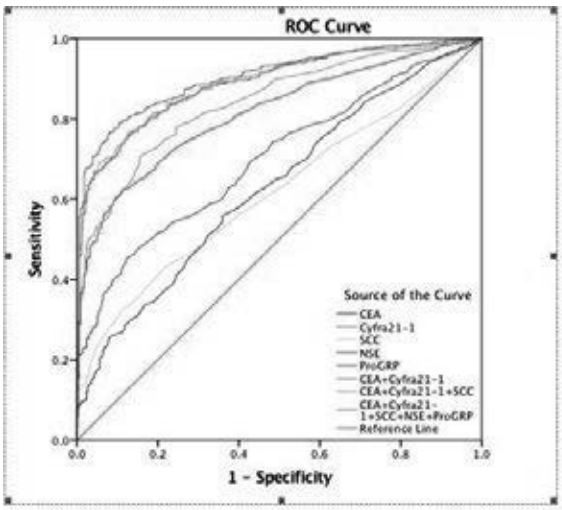

Figure ROC curve for individual and combined serum tumor markers

Conclusion: Combined TMs can potentially improve the specificity and sensitivity values in LC diagnosis

Keywords: tumor marker, lung cancer, diagnosis

P2.01-66 COMPARISON OF EGFR MUTATION STATUS IN TISSUE AND PLASMA CELL-FREE DNA DETECTED BY ARMS IN ADVANCED LUNG ADENOCARCINOMA PATIENTS

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Background: EGFR mutation is a reliable and sensitive biomarker for the treatment of advanced lung adenocarcinoma patients using EGFR-TKIs. Tumor tissue has been used as the standard sample for EGFR mutation detection in the clinical practice currently, but it has some limitations. Therefore, EGFR mutation detection in plasma cell-free DNA has been applied to the clinical practice, however, its diagnostic accuracy remains not consistent. **Method:** The present prospective study enrolled adult patients presenting with advanced lung adenocarcinoma. EGFR mutations detection in plasma cfDNA and tumor tissues by ADx-ARMS were tested. NGS in plasma was performed in patients with inconsistent gene regions mutation in the paired plasma and tissue samples by ADx-ARMS. We calculated the clinical sensitivity, specificity, positive prediction value (PPV), and negative prediction value (NPV) of ADx-ARMS for EGFR mutation status in plasma cfDNA, considering the mutations in tumor tissues as gold standard for measurements. The objective response rate (ORR) and progression-free survival (PFS) were also calculated in patients with EGFR mutation and receiving first-generation EGFR-TKIs therapy.The study protocol was approved by the Institutional Review Board of the first affiliated hospital of Wenzhou Medical University(2016-017). **Result:** 203 patients were enrolled, mutations were discovered in 58.6% (119/203) of tumor tissues and same mutations in 31.0% (63/203) of the matched plasma using ADx-ARMS. The overall rate of consistency of the EGFR mutation statuses for the paired plasma and tissue samples was 71.9%. The sensitivity and the specificity of detecting EGFR mutations in the plasma by ADx-ARMS were 52.9% and 98.8%, respectively.There were 3 cases inconsistent tissue with plasma in gene regions: 1 carried both 19-Del +T790M in tumor tissue but carried single 19-Del in plasma, and 2 carried both L858R +T790M but single L858R in plasma. We validated by NGS. An objective response rate (ORR) of 58.3% was observed among the 72 patients who were mutation-positive in tumor tissues and received Gefitinib or Icotinib as first-line treatment. And the ORR was 61.9% among the 42 patients with EGFR mutations in plasma. The median PFS of patients with EGFR mutations detected by ADx-ARMS in tumor tissue and plasma were 9.50 months versus 10.25 months. The median PFS of patients with EGFThe median PFS of patients with EGFR wild-type in plasma was 8.50 months There were no significant differences among them (P=0.277). **Conclusion:** ADx-ARMS is an approach with high specificity but moderate sensitivity to detect the EGFR mutations in plasma cfDNA for patients with advanced lung adenocarcinoma.

Keywords: EGFR, cell-free DNA, lung adenocarcinoma

P2.01-67 THE PROGNOSTIC ANALYSIS OF LUNG CANCER PATIENTS WITH OCCULT MALIGNANT PLEURAL DISEASE AT THORACOTOMY

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Background: This study aims to determine the clinicopathological prognostic factors for occult malignant pleural disease (MPD) first detected at thoracotomy in patients with non-small cell lung cancer (NSCLC) and assess the outcome of surgical intervention. **Method:** A total of 120 patients with MPD at thoracotomy from January 2006 to October 2016 were evaluated. Survival curves were estimated by the Kaplan–Meier method, and Cox regression analysis was performed to validate the selected risk factors. Clinical and pathologic parameters were balanced by propensity score matching when assessing surgical intervention. **Result:** With a median follow-up of 34 months, the 5-year overall survival of 120 patients was 28.0%. Multivariate analyses showed male (p=0.044), advanced T stages (p<0.001), advanced N stages (p=0.02), pleural invasion in image (p=0.005), pleural effusion (p=0.027), surgical intervention (p=0.008) and EGFR status (p=0.003) were independent predictors of survival. The 5-year survival rate and median survival time (MST) for 21 patients with lobectomy were 71.6% and undefined, compared with 25.6% and 40.0 months in 46 patients with sublobectomy. When 53 patients only subjected to open-close surgery, their 5-year survival rate and MST were 23.4% and 30.2 months. After propensity score matching, both 21 patients were included in lobectomy group and sublobectomy /open-close group. The overall survival of lobectomy group was better than the control group (p=0.046). **Conclusion:** The prognosis of MPD patients first detected at thoracotomy was affected by gender, stage, pleural invasion, pleural effusion, surgical intervention and EGFR status. Lobectomy maybe confers better survival compared with sublobectomy and exploratory thoracotomy.

Keywords: lung cancer, Malignant pleural disease, Surgery

P2.01-68 CAPTURE-BASED SEQUENCING DEPICTS EVOLUTION CHARACTERISTICS OF PULMONARY SARCOMATOID CARCINOMA

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Background: Pulmonary sarcomatoid carcinoma (PSC) is a very rare subset of highly aggressive and poorly differentiated non-small cell lung cancer. Mutation profiling of PSC was reported previously. However, the intratumor heterogeneity and evolution characteristics of PSC remains unknown. **Method:** This study enrolled 39 patients (pts) with PSC. A median follow-up time was 7 months (ranged from 3 to 33 months). Each tumor sample was divided to cancer tissue and sarcoma tissue by microdissection. Matched distant normal tissues were also collected for removing germline background. Capture-based sequencing was performed using a panel covering 1021 genes related to solid tumors. Somatic mutations were used to analyze intratumor heterogeneity and evolution characteristics. Tumor mutation burden (TMB) analysis interrogated single nucleotide variants, small insertion and deletion, with VAF ≥3 %. TMB-high pts were identified with ≥9 mut/MB (upper quartile of data from geneplus). **Result:** Capture-based sequencing had been done on 90 tissues, including cancer tissues, sarcoma tissues and matched distant normal tissues from 30 pts. Nine patients were excluded due to insufficient DNA samples. A median effective depth of coverage of 1299 × was obtained in tissue samples. A total number of 608 mutations were detected, including driver mutations in *TP53* (73%, 44/60), *MET* (22%, 12/60), *EGFR* (20%, 12/60), *KRAS* (20%, 12/60), and *NF1* (17%, 10/60). Interestingly, mutations in *MET* and *KRAS* were demonstrated to be mutually exclusive in cancer and sarcoma tissues. Shared mutations between cancer and sarcoma tissues were 43%. The median of TMB of sarcoma and cancer samples were both 8.6 mutations/Mb. High TMB were identified in 40% (12/30 pts) of sarcoma samples and 43% (13/30 pts) of cancer samples, respectively. TMB of sarcoma tissues was significantly correlated to that of cancer tissues (Pearson r= 0.92, *p*-value<0.01), with a consistence of 90 % Furthermore, the fraction of brunch mutations in cancer tissues was related to the worse OS of PSC (Log-rank, HR=3.2, 95% CI=1.1-9.4, *p*=0.04). **Conclusion:** Sarcoma tissues shared mutations with cancer tissues. Mutations and TMB analysis could help to guide treatment decisions of PSC in both tyrosine kinase and immune checkpoint inhibitors. Evolution characteristics could serve as potential prognostic factors in PSC.

Keywords: evolution, Pulmonary sarcomatoid carcinoma, mutation profiling

P2.01-69 EZH2-MEDIATED EPIGENETIC SUPPRESSION OF GDF15 PREDICTS A POOR PROGNOSIS AND REGULATES CELL PROLIFERATION IN NON-SMALL CELL LUNG CANCER

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Background: Growth differentiation factor 15 (GDF15), a member of the TGF-β superfamily of cytokines, has been reported to exert very heterogeneous functions in various tumors. However, the role of GDF15 and its underlying mechanism in mediating non-small cell lung cancer (NSCLC) progression remain unknown. **Method:** GDF15 expression level was analyzed in 66 NSCLC tissues by quantitative reverse transcription PCR (qRT-PCR). The effect of GDF15 on proliferation was evaluated by MTT and colony formation assays, flow cytometric analysis. NSCLC cells

transfected with pcDNA-GDF15 or empty vector were injected into nude mice to study the effect of GDF15 on tumorigenesis *in vivo*. Chromatin immunoprecipitation (ChIP) assay was used to investigate the mechanism of action of GDF15 in the NSCLC cells. **Result:** In this study, we found that GDF15 is down-regulated in paired NSCLC tissues and is correlated with poor clinical outcomes in NSCLC. Further experiments demonstrated that overexpression of GDF15 significantly repressed NSCLC proliferation both in vitro and in vivo. Mechanistic studies reveal that inhibition of EZH2 expression prevented its binding to the GDF15 promoter region and reduced the trimethylation modification pattern of H3K27. **Conclusion:** Together, our data uncover that GDF15 is a direct target of EZH2, and as a regulator of proliferation, might serve as a candidate prognostic biomarker and target for new therapies in human NSCLC.

Keywords: EZH2, GDF15, NSCLC

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-70 TUMOR TREATING FIELDS AND RADIOSURGERY FOR SUPRA- AND/OR INFRATENTORIAL BRAIN METASTASES (1-10) FROM NSCLC IN THE PHASE 3 METIS STUDY

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Background: Tumor Treating Fields (TTFields) are non-invasive, loco-regional, anti-mitotic treatment modality comprising low intensity alternating electric fields. TTFields has demonstrated efficacy in non-small cell lung cancer (NSCLC) in *in vitro* and *in vivo* models, and in a phase I/II clinical study. TTFields treatment to the brain was safe and extended overall survival in newly-diagnosed glioblastoma. This prospective, multicenter study [NCT02831959] investigated the efficacy, safety and neurocognitive outcomes of TTFields in NSCLC patients with brain metastases (BMs). **Method:** NSCLC patients (N=270) with 1-10 BMs are randomized 1:1 to stereotactic radio surgery (SRS) followed by continuous TTFields ((150 kHz, > 18 hours/day) within 7 days of SRS or supportive care. The TTFields portable device delivers TTFields to the brain using 4 transducer arrays and allows normal daily activities. Patients receive the best standard-of-care for their systemic disease. Patients are followed every two months until second intracranial progression. Patients in the control arm could cross over to TTFields at the time of second intracranial progression. Key inclusion criteria: KPS ≥70, new diagnosis of 1 inoperable or 2–10 supra- and/or infratentorial BMs from NSCLC amenable to SRS; KPS ≥70; and optimal therapy for extracranial disease. Prior WBRT or surgical resection of metastases, a single resectable lesion or recurrent BMs were exclusionary. Primary endpoint was time to 1st intracranial progression. Secondary endpoints included time to neurocognitive failure (HVLT, COWAT and TMT), overall survival, radiological response rate (RANO-BM and RECIST V1.1); quality-of-life; adverse events; time to first/second intracranial progression for patients with 1–4 and 5–10 BMs; bi-monthly intracranial progression rate from 2–12 months; and time to second intracranial and distant progression. The sample size (N=270) was calculated using a log-rank test (Lakatos 1988 and 2002) with 80% power at a two sided alpha of 0.05 to detect a hazard ratio of 0.57. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Tumor Treating Fields; brain metastases; NSCLC

P2.01 ADVANCED NSCLC
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P2.01-71 CLINICAL OUTCOME OF INDUCTION CHEMORADIOTHERAPY FOLLOWED BY SURGERY FOR THE PATIENTS WITH CN2 NON-SMALL CELL LUNG CANCER

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Background: The treatment strategy for clinical N2 (cN2) non-small cell lung cancer (NSCLC) is still controversial, because its clinical outcome is unsatisfactory and cN2 NSCLC harbors various conditions. In this study, we investigated the clinical outcome of induction chemoradiotherapy (iCRT) followed by surgery in the patients with cN2 NSCLC. **Method:** During 1999 to 2016, 92 patients with cN2 NSCLC were surgically treated after iCRT in our hospital. Overall survival (OS) and relapse-free survival (RFS) were evaluated by the Kaplan-Meier method with log-rank test (univariate analyses) and by the cox proportional hazard model (multivariate analyses). **Result:** Median follow-up was 49.3 months (range 3.0 - 216). Median age was 62 (21 - 79). Sixty-nine patients (75%) were male. Fifty-four and 38 patients were cStageIIIA and IIIB, respectively. Forty-six (50%) patients were adenocarcinoma. As for iCRT, the CDDP plus DTX regimen was applied for most of patients (96.7%), and the median radiation dose was 46Gy (36 - 60). Complete/major/minor pathological responses were exhibited in 29/36/27 patients, respectively. pCR was observed in 22 patients. The 5-year rates of OS and RFS were 64.1% and 48.1%, respectively. The patients with lower-lobe origin, cStage IIIA (UICC8th), poor radiological response (progressive or stable disease), minor pathological response, re-operation within 30days after surgery, or recurrence showed significantly worse OS than the others. In addition, the patients with lower lobe origin, cStageIIIA, multi-station N2, poor radiological response, or minor pathological response showed significantly worse RFS. The multivariate analysis revealed that the patients with lower-lobe origin tumors and multi-station N2 showed significantly worse OS [Hazard Ratio (HR) 2.55, 95% confidence interval (CI) 1.11 - 5.71, *P*= 0.028] and RFS (HR 2.45, 95%CI 1.34 - 4.69, *P*= 0.003), respectively. Adenocarcinoma, lower-lobe origin, multi-station N2, cStageIIIA, poor radiological response, and minor pathological response significantly correlated to recurrence. Among them, adenocarcinoma (odds ratio (OR) 3.27, 95%CI 1.21 – 8.89, *P*= 0.02), lower-lobe origin (OR 5.22, 95%CI 1.48 – 18.40, *P*= 0.01), and multi-station N2 (OR 3.63, 95%CI 1.32 – 9.88, *P*= 0.012) independently correlated to recurrence. **Conclusion:** iCRT followed by surgery may be one of the feasible treatment options for the patients with cN2-NSCLCs, especially for those which harbor non-lower lobe origin and multi-station N2 .

Keywords: induction chemoradiotherapy, cN2 non-small cell lung cancer

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-72 BRONCHIAL SLEEVE VS PNEUMONECTOMY: COMPLICATIONS, RECURRENCES AND SURVIVAL

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Background: The present study describes and compares the rate of complications in hospital length of stay (LOS), recurrences and long-term survival between pneumonectomies and bronchial sleeves in our center's experience. **Method:** This is a descriptive, retrospective study. All patients who underwent bronchial SL or PN for NSCLC in our center between 2011 and 2017 were included. Individual clinical report was done, other indications for surgery were excluded. General demographics, preoperative lung function, histology and postoperative complications were included. Oncologic follow-up was done to detect recurrence and death. The statistical program used was SPSS. **Result:** From of 87 patients registered, 47 had bronchial sleeve resection (54,02%) and 40 pneumonectomy (45.97%). The average age: SL 63.7, PN 61,7 years. Males were predominate in both groups (SL 83%, PN 75%). The average size tumoral were: SL 4,8 cm, PN 7,5 cm, p=0.46). Histological type predominant was C. squamous: SL 57,44%, PN 60%, p=0,46). The average LOS was higher SL than PN (2,37 and 6,37 respectively). Upper SL were most frequent: LSD 23 cases, LSI 17 cases, left pneumonectomies were the most accomplished. 25 patients had postoperative complications: SL 17 (68%), PN 8 (32%). The most frequent complications were persistent air leak (SL 6 cases, PN 0 cases, p=0.09) and cardiac arrhythmias. (SL 3 cases, PN 4 cases p=0.09) No case of local recurrence was found after both techniques and 8 cases of regional recurrences (SL 6, PN 2, p=0,81). No differences in terms of overall survival were detected when both techniques were compared (median survival in months, p=0.35). **Conclusion:** More postoperative complications were found in SL group with equal postoperative mortality, this is mostly because persistent air leak and bronchial stenosis, this could explain increase of LOS. There are no local recurrences in any groups, this could mean that both techniques are oncologically equivalent. Our definition of regional recurrences as tumor involving the ipsilateral lung might again explain the higher incidence in SL. There are no statistically differences in terms of OS in both techniques. However, long-term survival tendency appears to be in favor of SL specially after 5 years. This might be related to non oncologic late complications related to pneumonectomy. In conclusion, we consider SL as a feasible and secure technique with a reasonable incidence of inherent complications and equal oncological results.

Keywords: pneumonectomy, bronchial sleeve, long term survival

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-73 AUTOMATED IMAGE ANALYSIS TOOL FOR TUMOR VOLUME GROWTH RATE TO GUIDE PRECISION CANCER THERAPY: EGFR-MUTANT NSCLC AS A PARADIGM

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Background: Imaging remains a crucial component in the evaluation of the therapeutic benefit of precision cancer therapy, because it objectively characterizes tumor burden changes during therapy and provides guides for treatment decisions. The purpose of the present study is to develop an automated analytic module for calculation of tumor growth rate from serial CT scans and evaluate the module functionality and reproducibility in a pilot cohort of advanced NSCLC patients with EGFR mutations treated with EGFR tyrosine kinase inhibitors. **Method:** The module utilized a commercially available image-processing workstation equipped with a validated tumor volume measurement tool. A novel analytic software module was programmed with the capability to record and display serial tumor volume changes and to calculate tumor volume growth rate over time and added to the workstation. The functionality and reproducibility of the module was evaluated using a pilot cohort of 24 EGFR-mutant patients treated with EGFR inhibitors by two independent thoracic radiologists. **Result:** The module analyzed chest CT scans from 24 patients (5 males, 19 females; median age: 61) with a median of 8 scans per patient, totaling 227 scans and provided a graphical display with an automated calculation of tumor growth rate after the nadir volume for each patient. High inter and intraobserver agreements were noted for tumor growth rates, with concordance correlation coefficients of 0.9323 and 0.9668, respectively. Interpretation of slow versus fast tumor growth using previously identified threshold of ≤0.15/month had a perfect interobserver agreement (κ=1.00), and an excellent intraobserver agreement (κ=0.895). **Conclusion:** The present study describes the development of an image analytic module for assessing tumor growth rate and the data demonstrates the functionality and reproducibility of the module in a pilot cohort of EGFR-mutant NSCLC patients treated with EGFR-TKI. The image analytic module is an initial step for clinical translation of the tumor growth rate approach to guide cancer treatment in precision oncology.

Keywords: epidermal growth factor receptor inhibitor, computed tomography, Non-small-cell lung cancer

P2.01 ADVANCED NSCLC
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P2.01-74 DOCETAXEL-RELATED FEBRILE NEUTROPENIA (FN) AND PATIENT REPORTED SYMPTOMS/ QOL (PROS) IN EAST ASIAN (EA) AND NON-EA PATIENTS

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Background: A post hoc analysis of JVCG, a Japanese phase 2 trial suggested that the QOL (quality of life) deteriorated more rapidly in patients with docetaxel-related FN than in patients without FN. A post hoc analysis of REVEL, a global phase 3 trial, was performed to explore the association between FN and PROs in East Asian (EA) (Korea, Taiwan) and Non-EA patients. **Method:** Lung Cancer Symptom Scale (LCSS) and EQ-5D-3L were assessed at baseline, every cycle, at discontinuation and 30-day follow up. The summary statistics of LCSS total score and EQ-5D Visual Analog Scale (VAS) score were calculated. Time to deterioration (TtD) was defined as the time from randomization to the first 15-mm increase from baseline for the LCSS and first 15% decrease for the EQ-5D VAS and analysed with the Kaplan-Meier method and Cox proportional hazard model by treatment-emergent FN status regardless of assigned treatment. Also the changes in LCSS total score and EQ-5D VAS score from baseline to the treatment completion were summarized. **Result:** 1253 patients randomized to receive RAM+DOC (EA: n=43 and Non-EA: 585) or PLA+DOC (n=46 and 579). FN occurred in 21.3% of EA and 12.3% of Non-EA patients. Patient compliance with the LCSS and EQ-5D were 84.2% and 84.4%, respectively in EA and 82.7% and 83.2% in Non-EA patients. For EA patients, HRs (95% CI) for TtD were 0.572 (0.250, 1.313) in LCSS total and 0.792 (0.350, 1.790) in EQ-5D VAS, indicating longer TtD in PROs for patients without FN. For Non-EA patients, HRs (95% CI) for TtD were 0.994 (0.728, 1.357) in LCSS total and 1.023 (0.787, 1.330) in EQ-5D VAS and there seemed to be no difference in TtD between patients with and without FN. At treatment completion, the unadjusted mean change from baseline of LCSS total was numerically lower in EA patients without FN: 12.97 (with FN) vs 5.94 (without FN) (p=0.1748) and significantly lower in Non-EA patients without FN: 10.50 (with FN) vs 5.55 (without FN) (p=0.0147), demonstrating a greater PROs deterioration in patients with FN. **Conclusion:** PROs of EA patients with FN deteriorated more rapidly than in those without FN in contrast with non-EA patients. This finding was consistent with a result in the Japanese phase 2 JVCG trial. Also Non-EA patients without FN maintained their PROs significantly better than patients with FN upon treatment completion. This trend was also shown in EA patients. Prevention of docetaxel-related FN may contribute to maintaining QOL.

Keywords: advanced NSCLC, antiangiogenesis, Patient reported outcomes (PRO)

P2.01 ADVANCED NSCLC
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P2.01-75 STUDY OF MOLECULAR ALTERATIONS IN CYTOLOGICAL SMEARS BY FISH IN PATIENTS WITH ADVANCED NON SMALL CELL LUNG CARCINOMA (NSCLC).

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Background: Lung cancer represents one of the leading causes of cancer mortality worldwide. In most cases, its diagnosis is made at an advanced stage of the disease when patients are no longer candidates for surgical resection of the primary tumor. In these cases, small biopsies and cytological samples obtained through minimally invasive procedures, often represent the only chance of obtaining diagnostic material. This includes molecular study which increasingly incorporates more genes of interest into the diagnostic routine to define therapeutic approach. At the Pathology Department of the Hospital Italiano de Buenos Aires, the study of ALK, ROS1 and more recently, the study of MET, is performed on paraffin samples by immunohistochemistry (IHC) or by fluorescence in situ hybridization (FISH). Aims: To incorporate the use of FISH on cytological material within the practices of our department. **Method:** We collected cytological smears of 1) lung nodule or lung cancer metastases needle biopsies from patients with non-surgical stage disease (n=10); 2) imprinted cytological samples from positive mediastinoscopies during the intraoperative staging of patients with lung cancer (n=11); 3) positive pleural fluid in patients with pulmonary nodule (n=2). Then we performed FISH technique, evaluated the quality of the signal obtained, and compared the results with those obtained on paraffin sections. FISH technique on paraffin blocks was performed using 2XSSC/ proteinase K pretreatment as standardized by our lab. Cytology smears were destained and fixed in 10% methanol and incubated with FISH probe (ALK, ROS1 and MET). Result: All cytology cases had scorable signals and were easy to interpret. Also, as no pretreatment was required, assay time was shorter. Depending on cellularity, one same slide was useful for analysis of the three probes. When comparing with IHC and FISH studies, we obtained a 100% correlation with ALK (n=23; positive=2, negative=21), ROS1 (n=5, all negative) and MET (n=5, all negative). **Conclusion:** This work allowed us to optimize the use of different cytology samples frequently available in advance stage NSCLC for FISH studies. The use of cytological material might improve turnaround time for results and can become a useful tool in pathology labs, in particular when paraffin included material is limited.

Keywords: cytology, FISH

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-76 THE IMPACT OF CONCORDANCE WITH A LUNG CANCER DIAGNOSIS PATHWAY GUIDELINE ON TREATMENT ACCESS IN PATIENTS WITH STAGE IV LUNG CANCER

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Background: Lung cancer is the leading cause of cancer mortality with the majority of cases diagnosed at an advanced stage. Timely access to treatment is dependent on efficient and appropriate patient assessment

and early referral for diagnostic workup. This study aims to assess the impact of referral concordance with a new Lung Cancer Diagnostic Pathway Guideline (LCDPG) on access to treatment in patients with stage IV lung cancer. **Method:** This is a retrospective cohort study of patients with clinical stage IV lung cancer referred to the Diagnostic Assessment Program (DAP) at a Canadian tertiary cancer centre between November 1, 2015 and May 31, 2017. Patient referrals were defined as concordant or discordant based on Cancer Care Ontario LCDPG. The primary outcome; time to treatment from initial healthcare presentation; was compared between the concordant and discordant referrals. **Result:** Two hundred patients were referred for clinical stage IV lung cancer during the study period. Of these referrals, 151 (75.5%) were assessed and referred in concordance with LCDP guidelines. Guideline concordant referrals were associated with reduced time to treatment from first healthcare presentation compared with guideline discordant referrals (55.3 vs 108.8 days, p<0.001). Time to diagnostic procedure (32.2 vs 86.7 days, p<0.001) and decision to treat (38.5 vs 93.8 days, p<0.001) was also reduced with guideline concordance. The most common reason for discordant assessment and referral was delayed or inadequate investigation of symptoms in a high risk patient (32.7% of discordant referrals). The mean time from referral to diagnostic procedure (19.4 [SD 16.0] days), decision to treat (23.3 [SD 17.1] days), and treatment initiation (39.7 [SD 26.3] days) did not significantly differ between concordant and discordant groups. Time from referral to decision to treat was within 28 days in 71.5% of patients. The mean number of hospital visits from referral to treatment was 4.9 (SD 3.5). Diagnosis was achieved with a single diagnostic test in the majority of patients (91%). The most common method of diagnosis was EBUS-TBNA (33.5%). The most common treatment modalities initiated were radiation (60.5%) followed by chemotherapy (43%) and targeted therapy (21.5%). **Conclusion:** Guideline concordant assessment and referral of patients with stage IV lung cancer results in reduced time to diagnosis and treatment. The utilization of a LCDPG for lung cancer provides a streamlined and efficient framework to facilitate early diagnosis and treatment. Future research and education should focus on improving factors leading to a delay in DAP referral.

Keywords: diagnosis, Stage IV Lung Cancer, Guideline Concordance

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-77 INTERCONVERSION OF TWO COMMONLY USED PERFORMANCE TOOLS: AN ANALYSIS OF 5844 PAIRED ASSESSMENTS IN 1501 LUNG CANCER PATIENTS

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Background: Karnofsky Performance Status (KPS) scale and Eastern Cooperative Oncology Group (ECOG) scale are the most commonly used performance status (PS) tools worldwide. The current study aimed to assess correlation between KPS and ECOG PS in a large cohort from a lung cancer (LC) clinic database and to determine KPS categories which were most equivalent to ECOG PS scores. **Method:** All patients attending LC clinic at a tertiary care centre over a 5-year period were assessed with both KPS and ECOG PS scales at each visit. Correlation between KPS and ECOG PS was assessed using Spearman's correlation coefficient. Different KPS categories equivalent to ECOG PS were compared using hit rate and weighted kappa (κ_w). **Result:** A total of 1501 patients were assessed over study period providing 5844 paired KPS and ECOG PS assessments. The cohort had a mean (standard deviation SD) age of 58.4 (10.8) years with majority being current/ex-smokers (76.9%) and males (82.3%). NSCLC was commonest histological type (n=1196, 79.7%) with majority having advanced (stages IIIB/IV) disease (83.4%). Mean baseline KPS and ECOG PS scores were 77.6 (SD=14.4) and 1.5 (SD=1) respectively. Overall correlation between KPS and ECOG PS was good [Spearman r = (-)0.84, P<0.0001] but ranged from -0.727 to -0.972 between visits. KPS categories derived from our cohort (10-40 [ECOG 4], 50-60 [ECOG 3], 70 [ECOG 2], 80-90 [ECOG 1], 100 [ECOG 0]) performed better (hit rate 78.1%, κ_w = 0.749 [0.736-0.762] P<0.0001) than those suggested in the past literature.

Table: Comparison of various suggested KPS categories for KPS-ECOG PS interconversion in the current cohort

Author, Year	N (Patients [assess-ments])	Suggested KPS Categories	Hit rate	κw (95% confidence interval)
AJCC, 1977	-	10-20, 30-40, 50-60, 70-80, 90-100	43.6%	0.376 (0.363-0.389) P<0.0001
Minna, 1985	-	20-30, 40-50, 60-70, 80-90, 100	75.2%	0.701 (0.687-0.714) P<0.0001
Buc-cheri, 1996	536 [1656]	10-50, 60-70, 80-100	83.2%	0.695 (0.679-0.711) P<0.0001
Ma, 2010	1385 (1385)	10-30, 40-50, 60-70, 80-90, 100	75.2%	0.701 (0.687-0.714) P<0.0001
de Kock, 2013	955 (674)	10-20, 30-40, 50, 60-100	43.2%	0.079 (0.068-0.090) P<0.0001
Current study	1501 (5844)	10-40, 50-60, 70, 80-90, 100	78.1%	0.749 (0.736-0.762) P<0.0001

Conclusion: The current study provides largest set of paired KPS-ECOG assessments till date. Although both PS tools had good correlation, the performance of the KPS categories previously suggested as being equivalent to ECOG PS categories was found to be highly variable. Cancer clinics should develop and validate their own population-specific KPS categories for interconversion of KPS to ECOG PS.

Keywords: performance status, ecog, kps

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-78 VALIDATION OF INVISIONFIRST CTDNA NGS PROFILING VIA DDPCR TESTING IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Tumor tissue based molecular profiling is widely utilized to guide therapy in advanced NSCLC and recently, ctDNA assays have been developed to detect actionable alterations in a non-invasive manner. However, there are frequent reports of discordance between analysis platforms and here we compare the Inivata NGS ctDNA assay with ddPCR based ctDNA analysis and tissue NGS sequencing in patients with advanced NSCLC. **Method:** InVisionFirst (Inivata) is a ctDNA NGS assay for detection of genomic alterations in 36 genes commonly mutated in NSCLC and other cancer types. A cohort of 52 patients underwent ctDNA analysis by InVisionFirst and were tested in a blinded manner for 4 actionable gene alterations (EGFR L858R & Ex19del, KRAS G12C & G12D) and 30 of the cohort also had testing for 5 additional alterations (EGFR T790, EML4-ALK fusions, ROS1 fusions, KRAS G12V and BRAF V600E) at one of two independent ddPCR laboratories. Finally, tissue analysis by NGS was available in 21 patients to arbitrate any discordance between the results of the 2 liquid biopsy techniques. **Result:** Across the 9 specific genetic alterations investigated by both ctDNA platforms, 26 alterations were detected by the InvisionFirst platform and 23 were detected by the ddPCR platforms. The overall concordance of gene alterations was 98.5% (320/342) with positive agreement of 95.5% and negative agreement of 98.8%. Discordance was observed in 6 detected gene alterations, with 1 EML4-ALK fusion, 1 EGFR exon19 deletion and 2 KRAS G12Cs being detected by InVisionFirst but not by ddPCR, and 1 EGFR L858R and 1 KRAS G12D detected by ddPCR but not InVisionFirst. One G12C, the EML4-ALK, and the L858R alteration were confirmed by tissue NGS. The KRAS G12D was not confirmed by tissue NGS. No tissue was available to examine for the detection of the EGFR exon 19 deletion or the other KRAS G12C mutation. All other results were concordant. **Conclusion:** This study in NSCLC patients demonstrates excellent concordance of the InVisionFirst ctDNA NGS assay with ddPCR based ctDNA analysis via blinded independent laboratories. The excellent sensitivity and specificity support the use of the InVisionFirst assay as a non-invasive "liquid biopsy" for molecular profiling.

Keywords: advanced NSCLC, liquid biopsy, next generation sequencing

P2.01-79 NEUROLOGICAL DEATH IS COMMON IN PATIENTS WITH EGFR MUTANT NON-SMALL CELL LUNG CANCER

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Background: Patients with EGFR mutant non-small cell lung cancer (EGFRmNSCLC) have a high incidence of brain metastases (BM). We sought to determine the rate of neurologic death in EGFRmNSCLC patients diagnosed with brain metastases. **Method:** A single-institution prospectively managed database identified 204 patients with EGFRmNSCLC treated for brain metastases between 2000 and 2016. We estimated actuarial survival rates using the Kaplan-Meier method. The incidence of neurologic death (ND) was determined using a competing risks analysis. ND was correlated to clinical and treatment variables using Fisher's exact test. Survival was calculated from the date of BM diagnosis. We defined neurologic death as death due to brain metastases or leptomeningeal disease. **Result:** Fifty-six percent of patients had BM at the time of initial diagnosis. The initial BM treatment was up front stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), or tyrosine-kinase inhibitor (TKI) alone in 22, 60, and 18 percent of patients, respectively. Two-year rates of OS in these subgroups were 64%, 38%, and 50%, respectively (p=0.016). The 5-year rate of neurologic death was 38%. Thirty-four percent died of non-neurologic causes, 8% died of unknown causes, and the remaining patients were alive at last follow-up. Median survival (MS) was 19 months; MS in patients who died of non-neurologic causes and neurologic causes was 23, and 15 months, respectively. Of age, staging, BM at diagnosis, history of TKI therapy, initial treatment of BM, staging at diagnosis, and leptomeningeal disease at diagnosis (LMD), only LMD was significantly associated with ND (p=0.047). **Conclusion:** Neurologic death due to EGFRmNSCLC BM was more common in our cohort than has been previously reported, highlighting the need for dedicated studies focused on the best management of BM in this population.

Keywords: NSCLC, EGFR, radiation therapy

P2.01-80 PERFORMANCE STATUS AND RESOURCE UTILIZATION IN PATIENTS RECEIVING PALLIAITVE CARE WITH STAGE IV NON-SMALL CELL LUNG CANCER

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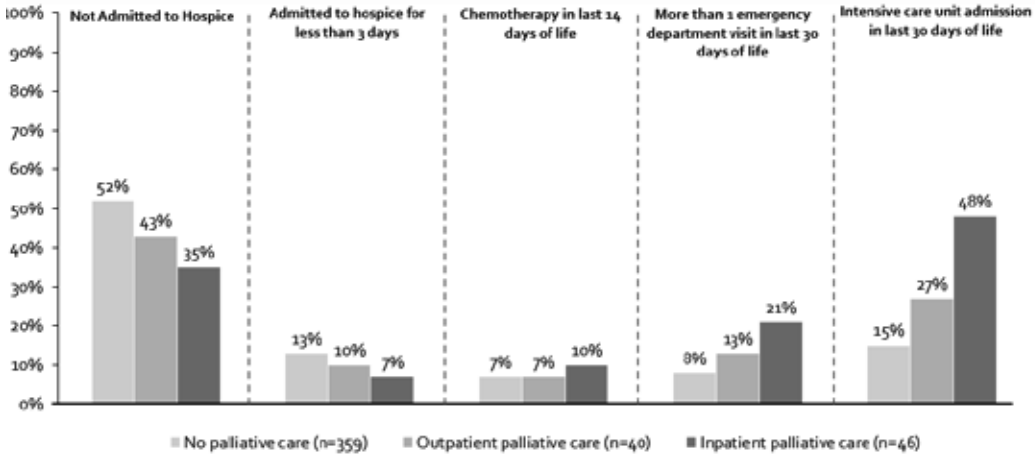
Background: Palliative care (PC) services assist with the end-of-life needs of patients with advanced cancer; and clinical trials have associated early implementation of outpatient PC with increased survival, improved quality of life and reduction in healthcare utilization in stage IV non-small cell lung cancer (NSCLC). However, these studies only included patients with Eastern Cooperative Oncology Group (ECOG) performance status scores of 2 or less, which does not fully represent the spectrum of patients with stage IV NSCLC. The National Quality Forum (NQF) endorses metrics to measure quality and aggressiveness of end-of-life care. We aimed to determine the overall utilization of PC and the performance status of patients receiving outpatient versus inpatient PC and their resource utilization based on the NQF elements. **Method:** We reviewed patients diagnosed with cIV NSCLC between 6/1/2013-6/1/2017, managed at 7 sites with access to dedicated PC services. Patients were initially categorized by whether or not they received PC consultation, and then further stratified into outpatient and inpatient PC. **Result:** We analyzed 445 patients, of which 19% (86/445) received a PC consultation. Of the 86 patients receiving PC, 47% (40/86) were outpatient and 53% (46/86) were inpatient. Median (25th-75th interquartile range) ECOG scores at PC consultation were 1 (1-3) and 4 (3-4) for outpatient and inpatient PC, respectfully (p<0.001). The NQF's endorsed data elements for each group are shown in the figure (see below). **Conclusion:** Patients receiving inpatient PC had a significantly worse performance status with higher emergency department and intensive care unit usage than outpatient PC, suggesting inpatient PC accesses a different, sicker population with greater clinical needs. Comprehensive multidisciplinary initiatives focused on increased outpatient PC utilization and targeting the NQF metrics of quality and resource utilization are needed.

Keywords: Stage IV NSCLC, palliative care, advanced NSCLC

Figure. National Quality Forum Endorsed Measures



P2.01-81 TREATMENT OF SUPERIOR SULCUS TUMOR: A TWELVE-YEAR SINGLE-CENTER EXPERIENCE

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Background: Superior sulcus tumor (SST), also known as Pancoast tumor, occurs in up to 5% of all non-small cell lung cancer patients. Owing to its proximity to vital thoracic structures, SST remains one of the biggest challenges of thoracic surgery. The results of the Southwest Oncology Group Trial 9416, in which SST patients were subjected to induction chemoradiation followed by surgical resection, established a widely accepted standard-of-care. Data on the efficacy of this approach outside of clinical trial setting are scarce. We present long-term outcomes in a large group of patients with SST who underwent surgery with or without preoperative treatment (PT) in a single tertiary referral center. **Method:** Study group included 76 consecutive patients treated between February 2006 and June 2017. All patients had histologically-proven and radiologically-defined T3-T4 N0-N1 M0 superior sulcus non-small cell lung cancer. Study group included 50 men (66%) and 26 women (34%) with a mean age of 56 years (range, 41-81 years). Squamous cell lung cancer constituted 55% of the population. **Result:** Fifty-four patients (71%) underwent PT, 44 of whom received radiochemotherapy (58%), 4 radiotherapy (5%) and 6 chemotherapy (8%), and 22 (29%) were managed with surgery alone. All patients selected to PT underwent subsequent pulmonary surgery including lung and chest wall en bloc resection, and complete lymphadenectomy. In the entire group 71 lobectomies (93%), 3 segmentectomies (4%) and 2 pneumonectomies (3%) were performed. Surgery in patients managed with PT included 52 lobar resections (96%) and 2 pneumonectomies (4%). Complete or near complete pathologic response following PT was achieved in 67% of operated patients. In the entire group resection was complete (R0) in 62 patients (82%). Overall 30-day and 90-day mortality in the entire treatment group was 2.6% and 6.6%, respectively. Overall 3-year and 5-year survival probabilities were 44% (95% CI: 32%–56%) and 38% (95% CI: 26%–50%) respectively. A non-significantly higher 3-year survival probability was recorded in patients, who underwent PT compared to those managed with surgery alone (50% vs. 36%, respectively; log-rank p=0.27). **Conclusion:** Real-world treatment outcomes in SST patients amenable to surgery are similar to those obtained in the general population of lung cancer patients. PT may increase long-term survival rate and is associated with low perioperative mortality, which justifies its routine application.

Keywords: superior sulcus tumor, non-small cell lung cancer, Pancoast tumor

P2.01-82 NEUTROPHIL-TO-LYMPHOCYTE RATIO COMPLEMENTS THE PROGNOSTIC ABILITY OF PD-L1 IN NON-SMALL CELL LUNG CANCER TREATED WITH PD-1/PD-L1 INHIBITORS

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Background: PD-L1 expression is an imperfect predictor of outcomes for patients (pts) with advanced non-small cell lung cancer (aNSCLC) treated with PD-1/PD-L1 inhibitors (PD-1/L1i). This was demonstrated in the recent ARCTIC trial in which PD-L1 expression did not significantly correlate with outcomes. In the quest for additional markers, a high neutrophil-to-lymphocyte ratio (NLR) has been associated with poor outcomes and may reflect a higher myeloid-to-lymphoid balance. Here we show improved prognostic ability for response to PD-1/L1i when baseline NLR is added to PD-L1 expression. **Method:** We used a retrospective cohort of 146 aNSCLC pts from the authors' institutions in the United States and Japan who received single-agent PD-1/L1i. We categorized patients into three groups; favorable: PD-L1 ≥ 1% and NLR < 5, intermediate: PD-L1 ≥ 1% or NLR < 5, and poor: PD-L1 < 1% and NLR ≥ 5. We correlated the outcome of each group with overall survival (OS) and progression free survival (PFS). **Result:** Median follow-up was 11.1 months (M) (95% Confidence Interval [CI]: 9.1-13.1). 47 pts had PD-L1 <1% and 99 pts ≥1%, 81 pts had NLR <5 and 65 pts ≥5. There were 52, 76, and 18 pts in the favorable, intermediate, and poor groups, respectively. Median OS for the favorable group was not reached and it was 14.7 M (CI: 10.5-19.0) and 3.5 M (CI: 0-13.1), respectively for the intermediate and poor groups. Median PFS was 9.9 M (CI: 3.7-16), 3.2 M (CI: 2.1-4.3), and 1.1 M (CI: 0.8-1.4), respectively. The poor group (PD-L1 < 1% and NLR ≥ 5) was significantly associated with progressive disease (Odds ratio [OR]: 5.0, p=0.01) in comparison to the PD-L1 < 1% group (OR: 2.6, p=0.013). **Conclusion:** Prognostic ability of PD-L1 expression is enhanced when combined with baseline NLR for aNSCLC pts treated with single-agent PD-1/L1i. This study raises the hypothesis that high NLR and low PD-L1 expression could serve to identify those pts less likely to benefit from these therapies.

Keywords: Immunotherapy, biomarker

P2.01-83 EVALUATION OF DYNAMIC THIOL/DISULPHIDE HOMEOSTASIS IN ADVANCE NON-SMALL CELL LUNG CANCER AND SMALL CELL LUNG CANCER

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Background: The complicated pathogenesis of lung cancer is the mainstay of all its different histological subtypes. Oxidative stress has detrimental effects on chronical diseases as well as cancer. Thiol groups which have high antioxidant capacity, turn to disulpide (DS) groups with biochemical reactions that neutralize different oxidant compounds. Thiol/Disulpide homeostasis (TDH) has significant effects on cell mechanisms, transcription and apoptosis. Here, we present the role of dynamic TDH in both advanced non-small cell (NSCLC) and small cell lung cancer (SCLC) patients. **Method:** The patients who diagnosed with NSCLC and SCLC between 2015 and 2017 prospectively analysed. Serum samples of the patients obtained at the time of diagnosis and after first-line treatment. TDH tests were measured by the automated spectrophotometric method. **Result:** 57 patients (43 NSCLC and 14 SCLC) and 50 healthy controls enrolled to study. There was no statistical difference in age (median 61 and 60.5) and sex status between groups.Native thiol (NT) and total thiol (TT) levels were significantly lower in the patients' group (Table 1).DS/NT ratio which is the best indicator of antioxidant capacity reached statistical significance between NSCLS patients and controls (p=0.04). After median 27.2 months follow-up,median overall survival (OS) was 9.5 months in NSCLC and 12.3 months in SCLC groups.Thiol or DS variables had no effect on survival.13 of the 30 patients had progressive disease after first-line chemotherapy. DS levels and DS/NT ratio were lower in patients after progression compared with levels at the time of diagnosis (p=0.013 and 0.033).

Variable	Patients Median (min-max)	Controls Median (min-max)	p
Native Thiol	358 (215-3261)	429 (313-607)	<0.001
Disulpide	20.8 (0.05-55)	20 (8.4-37)	0.98
Total Thiol	398 (253-573)	464 (354-632)	<0.001
Disulpide/ Native Thiol	0.05 (0.01-0.19)	0.05 (0.02-0.14)	0.08

Conclusion: Lower levels of thiol groups may contribute to lung cancer pathogenesis as a result of enhanced oxidative stress.The deficiency of this antioxidant compounds may relate to structural damage of signal, transcription, apoptosis mechanisms in lung cancer cell lines. The lower levels of DS and DS/NT ratio after progression may be an indicator of the high tumor volume and enhanced cell turnover.

Keywords: oxidative stress, thiol, disulphide

P2.01-84 PATTERNS OF CENTRAL NERVOUS SYSTEM METASTASES IN EGFR MUTATED OR ALK REARRANGED NON SMALL CELL LUNG CANCER PATIENTS

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Background: Development of brain and leptomeningeal metastases has prognostic and therapeutic implications in oncogene driven non small cell lung cancer (NSCLC). A rising trend is being observed in the incidence

of central nervous system (CNS) metastases in such populations, probably due to better imaging techniques as well as improved survival of patients. The presence of EGFR and ALK mutations could have a significant impact on the pattern of metastatic disease spread. Data from the Indian subcontinent on this subject is scarce. The information gained from this study may have clinical relevance in today's era of first line use of second and third generation tyrosine kinase inhibitors (TKIs). **Method:** 286 EGFR mutated (220) or ALK rearranged (66) NSCLC patients were selected for this retrospective analysis. All patients with clinically suspected CNS metastases underwent contrast enhanced MR imaging of brain. Two groups of patients were identified as per their driver mutation status. The CNS lesions were analysed with regards to number, size, site (parenchymal or meningeal) and nature (morphological heterogeneity and central necrosis) **Result:** Incidence of brain metastases was found to be higher in the ALK group (24/66, 36.3 %) as compared to the EGFR group (68/220, 30.9%). Leptomeningeal spread in the ALK group was found to be less compared to the EGFR group (2/24, 8.3% as opposed to 18/68, 26.4%). Morphological heterogeneity and central necrosis in parenchymal lesions was more common in the ALK group (8/24, 33.3%) as opposed to EGFR group (2/68, 2.94%). **Conclusion:** The incidence, type and morphology of CNS lesions vary with the driver mutation status in NSCLC patients. This may have prognostic and therapeutic implications, especially in identifying patients who may benefit from upfront second or third generation TKI's.

Keywords: NSCLC, CNS metastases, EGFR, ALK

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P2.01-85 THE EFFICACY OF THE TRADITIONAL CHINESE MEDICINE AS MAINTENANCE THERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER: A META-ANALYSIS

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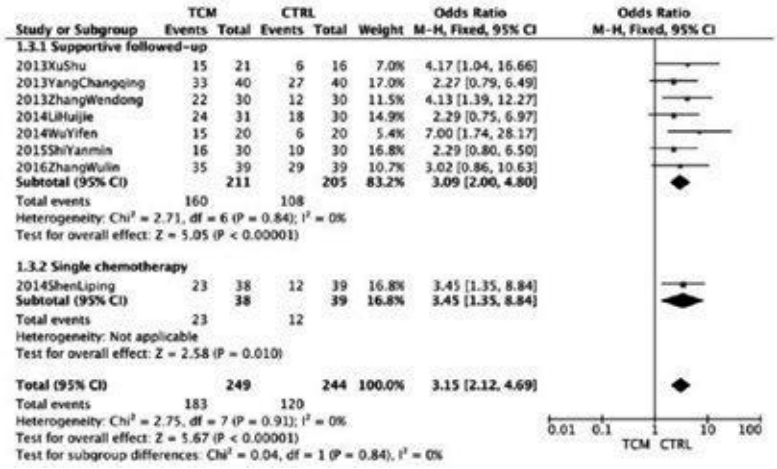
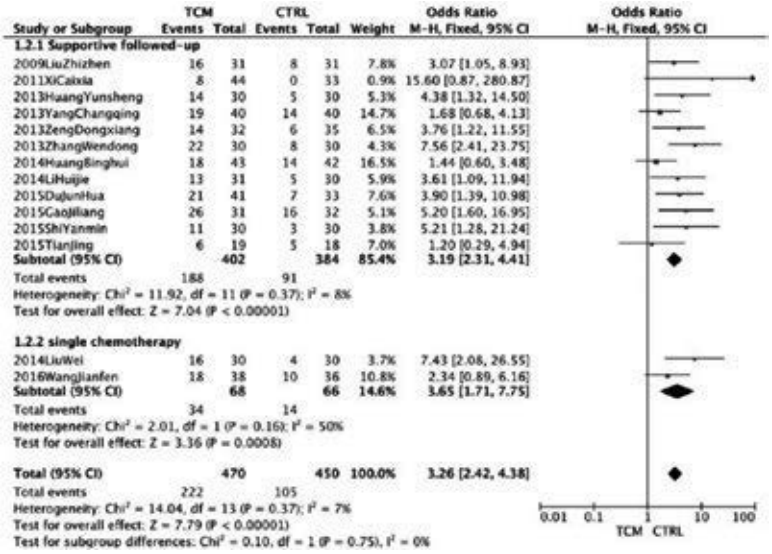
Background: Maintenance therapy is very important for patients with advanced non-small cell lung cancer (NSCLC). To evaluate traditional Chinese medicine (TCM) as maintenance therapy for advanced NSCLC patients, we performed a meta-analysis of prospective randomized controlled trials (RCTs). **Method:** 12 databases were searched up to April 2016. All RCTs comparing TCM and control treatment as maintenance therapy for stage III to IV NSCLC patients in non-progression status after completing first-line chemotherapy were retrieved. Total 25 RCTs with 1654 patients were enrolled from March 2005 to June 2014. **Result:** We found that TCM as maintenance therapy significantly increased the overall response rate (ORR) (risk ratio (RR)=2.23 95% confidence interval (CI)=1.28-3.88 P=0.004) and the disease control rate (DCR) (RR=3.15 95% CI=2.12-4.69 P<0.00001, Fig 1), while no significant difference was observed in the overall survival (OS) (P=0.44). Significant improvement was found in progression free survival (PFS)(HR=1.67 95% CI=0.40-2.93 P=0.01) and karnofsky performance status (KPS) in the TCM group (RR=3.26 95% CI=2.42-4.38 P<0.00001, Fig 2). There was no complication reported in these studies. **Conclusion:** TCM appears to be efficacious and well tolerated to be used as maintenance therapy for advanced NSCLC patients in non-progression status after completing the first-line chemotherapy. TCM as maintenance therapy is worth further study in future investigations.

Keywords: Traditional Chinese medicine, Advanced Non-Small Cell Lung Cancer, maintenance therapy





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Keywords: Traditional Chinese medicine, Advanced Non-Small Cell Lung Cancer, maintenance therapy

P2.01 ADVANCED NSCLC
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P2.01-86 GENETIC PROFILING OF CIRCULATING CELL-FREE DNA FROM CEREBROSPINAL FLUID AND PLASMA IN ALK-POSITIVE LUNG CANCER WITH BRAIN METASTASES

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Background: Brain metastases (BMs) occur in approximately 30% of patients with ALK-positive non-small-cell lung cancer (NSCLC), and in patients treated with crizotinib, central nervous system progression occurs in up to 70% of patients. Resistance mechanisms of BMs with ALK rearrangement remained unclear due to limited access to BMs lesions. **Method:** Ten NSCLC patients with BMs carrying ALK-positive in tumors determined by Ventana anti-ALK (D5F3) immunohistochemistry assay were enrolled. Cell-free DNA (cfDNA) of cerebrospinal fluid (CSF) and plasma were tested by next-generation sequencing (NGS) with 168 genes panel. **Result:** Out of 10 patients, three were females and seven males aged from 29 to 57 years old (median age of 34 years old). In all of cases, CSF cytology were negative. In NGS assays, In patients with ALK-positive, fusion gene positive genes were detected in 30.0% (3/10), 80.0% (8/10) and 100% (8/8) patients of CSF cfDNA, plasma and tumor, respectively; and in ALK-positive of CSF, all of them had much higher allele fractions in CSF cfDNA than the other two media. **Conclusion:** For ALK-positive lung cancer with BMs, CSF may serve as liquid biopsy by detecting cfDNA within CSF to characterize the driver and resistant genes, dynamic genetic profiling of CSF would be an appropriate choice.

Keywords: brain metastases, ALK-positive, cell-free DNA

Table Characteristics of 10 Patients with BMs

Patient	Gender	Age (years)	Smoking Status	ECOG PS at BMs	Initial Diagnosis with BMs	No. of BM	Neurologic symptoms	Systemic Treatment
1	Male	50	Never	1	No	>3	None	Crizotinib
2	Male	29	Current	0	No	>3	None	Crizotinib
3	Male	54	Never	1	No	>3	None	Crizotinib
4	Female	30	Never	1	Yes	1	Dizziness and vomiting	Crizotinib
5	Male	54	Current	1	No	>3	Dizziness and headache	Crizotinib
6	Male	31	Current	1	No	>3	None	Alectinib
7	Male	35	Current	0	Yes	>3	None	Crizotinib
8	Female	57	Never	0	No	>3	None	Crizotinib
9	Female	33	Never	1	Yes	1	Dizziness and vomiting	Ensartinib
10	Male	32	Never	1	No	>3	None	Alectinib

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P2.01-87 PROFILING THE SYMPTOM BURDEN OF PATIENTS WITH METASTATIC NSCLC RECEIVING EITHER CHEMOTHERAPY OR TARGETED THERAPY: REAL-WORLD DATA

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Background: An understanding of the patient experience is lacking for newly developed cancer treatments, such as targeted therapies. We profiled the patient-reported outcome (PRO)-measured symptom burden experienced by patients with metastatic non-small cell lung cancer (mNSCLC) during 6 months of conventional chemotherapy or targeted therapy. **Method:** During 2017, patients with mNSCLC at a single institution were recruited and completed the MD Anderson Symptom Inventory lung cancer module (MDASI-LC) at clinic visits. The MDASI-LC assesses the severity of 13 core and 3 lung-cancer-specific symptoms and 6 interference items on 0-10 scales (0=no symptom or interference, 10=worst imaginable symptom or complete interference). Descriptive statistics for MDASI-LC scores over 6 months of treatment were summarized. Symptom trajectories for the chemotherapy patients versus the targeted-therapy patients were compared via linear mixed-effects models. **Result:** Of 65 patients receiving chemotherapy and 27 receiving targeted therapy, the targeted-therapy group had more women (74% vs. 49%, P=0.029) and younger patients (57.6±12.2 vs. 64.2±9.9 years, P=0.012). Before treatment, both groups reported similar symptom burden, although sadness was worse in the targeted-therapy group (2.4±1.6 vs. 0.8±1.5, P=0.021). During the first 60 days of treatment, patients receiving chemotherapy reported significant increase in pain (estimate (est)=0.03, P=0.037) and interference with walking (est=0.04, P=0.025). Compared with those receiving chemotherapy, patients receiving targeted therapy experienced significantly less severe pain (est=-1.17, P=0.024), fatigue (est=-1.16, P=0.019), and shortness of breath (est=-1.23, P=0.028) and less interference with walking (est=-1.23, P=0.042) (figure 1). More severe dry mouth was reported by patients undergoing targeted therapy (est=1.17, P=0.027). **Conclusion:** This real-world data demonstrates that, compared with conventional chemotherapy, targeted therapy correlates with less impairment of physiological condition and functioning in patients with mNSCLC. Additional follow up will confirm and expand these findings about the patient experience relative to treatment response.

Keywords: longitudinal symptom profiles, Targeted therapy, Patient-reported outcomes

P2.01-88 C-REACTIVE PROTEIN (CRP) AS A PREDICTIVE MARKER FOR SURVIVAL IN PATIENTS WITH ADVANCED NSCLC TREATED WITH FIRST LINE PEMBROLIZUMAB MONOTHERAPY

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Background: Pembrolizumab have shown longer activity in patients with advanced non-small cell lung cancer (NSCLC) especially when PD-L1 expression was high. But even with high PD-L1 expression, more than half of them failed to response. We focused on C-reactive protein (CRP), inflammatory protein measured routinely in clinical practice, to find out its role as predictive biomarker for pembrolizumab. **Method:** We analyzed advanced NSCLC patients with PD-L1 high expression (EGFR mutation (-), EML-4-ALK fusion (-)) who were treated with pembrolizumab as first-line therapy in our clinical practice. Patients received pembrolizumab (200mg/body, q3W) until progressive disease or unacceptable toxicity. During treatment period we measured serum biochemistry and blood cell count regularly. We evaluated the association the factors such as serum marker including inflammatory protein, age, performance status, histology, smoking status, prior radiation therapy and presence or absence ofimmune-related adverse events after treatment with the effect such as antitumor response, progressionfree survival (PFS) and overall survival (OS). **Result:** A total of 31 patients treated with pembrolizumab from March 2017 to February 2018 were analyzed for this research. Their characteristics were: median age 72 (range 37-84),male/female 24/7, adenocarcinoma/squamous cell carcinoma/pleomorphic carcinoma/neuroendocrine carcinoma/NOS 17/5/3/1/5, clinical stage IIIB/IV/recurrence 3/21/7, median CRP level at pretreatment 1.15mg/dL (0.07-15.27). Among the candidate biomarker, there were no association except for CRP. Serum CRP level at pretreatment was not predictive, but change of serum CRP level at 6 weeks after anti-PD-1 therapy initiation was most predictive in the analysis. Depressed CRP group showed longer PFS and OS than elevated group (PFS: p=0.08, HR 0.29, OS: p=0.08, HR 0.28, log-rank test). **Conclusion:** Our analysis suggests that serum CRP elevation at 6 weeks of treatment predict for longer survival when pembrolizumab was given as first-line treatment.This finding might be related to inflammation status of patients and efficacy of anti-PD-1 inhibitor.

Keywords: pembrolizumab, predictive marker, CRP

P2.01-89 SYNERGISTIC CYTOTOXICITY THROUGH MAPK/ERK PATHWAY AND ALK INHIBITION IN CRIZOTINIB RESISTANT EML4-ALK-POSITIVE LUNG CANCER

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Background: Anaplastic lymphoma kinase (ALK)-positive lung cancer is an aggressive cancer that most commonly arises through EML4-ALK chromosomal fusion. Crizotinib is the first-line treatment for ALK-positive lung cancer, providing a greater progression free survival and overall response rate than chemotherapy. However, patients invariably develop acquired resistance, usually within a year. Mechanisms of resistance include copy number gain, secondary mutations in ALK, or activation of bypass signalling pathways. The aim of this study was to investigate the combination effect of ALK inhibitor, crizotinib, and MEK inhibitor, selumetinib, in crizotinib resistance ALK-positive lung cancer cells.

Method: Cytotoxicity of single and combined treatment of crizotinib and selumetinib in ALK-positive (H3122), ALK-negative (A549) and crizotinib resistance ALK-positive (CR-H3122) cells was determined by Sulforhodamine B assay. Chou-Talay analysis was performed to determine the nature of interaction between the two drugs used in combination treatment. Endogenous expression of p-ALK and p-ERK was determined by western blotting. The effect of combination treatment on cell cycle arrest and apoptosis induction was determined by flow cytometer.

Result: Combined treatment with crizotinib and selumetinib had significantly greater cytotoxicity and showed a synergistic effect compared to the single drug treatments in H3122 cells. The combination treatment had no synergistic effect in A549 cells, indicating that the cytotoxic effect was specific to ALK. The most prominent cytotoxic effect of the combination treatment was observed with CR-H3122 cells, with synergistic suppression of cell viability even at low drug concentrations. Endogenous protein expression of p-ALK and p-ERK was decreased by combination of crizotinib and selumetinib. Moreover, combination treatment lead to increased G1 arrest and apoptosis compared to single treatment in H3122 cells.

Conclusion: Our results showed that combination of crizotinib and selumetinib have potent cytotoxic effects in crizotinib resistant ALK-positive lung cancer. The proposed combination treatment could be a promising therapy for acquired crizotinib resistant ALK-positive lung cancers.

Keywords: orthotopic mouse model, ALK-positive lung cancer

P2.01-90 PD-L1 EXPRESSION AS A PREDICTIVE BIOMARKER IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS WITH OR WITHOUT EGFR MUTATION

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Background: The prognostic value of PD-L1 expression and its clinical relevance of NSCLC is controversy. The impact of PD-L1 expression as the predictive biomarker for EGFR-TKIs treatment is needed to explore. **Method:** Medical records of metastatic NSCLC during September 2015-2016 had been reviewed. PD-L1 immunohistochemistry (IHC) staining with Antibody clone 22C3 was used. The PD-L1 positive was defined by tumor proportion score (TPS) $\geq$1%. **Result:** 204 patients were included. Patients with positive PD-L1 expression had significantly increased numbers of metastatic sites (*P*=0.009) and lung metastasis (*P*=0.045) compared to PD-L1 negative patients. Overall survival (OS) was longer in PD-L1 negative patients (22.7 months) compared to PD-L1 positive groups (13.6 months) (HR=1.48; P=0.03). Median OS were significantly different with the number of 7.2, 11.1, 25.7, 42.6 months in EGFR-/PD-L1+, EGFR-/PD-L1-, EGFR+/PD-L1+ and EGFR+/PD-L1- , respectively (P<0.001). Among EGFR positive patients, mOS of T790M-/PD-L1+, T790M-/PD-L1-, T790M+/PD-L1-, and T790M+/PD-L1+ were 22.1, 28, 42.6 and 48.4 months, respectively (P=0.03).

Patient characteristics categorized by PD-L1 expression (N = 204)

Characteristics	PD-L1 Negative N=134 (65.69%)	PD-L1 Positive N=70 (34.31%)	P value
Age - Median age (range) - < 65 years - $\geq$ 65 years	65 (36-85) 64 (47.76) 70 (52.24)	65 (35-86) 33 (47.14 37 (52.86)	**0.933**
Sex - Male - Female	62 (46.27) 72)53.73)	37 (52.86) 33 (47.14)	**0.371**
ECOG PS - 0-1 - $\geq$ 2	116 (86.57) 18 (13.43)	57 (82.61 12 (17.39)	**0.452**
Smoking status - Never - Ex-smoker - Current smoker	82 (61.65) 36 (27.07) 15 (11.28)	36 (52.17) 18 (26.09) 15 (21.74)	**0.131**
Mean smoking pack-year (range)	**29.72 (2-100)**	**25.68 (2-40)**	**0.873**
Initial staging - Recurrent - Denovo metastasis	32 (23.88) 102 (76.12)	14 (20) 56 (80)	**0.529**

Patient characteristics categorized by PD-L1 expression (N = 204)			
Characteristics	PD-L1 Negative N=134 (65.69%)	PD-L1 Positive N=70 (34.31%)	**P value**
Histology - Adenocarcinoma - Squamous cell carcinoma - Adenosquamous carcinoma - Others	117 (87.31) 1 (0.75) 2 (1.49) 14 (10.45)	58 (84.06) 3 (4.35) 2 (2.9) 6 (8.7)	**0.288**
EGFR mutation - Negative - Positive	47 (35.07) 87 (64.93)	32 (45.71) 38 (54.29)	**0.092**
Exon 19 deletion - No - Yes	87 (64.93) 47 (35.07)	50 (71.43) 20 (28.57)	**0.348**
L858R - No - Yes	100 (74.63) 34 (25.37)	53 (75.71) 17 (24.29)	**0.865**
ALK results - Negative - Positive	79 (92.94) 6 (7.06)	47 (97.92) 1 (2.08)	**0.421**
Number of site of metastasis - 0-1 - > 2	88 (65.67) 46 (34.33)	37 (52.86) 33 (47.14)	**0.009**
Lung metastasis - No - Yes	92 (69.17) 41 (30.83)	38 (54.29) 32 (45.71)	**0.045**
Bone metastasis - No - Yes	101 (75.37) 33 (24.63)	53 (75.71) 17 (24.29)	**0.957**
Liver metastasis - No - Yes	122 (91.04) 12 (8.96)	62 (88.57) 8 (11.43)	**0.573**
Pleural metastasis - No - Yes	91 (67.91) 43 (32.09)	62 (88.57) 20 (28.57)	**0.606**
Brain metastasis - No - Yes	117 (87.31) 17 (12.69)	58 (82.86) 12 (17.14)	**0.387**
Adrenal metastasis - No - Yes	122 (91.04) 12 (8.96)	62 (88.57) 8 (11.43)	**0.573**

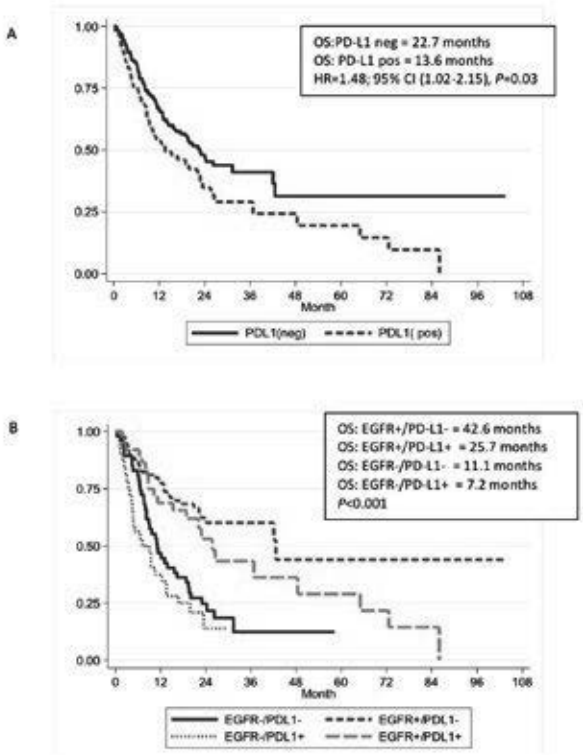

Figure: Overall survival according to PD-L1 expression
(A) Overall population
(B) Population categorized by EGFR mutation and PD-L1 expression

Conclusion: PD-L1 expression was associated with poorer survival outcomes among advanced NSCLC patients regardless of EGFR mutation status. PD-L1 expression is also the potential of predictive biomarker for EGFR TKIs treatment. The larger studies are needed to identify the prognostic and predictive values in T790M mutation population.

Keywords: NSCLC, PD-L1, EGFR mutation

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-91 TREATMENT PATTERNS IN PATIENTS WITH STAGE IIIB-IV NSCLC IN CLINICAL PRACTICE: RETROSPECTIVE ANALYSIS OF A UK TRUST DATABASE

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Background: I-O Optimise is a new pan-European data platform developed to enable real-world insights into the management of thoracic malignancies. As part of this initiative, the current analysis reports the characteristics and treatment patterns for adult patients diagnosed with stage IIIB or IV NSCLC at Leeds Teaching Hospitals Trust (LTHT), hosting one of the largest integrated cancer centres in the UK. **Method:** Retrospective cohort study using longitudinal data already collected from electronic medical records at LTHT, including all adult patients diagnosed with stage IIIB-IV NSCLC between January 2007 and August 2017. Minimum follow-up was 6 months. Distinct lines of therapy (LoT) were identified using a clinically-verified algorithm based on the name and date of systemic anti-cancer therapy (SACT) administered and the gap between two treatments. **Result:** Overall, 2119 patients were included. Mean age at diagnosis was 71.4 ± 11.2 years. Nearly one-third (32.7%) were clinically diagnosed without pathological confirmation (**TABLE**) and very few of these patients have SACT administration recorded. Following diagnosis, 648 patients (30.6%) received ≥1 LoT, 223 (10.5%) ≥2 LoT and 60 (2.8%) ≥3 LoT. Proportions of patients treated decreased with age (73.5% [25/34] aged 18-44 years; 52.7% [267/507] aged 45-64

years; 29.8% [310/1040] aged 65-79 years; 8.6% [46/538] aged 80+ years) and performance score (58.5% [387/662] PS0-1; 38.2% [158/414] PS2; 6.1% [52/848] PS3-4). Between the periods 2007-2011 and 2012-2017, increased proportions were treated (28.2% [263/933] and 32.5% [385/1186] respectively). Patient characteristics of the treated cohort and regimens administered for 1st and 2nd LoT are shown (**TABLE**). **Conclusion:** Around 70% of this real-world cohort did not receive any SACT, and the administration of treatment was strongly associated with age and performance status. The changing availability of treatment options over time (including the emergence of immunotherapy) and survival outcomes by LoT will be presented in more detail for the cohort described.

Keywords: stage III-IV NSCLC, Real world data, treatment

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-92 "ALL-IN-ONE" WINDOW: A NEW WAY OF LOOKING AT CHEST CT STUDIES IN THORACIC ONCOLOGY

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Background: Historically, CT studies are always viewed in several window settings, optimized to evaluate specific anatomic structures and regions (mediastinal, lung, bone and vascular window). A newly developed image processing technique fuses these conventional windows into a single "all-in-one" window. This new window is specifically designed for comparison and follow-up of CT studies in oncology. The purpose of this study is to compare lesion detection on this "all-in-one" window versus conventional window settings. **Method:** In this retrospective study, 50 consecutive thoracic oncology chest CT examinations, containing 417 documented lesions and features, were reviewed by 6 radiologists, subdivided into 2 groups of 3 radiologists each, with similar levels of expertise in each group (experienced, junior and radiology resident). All scans were reviewed in conventional window settings (as in routine daily practice), by one group and in the "all-in-one" window by the other group. Lesions were listed as 'missed' when they were not seen by at least two out of three observers and as 'well diagnosed' when seen by at least two out of three observers. **Result:** Out of the 417 lesions, 68 lesions were missed: 21 on the "all-in-one" window, 30 on conventional views and 17 on both views. Statistical analysis with linear mixed model showed that use of the "all-in-one" window did not result in an increase of missed lesions (p=1). Conversely, we found a tendency towards better lesion detection on the "all-in-one" window, though not strongly significant (p=0.07). Inter-observer agreement in both groups was similar (p=0.462). **Conclusion:** Our proposed new way of looking at chest CT images seems promising. In this study, we showed that lesion detection on a single "all-in-one" window is at least as good as on multiple conventional window settings. In further research, we will investigate the effect on lesion measurement and characterization.

Keywords: computed tomography, lung cancer, imaging

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-93 THE ANALYSIS OF THE SOLUBLE PROGRAMMED DEATH-1 OF LUNG CANCER PATIENTS WITH DIFFERENT CHARACTERISTICS

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Background: Programmed death 1 ligand-1(PD-L1) is important regulators in cancer immunity. The aim of this study was to evaluate the values of the expression of the soluble programmed death-1(sPD-L1) in the plasma of patients with lung cancer, and to investigate the associations between the expression level of sPD-L1 and clinicopathological features as well as effective and survival outcomes. **Method:** A total of 200 patients with non-small cell lung cancer(NSCLC) (n=188) and small cell lung cancer(SCLC)(n=12) treatment naive were explored, 96 samples of healthy subjects and 13 samples of benign tumours were studied as control. The sPD-L1 expression was scored by the way of anenzyme-linked immunosorbent assay (ELISA). We followed up 67 patients with NSCLC before and after standard treatment, and blood samples were taken every two months. We compared sPD-L1 expression with clinicopathological features and patients outcomes. **Result:** The Expression of sPD-L1 in patients of lung cancer was significantly higher than benign tumour group and healthy group (3.01±3.00ng/ml, 1.76±1.74ng/ml, 1.82±1.20ng/ml, P=0.002). The level of sPD-L1 in lung cancer was not associated with gender, age, smoking history, and histologic subtypes(P >0.05). The level of sPD-L1 was significantly higher in patients of worse PS(performance status) (PS≥2) than better PS(PS<2) (6.40±6.53 vs. 2.68±2.06 P=0.005). The level of sPD-L1 with later stages were remarkable higher than earlier stages(P<0.001) in NSCLC patients. The expression of sPD-L1 of the patients with epidermal growth factor(EGFR) mutated adenocarcinoma was higher than EGFR-wild group(4.30±1.82ng/ml vs. 3.76±1.57ng/ml, P=0.271). The decline of the level of sPD-L1 was correlated with the effects of good response and progressive disease(PD)(0.49±1.48ng/ml vs. 0.11±0.52ng/ml, P=0.307). As for survival, there was no difference between the decline of level of sPD-L1 and the progress free survival(PFS). **Conclusion:** Our results indicated that the elevated expression of sPD-L1 of patients with NSCLC was associated with later stages and worse life conditions, and which may correlated with bad clinical response and poor prognosis. EGFR mutation status may affect the expression of sPD-L1. Further studies are needed to determine the role of sPD-L1 as a molecular prognosis marker for the treatment and prognosis of patients with lung cancer.

Keywords: lung cancer, non-small cell lung cancer(NSCLC), Soluble programmed death-ligand 1(sPD-L1)

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-94 DIAGNOSTIC PATTERNS OF NON-SMALL CELL LUNG CANCER AT PRINCESS MARGARET CANCER CENTRE

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Background: Accurate classification of lung cancer subtypes has become critical in tailoring lung cancer treatment. Our study aimed to evaluate changes in diagnostic testing and pathologic subtyping of advanced non-small cell lung cancer (NSCLC) over time at a major cancer centre. **Method:** A review of patients diagnosed with advanced NSCLC at the Princess Margaret Cancer Centre between 2007-2009 and 2013-2015 was performed. Diagnostic method, sample type and site, pathologic subtype, and use of immunohistochemical (IHC) staining and molecular testing were abstracted. **Result:** A total of 238 patients were reviewed in 2007-2009 and 283 patients in 2013-2015 (Table 1). Over time, the proportion of patients diagnosed with adenocarcinoma increased from 60.9% to 73.1% while NSCLC-not otherwise specified (NOS) diagnosis decreased from 18.9% to 6.4%, p<0.0001. There was a decrease in use of diagnostic bronchoscopy (26.9% vs 18.4%) and an increase with mediastinal sampling procedures including endobronchial ultrasound (9.2% vs 20.5%), p=0.0001. A substantial reduction in cases reported as NSCLC-NOS was observed among bronchoscopy, image-guided, and mediastinal sampling procedures. The reduction in NSCLC-NOS was also predominantly seen in cytology samples, from 22.0% to 4.0% (p<0.0001). IHC use increased over time from 41.6% to 76.3% (p<0.0001). Patients with larger samples and IHC analysis were more likely to have biomarker testing performed (both p<0.01). Within the group diagnosed with NSCLC-NOS, the use of IHC increased non-significantly from 64% (29/45) to 94% (16/18). With the exception of bronchoscopy samples, use of IHC increased significantly with each method of diagnosis and sample type.

(See next page)

Table 1. Patient Demographics and Diagnostic Sampling Characteristics

	2007-2009 count (%)	2013-2015 count (%)
Number of Patients	238	283
Median Age at Diagnosis (range), years	66 (30-87)	68 (36-94)
Gender		
Male	145 (60.9)	166 (58.7)
Female	93 (39.1)	117 (41.3)
Pathologic Subtype		
Adenocarcinoma	145 (60.9)	207 (73.1)
Squamous Cell Carcinoma	32 (13.5)	38 (13.4)
Large Cell Carcinoma	14 (5.9)	9 (3.2)
NSCLC-NOS	45 (18.9)	18 (6.4)
Other	2 (0.8)	11 (3.9)
Initial Sampling Method		
Bronchoscopy	64 (26.9)	52 (18.4)
Image-Guided	73 (30.7)	88 (31.1)
Surgical Resection	31 (13.0)	45 (15.9)
Mediastinal Sampling[1]	22 (9.2)	58 (20.5)
Other[2]	48 (20.2)	40 (14.1)
Initial Sampling Site		
Lung	139 (58.4)	133 (47.0)
Mediastinal Lymph Node	24 (10.1)	65 (23.0)
Metastasis	49 (20.6)	59 (20.8)
Effusion[3]	26 (10.9)	26 (9.2)
Initial Sampling Type		
Cytology, non-FNA	58 (24.4)	38 (13.4)
Cytology, FNA	106 (44.5)	111 (39.2)
Biopsy/Surgical	74 (31.1)	134 (47.4)
IHC Performed		
Yes	99 (41.6)	216 (76.3)
No	139 (58.4)	67 (23.7)

NSCLC-NOS: non-small cell lung cancer-not otherwise specified
IHC: immunohistochemistry

[1]including mediastinoscopy and endobronchial ultrasound (EBUS)
[2]including thoracentesis
[3]including pleural and pericardial effusions

Conclusion: Customizing treatment based on pathologic subtype and molecular genotype has become key in treating advanced lung cancer patients. Greater accuracy of pathologic diagnosis is being achieved including through use of routine IHC.

Keywords: diagnostic testing, pathologic subtype, Immunohistochemistry

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-95 ASSESMENT THE FITNESS FOR CHEMOTHERAPY OF NSCLC PATIENTS USING 6MWT

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Background: Decision making in chemotherapy in multimorbid advanced NSCLC patients is a complex and challenging task. Physcian reported ECOG performance status (PS), being reproducible, is the gold standard of functional status quantification, when planning an oncology treatment. Inaccurate assesment of PS score is associated with an increased risk of treatment complications and therapy related deaths. The aim of study was to measure the correlation between 6-minute walking test (6MWT), PS and chemotherapy endurance and to study the role of 6MWT in predicting treatment complications and deaths. **Method:** 138 advanced stage (IIIA, IIIB, IV) NSCLC consented patients were enrolled in a prospective study. They were grouped according to their 6MWT results, and correlation with PS, BMI, FEV1, laboratory values, chemotherapy regimes and cycles were analyzed, with respect to the treatment complications and deaths as endpoints. Statistical analysis was performed with SPSS, Inc., Chicago, IL (level of significance < 0,05). **Result:** Statistical correlation was found between the 6MWT and chemotherapy endurance. Low 6MWT results (with a cut-off of 360 and 300 m respectively) were significantly associated with a very high risk of hematologic complications (36% and 42%), hospitalization (42% and 56%) and 3-month mortality (45% and 69%). No statistical correlation was found between 6MWT to PS, age, FEV1, BMI and initial lab values. **Conclusion:** 6MWT seems to be a simple, reliable and objective tool in assessing a patient's fitness to palliative chemotherapy for advanced NSCLC. Optimisation of treatment protocols, using 6MWT as a supportive tool to facilitate PS assesment, might prevent overtreatment of the patient and abuse of health service/insurance budgets.

Keywords: patient fitness, performance status (PS), 6 minute walking test (6MWT)

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-96 DYSGEUSIA ASSOCIATED WITH NUTRITIONAL AND QUALITY OF LIFE PARAMETERS IN NON-SMALL CELL LUNG CANCER PATIENTS NAÏVE TO CHEMOTHERAPY

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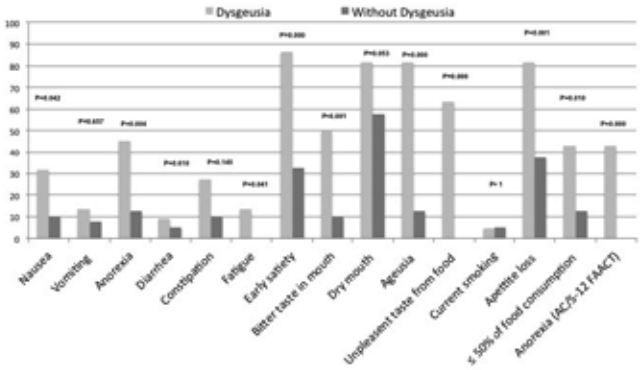
Background: Dysgeusia (taste alteration) has been reported in more than 50% of patient undergoing chemotherapy, however, it can be present before treatment, and it can be associated with nutritional and quality of life parameters. **Method:** We evaluated 65 patients naïve to chemotherapy, the alteration of taste by self-reporting questionnaire and through rinse stimuli to identify detection and recognition thresholds of umami, sweet and bitter taste; as well as, their association with nutritional and quality of life parameters. **Result:** Dysgeusia, perceived as a different taste from food was reported in 35% of patients. Those with dysgeusia presents less mean of weight (p=0.059), less lean body mass (p=0.027), higher Fat Mass (p= 0.027), less consumption of protein (0.059), iron (0.022) and sodium (0.034). Patients with dysgeusia reported unfavorable score in functional scales of Health Related Quality of Life (HRQL), than those without dysgeusia; including, Role Functioning (p=0.182*), emotional functioning (p=0.038), cognitive functioning (p=0.017) and social functioning (0.325*). And, the same for symptomatic scales: fatigue (p=0.016), nausea and vomiting (p=0.021), pain (p=0.133*), appetite loss (p<0.001) and constipation (p=0.005).

Table 1. Detection and recognition thresholds of umami, sweet and bitter taste in NSCLC patients naïve to chemotherapy

Taste	Estimuli	Concentration µmol/ml n (%)					
Umami	MSG	0.3	0.9	1.5	2.1	2.7	>2.7
Perception thresholds		**30 (46.2)**	14 (21.5)	7 (10.8)	3 (4.6)	2 (3.1)	9 (13.8)
Recognition thresholds		6 (9.2)	16 (24.6)	5 (7.7)	6 (9.2)	5 (7.7)	**27 (41.5)**
Sweet	Saccharose	3.5	6.5	9.5	12.5	15.5	>15.5
Perception thresholds		**39 (60)**	3 (4.6)	5 (7.7)	5 (7.7)	3 (4.6)	10 (15.4)
Recognition thresholds		5 (7.7)	10 (15.4)	12 (18.5)	7 (10.8)	8 (12.3)	**23 (35.4)**
Bitter	Urea	91	97	103	109	115	>115
Perception thresholds		**30 (46.2)**	7 (10.8)	9 (13.8)	6 (9.2)	2 (3.1)	11 (16.9)
Recognition thresholds		9 (13.8)	7 (10.8)	8 (12.3)	4 (6.2)	10 (15.4)	**27 (41.5)**

MSG: Monosodium glutamate
µmol/ml= micromol/milliter

Figure 1. Association of dysgeusia with gastrointestinal and taste alteration parameters between NSCLC patients naïve to chemotherapy with or without dysgeusia.



Conclusion: Patients with non-small cell lung cancer present dysgeusia before treatment and affect clinical parameters, food consumption habits and quality of life. Nutritional- care must be provided opportunely.

Keywords: Dysgeusia, naïve to chemotherapy, NSCLC

P2.01-97 PROGNOSTIC FACTORS IN RESECTED LUNG MUCINOUS ADENOCARCINOMA: CLINICAL AND PATHOLOGICAL FEATURES

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Background: Mucinous adenocarcinoma is rare subtype of lung adenocarcinoma. This study aimed to discover which factors influenced prognosis of resected lung mucinous adenocarcinoma. **Method:** From April 1997 to March 2017, we retrospectively reviewed the clinical and pathological features in resected lung mucinous adenocarcinoma patients. We specially focused on KRAS mutation and NRG1 fusion, which were reported that MA often harbored them. We also examined CT findings (solitary type or pneumonic type) and spread through air space(STAS). The Kaplan-Meier method and log -rank test were used for the survival analyses. **Result:** 57 patients were enrolled to the study. We detected KRAS mutation in 32 patients (56.1%) and NRG1 fusion in one patient (1.8%). G12D was the most common in terms of amino acid change of KRAS mutation (78%). There were no significant differences in overall survival (OS) and disease-free survival (DFS) between patients with KRAS wild type and those with KRAS mutation (p=0.70 and p=0.85[Office1] , respectively). In point of CT finding, there were 42 solitary type of tumors and 15 pneumonic type of tumors. OS and DFS were significantly worse in pneumonic type patients (p<0.01 and p<0.01[Office2] , respectively). STAS was observed in 32 patients. DFS was significantly shorter in patient with STAS(p=0.03) although OS was not(p=0.07).[Office3] Multivariate analysis revealed that CT finding (pneumonic type) was an independent prognostic factor of DFS. **Conclusion:** Pneumonic type on CT finding was an independent prognostic factor in patients with completely resected lung mucinous adenocarcinoma. KRAS status was not significantly related to the prognosis in our cohort.

Keywords: CT findings, invasive mucinous adenocarcinoma, KRAS

P2.01-98 SINGLE-ISOCENTER VOLUMETRIC-MODULATED ARC RADIOSURGERY FOR NON-SMALL-CELL LUNG CANCER PATIENTS WITH MULTIPLE BRAIN METASTASES

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Background: Radiosurgery for multiple brain metastases (BMs) in patients with non-small-cell-lung cancer (NSCLC) is a well-established treatment option. However, only 1–4 BMs can be treated by conventional linear-accelerator-based radiosurgery because the treatment time becomes longer as the number of BMs increases. Advanced volumetric modulated arc therapy combined with image-guided radiotherapy enables the realization of single-isocenter volumetric-modulated arc radiosurgery (VMAR), a novel irradiation technique. VMAR irradiates multiple BMs simultaneously using only one isocenter and within a short treatment time. Here we report our initial experience with VMAR. **Method:** The clinical records of 19 patients with 115 BMs from NSCLC were retrospectively analyzed. All patients were treated by VMAR for multiple BMs from October 2015 to September 2017 at our institution and received follow-up magnetic resonance imaging at least once after VMAR. The median patient age was 69 years. The median Karnofsky Performance Scale score was 90; five patients had been previously treated with whole-brain radiotherapy. The histology of the primary tumor was squamous-cell carcinoma in one patient and adenocarcinoma in 18 patients; 12 patients had either an EGFR or ALK alteration. A planning target volume (PTV) was created by expanding the contrast-enhanced lesion with a 1- or 2-mm margin. The median peripheral prescribed dose was 28 Gy, delivered in five fractions. All lesions were set to be covered by ≥99.5 % of the prescribed dose. **Result:** The median follow-up period was 8.5 (range, 1.7–29.9) months. The median number of PTVs was four (range, 2–18). The median PTV was 0.49 (range, 0.13–13.49) cm^3, and the median total PTV 8.3 (range, 1.52–18.87) cm^3. The median PTV was significantly smaller in patients with than without genetic alterations to their tumor. The probabilities of local control, overall survival, and developing new BMs at 12 months were 100%, 68.4%, and 51.1%, respectively. Acute adverse events included grade 2 alopecia in four patients and seizure in one patient. The number of PTVs in patients with grade 2 alopecia was more than six. Two patients developed grade 2 central nervous system necrosis as a late adverse event. No grade 3 or higher toxicities were noted. **Conclusion:** While VMAR achieves good local control, the development of temporary alopecia remains to be addressed. More cases and a longer- follow-up period are required to verify the efficacy of VMAR.

Keywords: brain metastases, single-isocenter volumetric raidosurgery, NSCLC

P2.01-99 CAN NGS NSCLC TESTING BE IMPLEMENTED WITHOUT IN HOUSE EXPERTISE? CLINICAL UTILITY OF THE FIRST FDA-APPROVED LUNG CANCER NGS END-TO-END SOLUTION

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Background: Clinical utility and advantages of in-house NSCLC NGS testing compared with send-out testing are: shorter turn-around times for faster treatment, better tissue stewardship, and maintenance of specimen control within institutions, fostering direct communication between pathologists and oncologists on the most effective testing and treatment paradigms. Despite obvious benefits, in-house NGS testing widespread use has not occurred due to the need for specialized personnel, extensive hands-on time, and complexity in developing/validating home-brew panels, and bioinformatics result interpretation. To overcome these difficulties, Thermo Fisher Scientific developed the Oncomine™ Dx Target Test (ODxTT) to identify NSCLC guideline-recommended EGFR, ROS1, or BRAF mutations for their associated treatment with gefitinib, crizotinib, or dabrafenib/trametinib, respectively. This is the first FDA-approved NGS companion diagnostic test commercially available that can be implemented in local laboratories. **Method:** Clinical utility measured by objective response rate (ORR), and duration of response (DOR) in NSCLC patients was evaluated initially utilizing local laboratory tests (LLTs) and compared with the ODxTT across mutations and associated therapies. **Result:** Comparison of ODxTT with the NSCLC BRAF V600E PCR assay in patient samples showed 100% (181/181; 95%CI 97.9-100%) overall percent agreement (OPA, excluding no calls). Clinical efficacy of the ODxTT in 2 cohorts with stage IV NSCLC treated with dabrafenib/trametinib (BRF113928 clinical trial) measured as ORR was 68.2% (15/22) for Cohort B and 60.9% (14/23) for Cohort C, which was similar to the results achieved with the LTT 63.2% ORR (36/57) for Cohort B and 61.1% ORR (22/36) for Cohort C. ORR of 83.3% (5/6; 95%CI: 35.88-99.58%) was achieved with crizotinib with an accompanying DOR of 17.5 months (N=5, 95%CI: 10.9-24.1) which tested positive with the ODxTT in patient samples (Phase-1, Pfizer-Study A8081001). OPA of 99.0% (188/190; 95%CI 96.25-99.87%) was achieved for EGFR Exon 19 deletion and 100% (197/197; 95%CI: 98.14-100%) for EGFR L858R with the ODxTT versus the Qiagen TheraScreen EGFR RGQ PCR Kit.Estimate repeatability of the ODxTT at each variant location was ≥98.8% (DNA) and 94.4% (RNA). **Conclusion:** The FDA approved ODxTT demonstrated clinical utility by accurately detecting guideline-recommended mutations for the selection of associated targeted therapies eliminating additional expertise required to validate, implement, and run NGS LLTs. "For In vitro diagnostic use"

Keywords: Clinical Utility ODxTT, NGS, NSCLC, IVD, Companion Diagnostic

P2.01-100 DIFFERENT GENETIC MUTATIONS ENRICHED IN CIRCULATING TUMOR DNA PREDICT DIFFERENT METASTATIC SITES IN LUNG ADENOCARCINOMA PATIENTS

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Background: The mutation map of the lung adenocarcinoma is clear. However, differences of genetic mutations related to metastatic sites have not been addressed before and remain to be explored. Identification of mutation signature may help to predict metastasis. **Method:** We reviewed 353 ctDNA samples from lung adenocarcinoma patients with definite metastasis at our institute. Somatic mutation profiles were analyzed using hybridization capture based next-generation sequencing (NGS), which enables the simultaneous detection of single-nucleotide variants, insertions/deletions, rearrangements, and copy-number alterations of 59 genes. **Result:** All the samples were divided into 2 groups based on

the distance of the metastases: 165 samples was in the distal metastasis group including bone or liver metastases; 188 samples was in the proximal group, including lung, pleural or thoracic lymph node metastasis. The gene mutation number of the distal metastasis is higher than the proximal metastasis (4.92 vs 3.85, P=0.031). Gene mutations for each group are shown in the figure below. Similar to the genetic profiling of lung adenocarcinoma in COMIC database, the most frequently mutated genes were *EGFR* and *TP53* in two groups. But the frequency mutation of *NTRK1* in proximal metastasis group is three times more than that of the distal metastasis group (11/188, 5.9% vs 3/165,1.8%). And the frequency of *ALK* mutation in the distal metastasis group is two times more than that of the proximal metastasis group (10/165, 6.1% vs 6/188, 3.2%). Moreover, for the top 9 frequently mutant genes, there was 78% overlap in the two groups. However, the overlap with COSMIC database was 55% for distal metastasis group and 44% for the proximal metastasis.

	Distant metastasis group		Proximal metastasis group		COSMIC database	
	gene	Mutation frequency	gene	Mutation frequency	gene	Mutation frequency
1	EGFR	70.30%	EGFR	73.94%	EGFR	31%
2	TP53	60.61%	TP53	61.17%	TP53	31%
3	KRAS	11.52%	ERBB2	9.04%	KRAS	18%
4	RB1	10.30%	KRAS	9.04%	STK11	8%
5	NF1	9.70%	RB1	7.45%	CDKN2A	7%
6	ERBB2	7.88%	NF1	7.40%	SMARCA4	6%
7	APC	6.67%	APC	6.91%	NF1	6%
8	ALK	6.06%	PIK3CA	6.38%	ATM	5%
9	ATM	6.06%	RET	5.85%	KDR	5%
10	PIK3CA	6.06%	NTRK1	5.85%		

Conclusion: Lung adenocarcinoma patients with *ALK* mutation are more likely to have distant metastasis. While the patients with *NTRK1* mutation are more likely to have proximal metastasis.

Keywords: genetic mutation, lung adenocarcinoma, metastasis

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-101 DYNAMIC MONITORING OF GENE ALTERATIONS WITH CTDNA BY NGS FOR EGFR MUTATED LUNG ADENOCARCINOMA TREATED WITH GEFITINIB IN BENEFIT STUDY (CTONG 1405)

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Background: Blood-based cell-free tumor DNA (ctDNA) could be dynamically monitored to provide gene alterations during EGFR-TKI treatment, which might offer critical clue for prognosis and clinical treatment decision. Here we reported the dynamic gene alterations monitoring using next generation sequencing (NGS) in BENEFIT study to explore the mechanisms of different responses and resistances to EGFR-TKI in EGFR-sensitizing-mutated lung-adenocarcinoma (LADC) patients. **Method:** Patients with systemic treatment-naïve, stage IV LADC and EGFR-sensitizing-mutation in ctDNA were enrolled to receive gefitinib. Blood samples were dynamically obtained at baseline, every 8 weeks and at disease progression (PD). The dynamic analysis of quantity of ctDNA, multiple driver genes and tumor suppressors were investigated with NGS (Nextseq500 sequencer, consisting of critical exons/introns of 168 genes), and were correlated with efficacy and resistance. **Result:** Totally 181 LADC patients with EGFR-sensitizing-mutation (exon-19-deletion and exon-21-L858R-point-mutation) provided sufficient blood samples for NGS analysis at baseline, of which 143 patients obtained at least four timepoints of dynamic blood sample collection until PD (baseline, 8 weeks, 8 weeks before PD and PD). At baseline, 180 of patients (99.4%) were confirmed as EGFR-sensitizing-mutation with NGS (92 EGFR-19-deletion and 88 EGFR-L858R-point-mutation) including 44 (24.3%) EGFR-amplification, 116 (64%) TP53-mutation, or other known oncogenic drivers including *MET (N=5, 2.8%), ERBB2 (N=7,3.9%), KRAS (N=6, 3.3%), BRAF (N=2, 1.2%), RET (N=1, 0.6%), ROS1 (N=1, 0.6%), or EGFR-T790M (N=4, 2.2%)*, which was correlated with poor efficacy compared with those with only EGFR-sensitizing-mutation (PFS 4.7 months [m] vs. 13.2m , p=0.002). Additionally, tumor suppressor genes exhibiting cumulative effect to poor prognosis: PFS for 164 patients with TP53&RB1&PTEN-mutation≤1 was 11.1m, while for 16 patients with TP53&RB1&PTEN-mutation >1,PFS was 4.7 m, p<0.0001. To cut-off date, 117 patients had PD, among them, 63 (54%) patients acquired EGFR-T790M-mutation presented as dominant resistance mechanism besides MET-amplification/ERBB2-amplification/ERBB2-S310F (N=16, 14%), RET fusion/splice (N=2, 1.7%), ROS1-C2336F-mutation (N=1, 0.9%), RB1-nonsense-mutation (N=2, 1.7%), TP53-Y205S-mutation (N=1, 0.9%) and TP53-Y205S-mutation accompanied with FGFR1-amplification (N=1, 0.9%). The remaining resistance mechanisms (31%) were unknown. Patients with only T790M-mutation had a significantly longer PFS (11.5m) compared with patients obtaining other acquired resistant mechanisms (3.0m). Interestingly, seventy-five (53.2%) patients had molecular progression before radiographic progression, and the median time difference was 8.7 weeks. **Conclusion:** Dynamic alterations of multi-drivers and suppressors together with EGFR-sensitizing-mutation and T790M-mutation could separate LADC into different subgroups with distinguished molecular features, which may play a vital role during EGFR-TKI treatment for resistance-predicting, and initial/subsequent treatment decision-making.

Keywords: multi-drivers, ctDNA, EGFR mutation

P2.01 ADVANCED NSCLC
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P2.01-102 COMPREHENSIVE NEXT-GENERATION SEQUENCING GUIDED TARGETED THERAPIES IMPROVE CLINICAL OUTCOMES OF LUNG CANCER PATIENTS

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Background: Next-generation sequencing (NGS) has been increasingly involved in the clinical decision-making of cancer care, the primary applications of which are the identification of sensitizing mutations for targeted therapies and drug-resistant mechanisms. Along with more clinical validations and approvals of several commercially available targeted NGS panels by FDA for mutation profiling, it has been debated that whether comprehensive NGS test should be used as a standard procedure in clinical practice. **Method:** In this study, we recruited 24 patients with stage IV lung cancer. 22 of them are adenocarcinoma and the other 2 are small cell lung cancer and squamous cell carcinoma, respectively. Genomic DNA from 13 tumor tissues, and circulating tumor DNA from 8 pleural effusions and 3 plasma samples in each corresponding patient were collected and subjected to targeted-NGS covering 416 cancer-related genes and 16 genes frequently rearranged in solid tumors. Targeted therapy or chemo/radiochemotherapy was applied in clinical practice with the consideration of patients' requests and their affordability due to financial barriers. Patients' clinical outcomes were further evaluated. **Result:** Of all patients, 54% of them (n=13) were detected with sensitizing mutations that have targeted drugs available, including *EGFR* exon 19 deletion (n=2), L858R (n=2) and L861Q mutations (n=1), *ALK* fusion (n=1), *ROS1* fusion (n=1), *MET* exon 14 skipping (n=1), as well as *EGFR* T790M (n=5) for 4 patients who had progressed on the first-generation tyrosine kinase inhibitors (1st-gen TKI) and 1 TKI-treatment naive patient. 69% of patients (n=9) with actionable mutations were subjected to targeted treatment, while the other 31% patients (n = 4) were treated with chemotherapy or radiochemotherapy. Consistent with clinical validations, the overall survival (OS) of targeted-treatment group is better than the systematic treatment group. On the other hand, for patients without detectable actionable mutations (n=11), 64% of patients (n=7) were underwent chemotherapy, while the rest were treated with 1st-gen *EGFR* TKI as requested by the patients. As expected, chemotherapy-treatment group had a similar OS as the TKI group. Collectively, patients with sensitizing mutations achieved significantly longer OS from the TKI treatments than those without actionable mutations (p=0.02). **Conclusion:** Our data demonstrated that the existence of sensitizing mutation is the determining factor for the treatment efficacy of targeted therapies. In the real world, NGS test can not only be involved into the decision-making for the first line treatment, but also be instructive for treatment changes after drug-resistance developed

Keywords: lung cancer, targeted treatment, next-generation sequencing

P2.01-103 NEUTROPHIL-TO-LYMPHOCYTE RATIO AS A PREDICTOR OF IMMUNOTHERAPY TREATMENT OUTCOMES IN ADVANCED NON-SMALL LUNG CANCER

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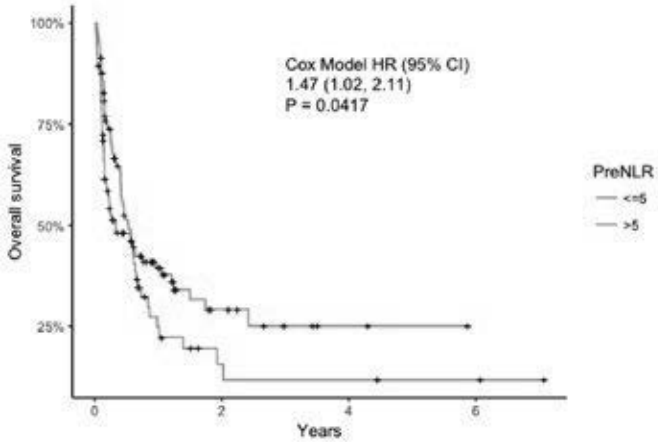
Background: Immune checkpoint inhibitors (ICIs) are a new class of therapy for patients with non-small cell lung cancer (NSCLC). Immunologic markers, such as serum neutrophil-to-lymphocyte ratio (NLR), are prognostic in patients with a variety of malignancies, with preliminary findings in patients on immunotherapy. In this study, we evaluate the association between NLR and ICI outcomes in NSCLC, including the development of immune-related adverse events (irAEs). **Method:** We conducted a retrospective analysis of advanced or recurrent NSCLC patients receiving ICI from 2011 to 2017. Demographics, disease and treatment history, and pretreatment labs were recorded. An NLR^{3}5 was defined as high and <5 as low, based on meta-analyses. Cox proportional hazards models and univariate and multivariate regressions were used to assess the association between NLR and overall survival (OS), progression-free survival (PFS), disease control rate at 10 weeks (DCR), and irAEs. **Result:** 183 patients were identified: 55.2% male, 76.5% Caucasian, mean age 65.3 years (range 38–90 years). Male sex, smoking history, prior radiotherapy, and pretreatment albumin were significantly associated with high versus low NLR ($p < 0.05$). In univariate analyses, pretreatment NLR was a significant predictor of OS (HR 1.47, $p < 0.05$, Fig. 1), PFS (HR 1.44, $p < 0.05$), and DCR (OR 0.49, $p < 0.05$), but not irAEs (OR 1.37, $p = 0.33$). These findings persisted with multivariate analyses (OS HR 1.76, PFS HR 1.64, DCR OR 0.24, all $p < 0.01$; irAE OR 1.52, $p = 0.33$).



Conclusion: High NLR was positively associated with OS, PFS, and DCR but not irAEs in NSCLC patients receiving ICI. Our results support the use of NLR as a biomarker for clinical outcomes. Prospective studies are needed to study this measure in patients undergoing ICI therapy, and further studies to identify predictive biomarkers of irAEs are warranted.

Keywords: Prognostic factors, Immunotherapy, advanced NSCLC

P2.01-104 PLASMA T-CELL-DERIVED CIRCULATING DNA IN ADVANCED NSCLC IS NOT CORRELATED WITH TIL BUT HAS A POTENTIAL OF PROGNOSTIC VALUE

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Background: Non-tumor derived circulating DNA (nt-cirDNA) of advanced non-small cell lung cancer (NSCLC) patient, even not yet clear originated, was associated with prognosis. In this study, we investigated whether T-cell-derived circulating DNA (T-cirDNA) was the majority part of nt-cirDNA nor correlated with tumor-infiltrating T-lymphocyte (T-TIL). **Method:** Prognostic impact including demographic characteristics were integrated into the model. Using Quantitative real-time PCR with Taqman assay specific to VDJ segment of TCRβ (T-cell-receptor beta chain) was used to represented amount of T-cirDNA in plasma of 106 advanced stage NSCLC. Quantitative CD3-specific immunohistochemistry (IHC) staining from biopsy specimen, represented T-TIL, was done using Aperio ImageScope. **Result:** T-cirDNA was detected in seventy-three advanced NSCLC patients with a median of 1.71 pg/ml [range 0-2260]. Forty-six patients were assessed for proportion of T-TIL per total cell with a median of 0.22 per mm^2 [range 0.02-2.34]. No correlation was found between T-cirDNA and T-TIL. From multivariable analysis, active smoking status was the only factor correlated with low T-cirDNA level ($P<0.001$). Kaplan Meier survival analysis of T-cirDNA ratio (T-cirDNA/total cirDNA) shown a trend of favor prognostic outcome for high T-cirDNA ratio (more than 0.03 %), HR 0.67 [95% CI 0.43-1.04, $P=0.07$]

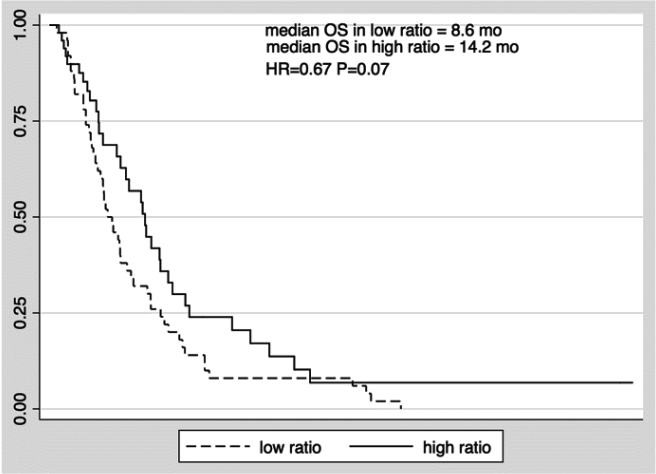

Figure : Kaplan and Meier survival graph showed survival of patients with high and low ratio of T cell derived cf DNA/RPP30 (median OS in low ratio = 8.6 months, median OS in high ratio = 14.2 months, HR0.67, P=0.07)

Conclusion: plasma T-cirDNA component, even not correlated with T-TIL, revealed a trend of prognostic impact in advanced stage non-small-cell cancer patients.

Keywords: non-small cell lung cancer, Non-tumor-derived circulating DNA, Tumor-infiltrating lymphocyte

P2.01-105 TUMOR TREATING FIELDS PLUS STANDARD OF CARE FOR NON-SMALL CELL LUNG CANCER FOLLOWING PLATINUM FAILURE: PHASE 3 LUNAR STUDY

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Background: Tumor Treating Fields (TTFields) is a non-invasive, anti-mitotic treatment approved for glioblastoma based on significant survival outcomes in a Phase 3 trial. Efficacy of TTFields in NSCLC has been shown preclinically and the safety confirmed in a phase I/II pilot study combined with pemetrexed. In the LUNAR study [NCT02973789], we investigated if adding TTFields to immune checkpoint inhibitors or docetaxel following platinum doublet failure will increase overall survival. **Method:** s: Patients (N=534), with squamous or non-squamous NSCLC, are stratified per selected standard therapy (immune checkpoint inhibitors or docetaxel), histology (squamous vs. non-squamous) and geographical region. Key inclusion criteria: disease progression while on/after platinum-based therapy, ECOG 0-2, no electronic medical devices in the upper torso, and absence of brain metastasis. Docetaxel or immune checkpoint inhibitors are given at standard doses. TTFields are applied to the upper torso for ≥18 hours/day, allowing patients to maintain daily activities. TTFields are continued until progression in the thorax and/or liver. Follow-up is performed once q6 weeks using CT scans of the chest and abdomen. On progression in the thorax and/or liver, patients have 3 post-progression follow-up visits and are then followed monthly for survival. The primary endpoint is superiority in OS with TTFields in combination with the standard of care treatments versus (vs) standard of care treatments alone. Key secondary endpoints compare the OS in patients treated with TTFields and docetaxel vs docetaxel alone, and patients treated with TTFields and immune checkpoint inhibitors vs those treated with immune checkpoint inhibitors alone. An exploratory analysis will test

non-inferiority of TTFields with docetaxel compared to checkpoint inhibitors alone. Secondary endpoints include progression-free survival, radiological response rate, quality of life based on the EORTC QLQ C30 questionnaire and severity and frequency of adverse events. The sample size is powered to detect a HR of 0.75 in TTFields-treated patients versus control group. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Tumor Treating Fields; stage 4 non-small cell lung cancer; platinum failure

P2.01 ADVANCED NSCLC
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P2.01-106 A COMPARATIVE ANALYSIS OF GENOMIC ALTERATIONS BY TUMOR TISSUE AND CIRCULATING TUMOR DNA IN ADVANCED NON-SMALL CELL LUNG CANCER

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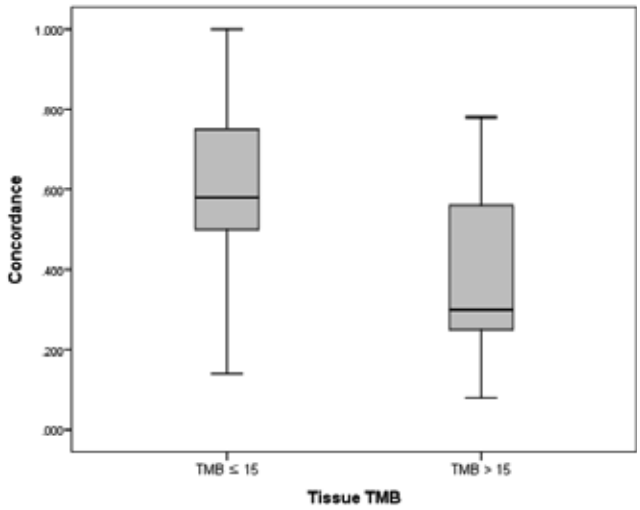
Background: Genomic profiling of lung cancers using circulating tumor DNA (ctDNA) in the blood of patients is rapidly becoming established as a useful source of information to aid clinical decision-making. We evaluated the concordance of genomic alterations by ctDNA and tumor tissue DNA in Advanced Non-Small Cell Lung Cancer (NSCLC). **Method:** Tumor tissue DNA from formalin-fixed, paraffin-embedded (FFPE) samples and ctDNA from plasma samples were obtained at the time of diagnosis or at the time of progressive disease after receiving targeted therapy in 41 patients with stage IIIB or IV NSCLC in this prospective study (NCT03235765). Hybrid-capture based genomic profiling (Axen Cancer Panel, Macrogen) was performed to sequence 170 genes in both samples. Concordance is defined as the number of genomic alteration present in both samples divided by the number of genomic alteration in FFPE. Tumor mutation burden (TMB) was also measured. **Result:** Most patients were adenocarcinoma (n=34, 82.9%). The total number of genomic alteration identified in FFPE and ctDNA were 751 and 561, respectively. Median concordance was 50% (8.0% – 100%). Among the clinical factors including smoking history, tumor size, PD-L1 status, EGFR mutation, TMB of tumor DNA, and concentration of ctDNA, concordance was negatively correlated with TMB of tumor DNA (Spearman's r= -0.504, P=0.001). When we divide low TMB (TMB-L) and high TMB (TMB-H) by the cut-off of 15/MB (median value), average concordance was 38.7% in TMB-H (N=20) and 59.7% in TMB-L (N=21) (Mann-Whitney, P=0.007). TMB by FFPE was significantly associated with the number of genomic alterations in FFPE (P<0.0001), but was not with the number of genomic alterations in ctDNA (P=0.128) or PD-L1 status (P=0.574).



Conclusion: This study suggests that ctDNA genomic profiling may replace tissue-based genomic profiling in NSCLC patients with low TMB. However, both tissue and blood-based genomic profiling may be necessary for NSCLC patients with high TMB.

Keywords: lung cancer, ctDNA, TMB

P2.01 ADVANCED NSCLC
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P2.01-107 ANALYSIS OF MUTATION DETECTION BY CTDNA ON THE BASIS OF METASTATIC SITES IN LUNG ADENOCARCINOMA PATIENTS

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Background: Circulating tumor DNA (ctDNA) testing represents a powerful tool to detect gene alterations in patients. However, differences in mutation detected by ctDNA related to metastatic sites in lung cancer have not been addressed before and remain to be explored. **Method:** We reviewed 317 ctDNA samples from 310 lung adenocarcinoma patients with definite metastasis at our institute. Somatic mutation profiles were analyzed using hybridization capture based next-generation sequencing (NGS), which enables the simultaneous detection of single-nucleotide variants, insertions/deletions, rearrangements, and copy-number alterations of 1021 genes. **Result:** Patients were divided into two groups according to metastatic sites. Any case with metastasis to the bone, liver or adrenal gland falls into the major organ metastasis group, while any case with metastasis to the lung, pleura or lymph node belongs to the local metastasis group. No genetic alteration was detected in 14 (11.5%) of 122 samples in the major organ group and 35 (17.9%) of 195 in the local group. And distant metastasis is associated with more mutations on average detected by ctDNA (5.26 for the major organ group *vs* 3.72 for the local group; p=0.0039). As for genes involved, the most common mutated ones are *EGFR* and *TP53* for both groups, with an overall mutation rate being 40.6% and 33.2% respectively. And just as average gene alterations mentioned above, the mutation rates of *EGFR* and *TP53 are* much higher in the major organ group (49.6% *vs* 35.2% for *EGFR*; 43.6% *vs* 26.9% for *TP53*). Besides, mutations of *NF1*, *MLL3*, *KRAS* and *KEAP1* are more frequent in the major organ group while mutation rate of *PIK3CA* is slightly higher in the local group (Table).

Table. Some mutated genes detected by ctDNA

	major organ metastasis (117)	local metastasis (193)
EGFR	58 (49.6%)	68 (35.2%)
TP53	51 (43.6%)	52 (26.9%)
KRAS	9 (7.7%)	7 (3.6%)
MLL3	9 (7.7%)	6 (3.1%)
NF1	9 (7.7%)	3 (1.6%)
ERBB2	5 (4.3%)	6 (3.1%)
PIK3CA	3 (2.6%)	7 (3.6%)
KEAP1	7 (6.0%)	3 (1.6%)

Conclusion: More gene alterations were detected by sequencing of ctDNA in patients of lung adenocarcinoma with major organ metastasis compared to those with only local metastasis.

Keywords: ctDNA, next generation sequencing (NGS), metastasis

P2.01 ADVANCED NSCLC
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P2.01-108 TEMPORAL HETEROGENEITY OF RESISTANT MUTATIONS IN SEQUENTIAL ALK TKI TREATED LUNG CANCER REVEALED BY NGS-BASED LIQUID BIOPSY

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Background: Crizotinib and several next-generation ALK TKIs have been widely applied in the treatment of *ALK*-positive lung cancer patients. However, drug resistance is eventually developed to these ALK TKIs via heterogeneous resistance mechanisms, which is needed to be further explored. Due to the invasiveness and feasibility of repetitive tissue biopsies, liquid biopsy has become a promising alternative for dynamically

monitoring tumor genomic evolution and guides decision-making for treatment adjustment. **Method:** Primary tumor sample of a 71-year-old male patient diagnosed with stage IV lung adenocarcinoma was subjected for targeted next-generation sequencing (NGS) for identification of driver mutations. Mutation profiles of circulating tumor DNA (ctDNA) from seven sequential plasma samples during the treatment course of crizotinib, brigatinib, and lorlatinib were closely monitored. **Result:** The dynamic mutation profiles during the disease course were represented in the Figure. As *EML4-ALK* v1 fusion was detected in the primary tumor, the patient was administrated with crizotinib and reached a progression-free survival (PFS) of 11 months when *ALK* G1269A was identified upon progression. As a result, brigatinib, a second generation ALK TKI overcoming G1269A-driven resistance, was applied. Dynamic monitoring of patient's ctDNA during brigatinib treatment showed a dramatic drop of G1269A mutant allele frequency (MAF) to undetectable level, whereas a novel F1174L became the dominant clone. The disease progressed after 9-month of brigatinib treatment, and the patient was switched to lorlatinib. A third mutation E1210K quickly overtook F1174L as the dominant clone with the accumulation of more concomitant mutations towards the end of the treatment (8 different mutations) with a PFS of 9 months. Interestingly, brigatinib-sensitive G1269A came back after 6-month of lorlatinib treatment. **Conclusion:** Temporal heterogeneity of *ALK* activating mutations was observed along the treatment course of different TIKs via NGS-based liquid biopsy, which could provide guidance for stepwise treatment strategy for better patient care.

Keywords: liquid biopsy, dynamic monitoring, ALK mutation

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P2.01-109 TREATMENT DURATION—A MORE REASONABLE DEFINITION TO EVALUATE THE EFFICACY OF CRIZOTINIB IN ALK POSITIVE ADVANCED NSCLC

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Background: Crizotinib has demonstrated its superior efficacy in ALK positive NSCLC patients when used as first-line regimen, with a median overall survival (OS) of more than 4 years, whereas a median progression-free survival (PFS) of only 10.9 months. Patients who continued crizotinib beyond progressive disease (CBPD) could still obtain additional survival benefits of 6-8 months after disease progression. In terms of that, PFS, the frequently used primary endpoint in clinical trials, may not be able to provide accurate information on impact of this intervention in multiple lines therapy. Here we proposed "treatment duration" as an intermediate clinical endpoint between PFS and OS that further define efficacy of crizotinib in multiple lines of treatment and reported the exploratory data in a real-world cohort. **Method:** We retrospectively enrolled 150 ALK positive NSCLC patients who had acquired crizotinib resistance from Aug 2011 to May 2017. The median PFS of crizotinib and median OS (from crizotinib initiation) were analyzed. Treatment duration of crizotinib, the time from crizotinib initiation to discontinuation, was also calculated. **Result:** The median PFS of crizotinib in the 150 ALK positive advanced NSCLC patients was 14.4 months (95% CI: 11.3-17.4). Overall, 58 patients (38%) continued CBPD and the median post-progression PFS was 10.4 months, resulting in a median treatment duration of crizotinib in the total cohort of 20.2 months (95% CI: 14.3-26.0). And median OS was 30.1months (95% CI: 21.3-38.8). 77 (51%) patients who received crizotinib as first-line therapy exhibited both longer median PFS (17.7 months, 95% CI: 12.5-22.9; vs. 12.2months, 95% CI: 7.6-16.8) and median OS (35.2 months, 95% CI: 23.2-47.1; vs. 25.4 months, 95% CI: 14.4-36.3) compared to those selected crizotinib as second- line and above therapy. The treatment duration among them were 23.1 months (95% CI: 14.7-31.4) and 18.9 months (95% CI: 11.4-26.3), respectively. **Conclusion:** Crizotinib showed superior efficacy in ALK positive NSCLC patients. Treatment duration may be more reasonable to define the efficacy of crizotinib in multiple lines therapy of ALK positive NSCLC.

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P2.01-110 UNIQUE GENOMIC PROFILE REVEALED BY MALIGNANT PLEURAL EFFUSION

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Background: The accumulation of malignant pleural effusion (MPE), often occurring in advanced lung cancer patients, is the result of pleural space invasion by malignant cells, which disrupt the drainage of pleural fluid. Numerous studies have confirmed the clinical utility of MPE for mutation detection from single gene perspective, often focusing on classic driver genes. Very few studies have interrogated MPE as a media for liquid biopsy using targeted sequencing. In this study we investigated the potential of using MPE as a media for liquid biopsy using targeted sequencing. **Method:** Matched plasma and MPE samples were obtained from 154 patients with advanced NSCLC. Among them, 17 patients had matched primary tissue sample and MPE precipitates. Ultra-deep targeted sequencing using a panel consisting of 168 lung cancer-related genes, spanning 160 kb of human genome was performed with an average sequencing depth of 10,000x for MPE and 1,000x for tissue samples. **Result:** Using tissue sample as a reference, detection rates of driver mutations in MPE cfDNA (supernatant), MPE precipitates and plasma are 100%, 70.6% and 82.3%, respectively. The median maximum allelic fractions (MAF) for MPE cfDNA, precipitates and plasma are 12.9%, 14.8% and 3.6%, respectively. MPE and tissue have comparable median MAF, which is significantly higher than plasma (p=0.01), demonstrating the superiority of MPE cfDNA in mutation detection. Next, we compared and contrast genomic profiles derived from MPE cfDNA and plasma cfNDA. Collectively, in 154 patients, we identified 939 variants from MPE and 865 variant from plasma; among them, 770 variants were shared by the two media; 169 variants were MPE specific and 95 variants were plasma specific. *EGFR* and *TP53* are the two most frequently occurring mutations in both MPE cfDNA and plasma cfDNA. MPE cfDNA of 56 patients had CNVs detected; in contrast, only 27 patients had CNVs detected from plasma sample, resulting in a significantly higher detection rate in MPE cfDNA (p<0.01). Collectively, we identified 201 CNVs; among them, 164 were shared by both media; 33 are MPE specific and the remaining 4 are plasma specific. **Conclusion:** Collectively, our study demonstrates superiority of MPE cfDNA as an alternative media for liquid biopsy. In addition to higher detection rate and MAF, MPE cfDNA also revealed a unique genomic profile, especially in capturing CNV.

Keywords: CNVs, malignant pleural effusion, cfDNA

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P2.01-111 CLINICAL FEATURES AND PROGNOSIS OF EIGHTY-FIVE PATIENTS WITH PRIMARY PULMONARY LYMPHOEPITHELIOMA-LIKE CARCINOMA

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Background: Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare subtype of lung cancer that is less reported and not well understood around the world. **Method:** A retrospective analysis of clinical features for 85 patients was conducted to determine the prognostic factors in terms of age, gender, radiographic features, serum tumor markers, TNM stages, pathological features, treatment and prognosis. **Result:** PLELC preferentially affects the young (< 60 years old: 71.8%) nonsmokers (72.9%), without significant difference in gender. The median follow-up time was 15 months (1-37 months) for the whole group and most patients were in the early stage with opportunity of operation (50.6%). For the advanced stage group, patients mainly received chemotherapies and radiotherapies, the 0.5-year and 1.5-year PFS rates were 61% and 29%, respectively. The TNM stage (P=0.014) and performance status (PS) (P=0.040) were associated with PFS significantly in the univariate analysis, while TNM stage was an independent prognostic factor in multivariate analysis (P=0.026). In the subtype analysis, patients in the advanced stage receiving Gemcitabine plus platinum (GP group) or Paclitaxel plus platinum (TP group) had better PFS than Pemetrexed plus platinum (PP group) (P=0.005). **Conclusion:** PLELC had a better prognosis compared with other types of non-small cell lung cancer (NSCLC) and was sensitive to radiotherapy and chemotherapy. The current results recommended that the GP and TP should be used as first-line treatment of PLELC. The TNM stage and PS were predictive in prognosis of PLELC patients.

Keywords: lung cancer, pulmonary Lymphoepithelioma-Like Carcinoma, clinical features

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P2.01-112 PROGNOSTIC VALUE OF CHANGES IN NEUTROPHIL-TO-LYMPHOCYTE RATIO IN PATIENTS WITH LUNG CANCER TREATED WITH NIVOLUMAB

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Background: Nivolumab, an anti-programmed cell death 1(PD-1) antibody, is a standard regimen for the second-line treatment of non-small cell lung cancer (NSCLC). However, compared with molecular-targeted drugs, the response rate to nivolumab is low, and biomarkers of efficacy are currently lacking. It has been recently reported that the neutrophil-to-lymphocyte ratio (NLR) can be a biomarker of efficacy. Here, we examined the possibility for NLR to predict efficacy of nivolumab. **Method:** We retrospectively examined all patients with NSCLC who were treated with nivolumab at our institution. **Result:** We compared 35 patients with NLR of ≥3 and 44 with NLR of <3, all of whom were treated with nivolumab. There was no difference in response rates between the two groups. The median (m) PFS and mOS were 130 and 583 days in the NLR≥3 group, whereas those were 169 days and not reached (NR) in the NLR<3 group. Longer PFS and OS were observed in the NLR<3 group than in the NLR≥3 group. Next, we analyzed the relationship between treatment efficacy and relative change of NLR (ΔNLR), the ratio of the value at 4 weeks after the administration of nivolumab to the value at baseline. In 42 patients with ΔNLR of ≥1, mPFS and mOS were 122 and 564 days, respectively. In 31 patients with ΔNLR of <1, mPFS and mOS were 280 days and NR, respectively. PFS and OS were significantly better in the group with ΔNLR of <1. With respect to adverse events, grade 1-2 rashes were observed in 29% of patients in the group with ΔNLR of <1 and in 9.5% of patients in the group with ΔNLR of ≥1. **Conclusion:** Relative ratio of NLR at 4 weeks/at baseline is a predictive biomarker in patients with NSCLC who are treated with nivolumab.

Keywords: biomarker, Nivolumab, Neutrophil-to-lymphocyte ratio

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P2.01-113 PROGNOSTIC ROLES OF NEOADJUVANT AND ADJUVANT CHEMOTHERAPY FOR TREATING PATIENTS WITH OPERABLE STAGE III-N2 NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: The therapeutic options for stage III-N2 positive NSCLC, including the diseases with ipsilateral mediastinal or subcarinal lymph node involvement, are with multidisciplinary approaches. The NCCN and ASCO guideline recommends the cisplatin-based adjuvant chemotherapy (Ad C/T). Meanwhile, some studies revealed the benefits of managing the N2 node disease with the neoadjuvant chemotherapy (Neo C/T) followed by surgery. We currently analyzed the clinical benefit of Neo C/T and Ad C/T for treating N2 positive NSCLC in a single-center cohort. **Method:** The study was done retrospectively. A total of 258 patients with N2+ who received surgical resection in dept. of surgery, National Taiwan University Hospital during 2004 to 2016 were enrolled. The mean follow-up duration was 44 months. Both the overall survival (OS) and progression-free survival (PFS) were compared between C/T (-) (patients without chemotherapy treatment) , neo C/T, and Ad C/T groups using multivariate analysis and Kaplan-Meier estimates . **Result:** There were 77, 55 and 126 patients in C/T (-), Neo C/T, and Ad C/T groups respectively. Patient's characteristics revealed the distributions of age and operation methods among these 3 groups were significantly differences. Patients treated with chemotherapy (combining Neo C/T and Ad C/T groups) were with significant reduced hazard for death compared to C/T (-) group (HR [95 % CI]= 0.55 [0.37-0.83), P=0.004). No significantly difference in overall survival was found between neo C/T and Ad C/T groups (HR [95 % CI]= 0.84 [0.54-1.32), P=0.451). The median overall survival time after surgery for the patients in neo C/T, and Ad C/T, and C/T (-) groups were also significant different (46.2, 56.9, and 26.9 months in C/T (-), Neo C/T, and Ad C/T groups respectively, P<0.001). However, there was no significant difference in patients received C/T or not in progression-free survival. **Conclusion:** Both Ad C/T and Neo C/T provide clinical benefit for the patients with operable stage III N2 NSCLC . These is no significantly difference between Ad C/T and Neo C/T groups in both overall and progression-free survival .

Keywords: stage III-N2 positive NSCLC, neoadjuvant chemotherapy, adjuvant chemotherapy

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P2.01-114 THE CORRELATION AMONG PD-L1 EXPRESSION, TMB AND LUNG IMMUNE PROGNOSTIC INDEX IN CHINESE PATIENTS WITH ADVANCED LUNG ADENOCARCINOMA

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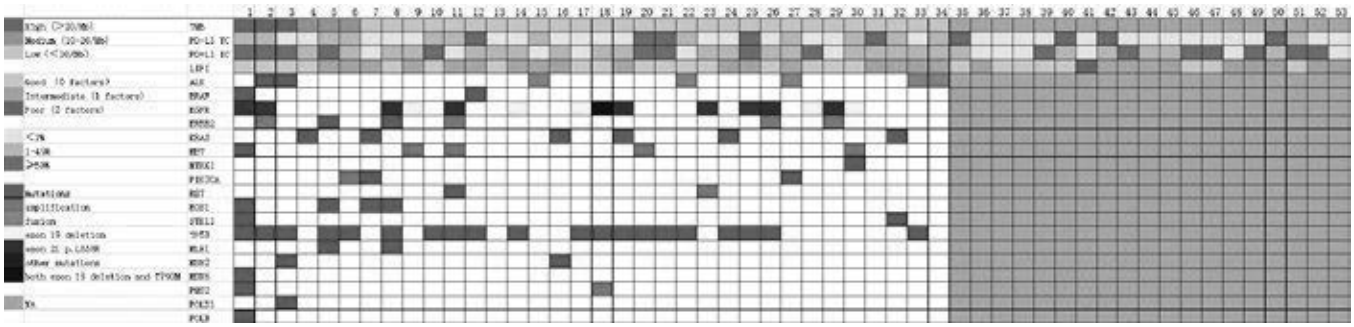
Background: Anti-PD-1/PD-L1 immunotherapy was approved as first-line treatment on the part of NSCLC patients, but not all can benefit, some studies have shown that PD-L1 expression, Tumor Mutation Burden (TMB) and Lung Immune Prognostic Index (LIPI) can be respectively used as an effect predictor of NSCLC immunotherapy. We aim to explore the correlation of the three predictors in Chinese patients with advanced lung adenocarcinoma. **Method:** We enrolled 53 biopsy specimens of the advanced lung adenocarcinoma patients from four China centers, measured complete blood cell counts and lactate dehydrogenase (LDH) before biopsy, detected PD-L1 level by three IHC assays (22C3, 28-8, SP263) ,driver genes and TMB by NGS. LIPI was divided into three groups. **Result:** In the cohort, 28 (52.8%) were male; median age was 59 (range, 34-81) years. There were 7 (13.2%, 7/53) with positive PD-L1(≥50%) based on 22C3. Three assays were highly concordant for tumor cells (ρ=*0.740-0.826),* lower for immune cells (ρ=0.462-0.543). Six (of 34,17.6%) were high TMB (at least 10/Mb). All were male (*p*=0.031), in which 5 were associated with TP53 mutation, 3 had DNA replication or damage repair–related gene mutations and 4 showed high PD-L1 on immune cells (*p*=0.031). LIPI didn't show significant correlation with PD-L1 or TMB (*p* >0.05). 3 of 20 with targetable driver gene alterations (ALK/EGFR/ROS1) were high PD-L1 or TMB. In the targetable driver gene wild cases, there were 8 (of 14) high PD-L1 or TMB.



Conclusion: 28-8, 22C3 and SP263 assays were aligned on tumor cell staining.There was no significant correlation among PD-L1, TMB and LIPI, which may be independent and complemented. High TMB might occur in male, show high PD-L1 on immune cells and accompanied with TP53 mutations. High PD-L1 or TMB was frequently found in the targetable driver gene wild cases.The prognostic value of PD-L1 and TMB on advanced NSCLC will be further followed.

Keywords: TMB, advanced lung adenocarcinoma, PD-L1

P2.01-115 EVALUATION OF EGFR T790M OF CELL FREE CIRCULATING DNA IN PLASMA BY DROPLET DIGITAL PCR FOR PROGRESSIVE NON-SMALL CELL LUNG CANCER

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Background: In Non-Small Cell Lung Cancer (NSCLC) harboring EGFR mutations, a second-site point mutation at position 790 (T790M) is associated with acquired resistance to the EGFR kinase inhibitors, gefitinib and erlotinib. Osimertinib is selective for T790M resistance mutation in patients with NSCLC. However, the mutation rate of EGFR T790M is unclear in Chinese patients.The purpose of this study is to understand the status of EGFR T790M in the real world. **Method:** 422 Patients with recurrent NSCLC who had been receiving TKI treatment at The First Affiliated Hospital of Nanjing Medical University were enrolled consecutively. Patient blood samples were drawn after the first generation TKI failure. Patients who met the following criteria : patients harboring EGFR activating mutation who developed PD during TKI treatment. Patients had received TKI alone therapy or TKI plus chemotherapy . The droplet digital PCR assay was conducted by droplets generation using QX200 generator (Bio- Rad Laboratories, Inc., Hercules, CA, USA). **Result:** 374 (88.6%) of them were successfully analyzed for EGFR T790M genotyping analysis by droplet digital PCR. 48(11.4%) of them failed to follow-up analysis owing to insufficient cfDNA amount,177(47%) plasma samples had found EGFR T790M mutation (Fig1a). Analyzing the allele frequency of EGFR T790M, we found 19% (33/177) positive patients of EGFR T790M was Less than 0.1% (Fig1b). The allele frequency of EGFR T790M between 0.1% and 0.5% was account for 38%(68/177). The 32% (56/177) of patents were more than 1%. This result indicated that the detection of EGFR T790M required higher sensitive method, otherwise it might cause missed detection.

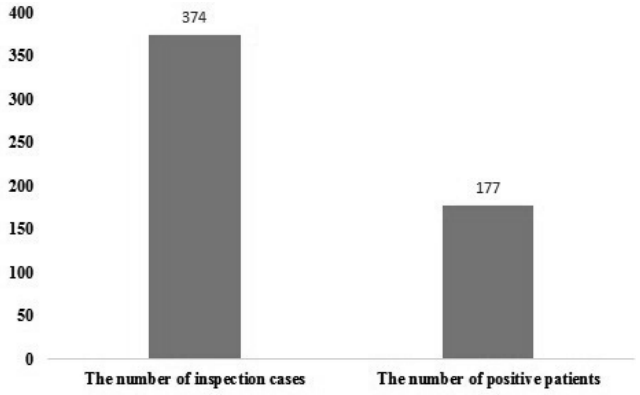

Fig1a.The detection rate of EGFR T790M in real world (China)

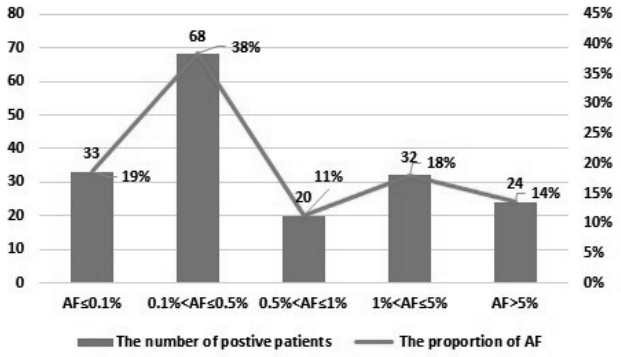

Fig1b. Allele frequency distribution of EGFR T790M

Conclusion: Droplet digital PCR is a highly sensitive, absolute quantitative detection technique. The EGFR T790M is detected in up to 47% of these patients in the real world. Almost 68% of the allele frequency of EGFR T790M is less than 1%. It means that the detection of EGFR T790M requires a higher sensitive detection method.

Keywords: allele frequency, EGFR T790M, droplet digital PCR

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P2.01-116 THE POTENTIAL OF ASSESSING BLOOD TUMOR MUTATION BURDEN (BTMB) USING A LARGE PANEL

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Background: TMB, measuring the number of non-synonymous mutation per megabase of DNA, has shown to associate with response to checkpoint inhibitors in a number of cancers, including lung cancer. Whole exome sequencing (WES), the gold standard for evaluating TMB, is less cost-effective. Multiple studies have shown large panels can yield comparable results in tissue samples. However, the feasibility of assessing bTMB using a large panel has not been extensively evaluated. In this study, we evaluated TMB of 30 treatment-naïve advanced NSCLC patients by performing WES on tissue samples as well as targeted sequencing on matched tissue and plasma samples. **Method:** WES was performed on tissue samples with an average sequencing depth of 300x. Targeted sequencing was performed on matched tissue and plasma using a panel consisting of 520 cancer-related genes, spanning 1.6Mb of human genome. An average sequencing depth of 1,000X and 10,000x were achieved for tissue and plasma samples, respectively. TMB was calculated as the ratio of mutation count to the size of coding region of the panel (1.26Mb), excluding copy number variations, fusions, large genomic rearrangements and mutations occurring on the kinase domain of *EGFR* and *ALK*. **Result:** In tissue samples, TMB derived from WES and our panel is comparable with a R^2 value of 0.87, and a correlation value of 0.86. cfDNA from 8 patients had no mutation detected using the 520 panel potentially due to low fraction of ctDNA present in the circulation. TMB derived from cfDNA of the remaining 22 patients showed a good correlation with TMB derived from tissue using either our panel (R^2=0.94, correlation =0.93) or WES (R^2= 0.85, correlation=0.87), demonstrating the feasibility of assessing TMB from cfDNA using a large panel. Next, using TMB calculated from WES as gold standard, we attempted to derive a cutoff to stratify TMB high patients from TMB low patients. Our data revealed 15 mutations per mb as an optimal cutoff using the 520 panel, achieving an AUC of 97.6% for tissue samples and 97.2% for plasma samples. **Conclusion:** Our study demonstrated the feasibility of evaluating TMB from cfDNA using a large panel, opening the avenue of TMB estimation using liquid biopsy. Further validations in prospective clinical trials are needed to solidify its predictive value in response to immunotherapy.

Keywords: blood, Tumor mutation burden, non small lung cancer

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P2.01-117 CONCURRENT GENE ALTERATIONS IN TREATMENT-NAÏVE EGFR-MUTANT ADVANCED NON-SMALL CELL LUNG CANCER

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Background: EGFR-TKIs is the standard first line treatment for *EGFR*-mutant advanced non-small-cell lung cancer (NSCLC). However, 20% to 30% of patients who receive EGFR-TKIs exhibit primary resistance. The gene alterations in treatment-naïve *EGFR*-mutant advanced NSCLC should be better explored. **Method:** We retrospectively reviewed gene test results of 980 treatment-naïve advanced NSCLC samples in our institute. Tumor biopsy, ctDNA, pleural effusion or cerebrospinal fluid samples were analyzed using hybridization capture-based NGS ER-seq method, white blood cells as control, which enables simultaneously assess single-nucleotide variants (SNV), insertions/deletions (indel), rearrangements and somatic copy-number(CNV) variation at least 59 genes (range 59-1021 genes). **Result:** Three hundreds and eighty one cases with *EGFR* sensitive mutation were identified, 358 adenocarcinoma,

7 squamous cell carcinoma, 1 adenosquamous carcinoma and 15 NSCLC. Among the patients, 88 patients (23.1%) harbored concurrent actionable mutations with *EGFR*, which 43 were exon 19 deletion, 37 were L858R and 8 were uncommon *EGFR* mutations. One patient had co-occurring L858R, T790M and CDKN2A frameshift mutation. The actionable mutations were from 23 genes, which involved in cellular signaling pathways, and some genes had been reported associated with EGFR-TKIs resistance (details in table). Except the actionable mutations, *TP53* mutations were detected in 225 samples (59.1%, 225/381), which 35.1% (79/225) in exon8. Bcl-2–like 11(*BIM*) deletion were detected in 31 (8.1%, 31/381) white blood cells.

Signaling Pathways	Concurrent gene alterations	Frequency(N=88)
Cell cycle*	CDKN2A	3.9%
	CDK4	2.1%
	CCNE1	0.8%
	CCND1	0.8%
	CCND3	0.3%
PI3K/AKT/mTOR*	PIK3CA	2.9%
	PTEN	1.3%
	TSC1/2	1.0%
	AKT2	0.3%
	NF1	0.3%
RTKs*	MET	0.8%
	HER2	0.8%
	FGFR2	0.3%
	FGFR3-TACC3	0.3%
Ras/Raf/MAPK*	KRAS	0.8%
Homologous Re-combination Repair pathway	BRCA2(sc+gm)	0.8%
	BRCA1(sc)	0.5%
	ATM	0.5%
	PALB2	0.3%
Others	CTNNB1	2.9%
	MDM2	2.4%
	SMARCA4	0.8%
	JAK2	0.5%

sc, somatic mutation; gm, germline mutation; *, genes had been reported associated with EGFR-TKIs resistance **Conclusion:** Concurrent gene alterations in treatment-naïve *EGFR*-mutant advanced NSCLC is common, and mutiple genes are involved. This maybe contribute to the primary resistance to EGFR-TKIs in *EGFR*-mutant advanced NSCLC. Indicate the importance of multiplex molecular test and further researches of target therapies.

Keywords: concurrent gene alterations, next generation sequencing (NGS), EGFR-mutant NSCLC

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P2.01-118 LINE-1 RETROTRANSPOSITION PROMOTES THE OCCURRENCE AND PROGRESSION OF LUNG SQUAMOUS CELL CARCINOMA

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Background: Retrotransposition is a kind of chromatin rearrangement containing the non-coding region, which makes up about half of the human genome. Long interspersed element-1 (LINE-1) retrotransposition is the only currently known active autonomous transposon in humans and might cause genetic instability, which was reported to occur with high frequency in a variety of tumor tissues. However, the relationship between LINE-1 and lung squamous cell carcinoma (LUSC) is unclear. **Method:** We analyzed 504 cases of LUSC samples based on the RNA-seq database in TCGA and screened out 13 LINE-1 retrotransposons with the high occurrence. The somatic LINE-1 retrotransposition were detected in 109 clinical LUSC samples in comparison with their matched adjacent normal tissue samples, as well as the correlation between expression of LINE-1 retrotransposon genes and patients' survival. Then we focused on L1-FGGY and explored its regulation on cell proliferation, apoptosis, migration and invasion in vitro, as well as its roles on promoting tumorigenesis in vivo. We also applied two nonnucleosidic reverse transcriptase inhibitors, nevirapine (NVR) and efavirenz (EFV) both in vitro and in vivo, to investigate whether pharmacological modulation of endogenous reverse transcriptase activity may represent a novel approach in the treatment of LUSC. **Result:** We found that 1/3 of tumor samples possessed LINE-1 inserted retrotransposons and the expression of retrotransposon genes in LUSC was significantly higher than that in the corresponding para-carcinoma tissues, indicating that the presence of LINE-1 retrotransposon was related to the occurrence of LUSC. Furthermore, we also found that the survival time of patients with low retrotransposon gene expression was long, while the survival time of patients with high retrotransposon gene expression was short. In this study, we focused on L1-FGGY and further investigated the mechanism of the LINE-1 retrotransposition in regulating the occurrence and progression of LUSC and discovered that the expression of L1-FGGY and FGGY was negatively correlated in LUSC patients. We then discovered that knockdown of FGGY could promote cell proliferation, inhibit cell apoptosis, as well as facilitate cell migration and invasion *in vitro*. Furthermore, inhibition of FGGY could promote tumorigenesis and tumor metastasis *in vivo*, which collectively indicated that FGGY might function as a tumor-suppressor gene. **Conclusion:** We not only uncovered that the LINE-1 retrotransposition L1-FGGY promotes the development of LUSC by inhibiting the expression and function of the tumor-suppressor gene FGGY, but also revealed that LINE-1 retrotransposon might be a new biomarker for early diagnosis, prognosis evaluation, and targeted therapy in the future clinical translation.

Keywords: Lung Squamous cell carcinoma, LINE-1 retrotransposition, L1-FGGY

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-119 PHASE III RANDOMIZED TRIAL OF PALONOSETRON AND DEXAMETHASONE WITH APREPITANT TO PREVENT FULL DOSE SINGLE-DAY CISPLATIN-BASED CINV IN LUNG CANCER

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Background: This study aimed to determine the efficacy and safety of aprepitant, palonosetron and dexamethasone to prevent chemotherapy-induced nausea and vomiting (CINV) in patients with locally advanced or metastatic lung cancer receiving full dose single-day cisplatin-based combination chemotherapy. **Method:** Patients diagnosed with locally advanced or metastatic lung cancer received full dose single-day cisplatin-based chemotherapy were randomized (1:1) to aprepitant plus palonosetron and dexamethasone, or placebo plus palonosetron and dexamethasone. Primary endpoint was complete response (CR; no vomiting/retching and no use of rescue medication) of nausea and vomiting in the overall period (0-120 h) in first cycle. The secondary endpoints were the proportion of nausea and vomiting, who received rescue antiemetic medication with metoclopramide, the response of cross over patients and safety were also evaluated. **Result:** 244 patients were randomized. There was no difference between two groups with personal characteristics. The aprepitant significantly improved CR for vomiting in the overall period (92.6% vs. 79.93%, $p<0.01$), rather than nausea-free (75.4% vs.71.3%, $p>0.05$) in first cycle. The percentage of patients who received rescue antiemetic medication was decreased for aprepitant group (14.8% vs. 37.1%, $p<0.001$). Patients without using aprepitant suffered with nausea and vomiting in cycle 1 were crossed over to aprepitant group (N=32), the rate of nausea and vomiting in cycle 2 were decreased to 37.5% ($p<0.05$) and 25% ($p<0.05$) respectively. There was no drug related i ntolerance side effects.

Primary and secondary endpoints

	aprepitant	placebo
CR for vomiting	92.60%	79.93%
nausea-free	75.40%	71.30%
received rescue antiemetic medication	14.80%	37.10%

Conclusion: Aprepitant plus palonosetron and dexamethasone proved to be effective and well-tolerated in preventing CINV for full dose single-day cisplatin-based combination chemotherapy.

Keywords: CINV, Efficacy and safety, aprepitant

P2.01-120 FIRST STUDY TO EVALUATE THE EFFICACY OF SB ORAL SOLUTION TO PREVENT NEUTROPENIA AND FN INDUCED BY PLATINUM-BASED CHEMOTHERAPY IN LUNG CANCER

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Background: The aim of this study is to investigate the efficiency of Shengbai Oral Solution to Neutropenia and Febrile Neutropenia induced by platinum-based chemotherapy in lung cancer. **Method:** A total of 295 lung cancer patients from January 2014 through December 2016 were treated with platinum-based chemotherapy including etoposide or paclitaxel liposome combined with cisplatin (75mg/m^2, one day finished) or carboplatin (AUC=6.25, one day finished), and 91 of them were treated with Shengbai Oral Solution. Using the ratio 1:2 with propensity score matching (PSM), the control group of 169 patients was matched to the experimental group of 91 patients, and the remaining 35 patients were excluded. The primary end point was to evaluate the effectiveness of Shengbai Oral Solution in preventing grade 2/3/4 drug-related toxicities of neutropenia. And the secondary outcome was to evaluate the rate of Febrile Neutropeniathe, cost and toxicity. All the patients were from this clinical trials with the NCT number of NCT01980212. **Result:** There were no difference between two groups, with gender, age, smoking status, histologic grade, and histologic type included. The study revealed that compared with the control group, the ratio of neutropenia in the experimental group was significantly lower (34.07% vs 64.50%, HR 0.53, $p<0.05$), as expected, the grade 2/3/4, 3/4 neutropenia had similar results (30.77% vs 55.62%, HR 0.55, $p<0.01$), (14.29% vs 23.67%, HR 0.60, $p<0.05$), respectively. And the secondary endpoint showed that Shengbai Oral Solution can signifcantly reduce the rate of Febrile Neutropenia and did not significantly increase the additional medical expenses. There was no intolerance drug related toxicity. **Conclusion:** This study suggested that Shengbai Oral Solution was effective on reducing neutropenia and Febrile Neutropenia caused by chemotherapy in patients with lung cancer and was worth promoting in clinical.

Keywords: SB Oral Solution, Neutropenia and Febrile Neutropenia, lung cancer

P2.01-121 GENOMIC PROFILING OF PULMONARY LYMPHOEPITHELIOMA-LIKE CARCINOMA

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Background: Pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare and distinct type of primary lung cancer which is characterized by Epstein-Barr virus (EBV) infection. Only a few hundred cases have been reported since its discovery in 1987. Due to its extreme rareness, its genomic landscape remains elusive. In this study, we performed targeted ultra-deep sequencing to interrogate the genomic profile and tumor mutation burden of 10 patients with pulmonary LELC. **Method:** Ten patients with advanced pulmonary LELC patients were enrolled. Tissue biopsy samples were subjected to targeted sequencing with an average sequencing depth of 1,000x, using a panel consisting of 295 cancer-related genes, spanning 2.02Mb of human genome. TMB was calculated as the ratio of number of mutations to the size of coding region of the panel, excluding copy number variations, fusions and large genomic rearrangements. **Result:** We enrolled 10 patients (4 males and 6 females) with advanced pulmonary LELC and a median age of 60. Eight of them are non-smokers and 2 are smokers. Collectively, we identified 65 somatic mutations spanning 52 genes, including 33 SNVs, 3 insertions or deletions (INDELs) and 29 copy-number amplifications (CNAs). No mutation in classic NSCLC driver gene was identified, in an agreement of published data. The most frequently mutated genes were *TP53*, *FGFR3*, *FGFR4*, *FGFR19* and *CCND1*, occurring in 30% (3/10) patients followed by *KIT* and *KMT2D*, occurring in 20% (2/10) patients. Interestingly, 7 patients had mutations in epigenetic regulators, such as DNA methyltransferase and chromatin remodelers. Pathway analysis also revealed an enrichment of genes participating in chromatin remodeling and organization. Next, we compared the genomic profile of pulmonary LELC with nasopharyngeal carcinoma and EBV positive gastric cancer mutation profiles obtained from TCGA, and revealed similarity with both of them. Patients in this cohort had a median TMB of 3.75/Mb (ranged from 1.25/Mb to 10/Mb), which is significantly lowered than lung adenocarcinomas. All patients had PD-L1 overexpression; 4 of them with PD-L1 expression in greater than 50% of tumor cells and the remaining 6 patients had PD-L1 expression between 5%-49% of tumor cells. **Conclusion:** In this study, we elucidated a distinct genomic landscape associated with pulmonary LELC with no classic NSCLC driver mutation but an enrichment of mutations in epigenetic regulators. The observation of high expression of PD-L1 and lack of canonical druggable driver mutation raises the potential of immunocheckpoint blockade therapy for LELC.

Keywords: Pulmonary lymphoepithelioma-like carcinoma, genomic profiling

P2.01-122 INDIVIDUAL PRECISION SURGERY FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER BASED ON MOLECULAR STAGING AND TYPING : THE CHINESE EXPERIENCE.

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Background: Lung cancer is the leading cause of cancer deaths in the world. For patients with advanced non-small cell lung cancer (NSCLC), survival prognosis is very poor with chemotherapy and radiotherapy. However, the possibility of occult metastases may lead to discrepancy between clinical and pathologic staging and under-estimation of the disease severity, and how to individualized choose the appropriate patients with locally advanced non-small cell lung cancer for surgery is controversies. In this study, we presented here the Chinese experience: individual precision surgery for locally advanced non-small cell lung cancer based on molecular staging and molecular typing. **Method:** We developed several molecular biomarkers and molecular models from Circulation Tumor Cell (CTC) detection, mi-RNA chip, Gene Chip from 1990. We used these Molecular biomarkers and molecular models for molecular staging, molecular typing, choosing indication of operation and neoadjuvant chemotherapy, predicting postoperative recurrence and prognosis of locally advanced non-small cell lung cancer. **Result:** We developed two molecular staging model for individualized surgical treatment for locally advanced non-small cell lung cancer involving heart, great vessels or both. 3728 patients with locally advanced non-small cell lung cancer were underwent completely resection of the cancer in the three medical center. The 1-, 3-, 5- and 10 year survival rate were 76.5%,63.7%,32.8% and 23.4%, respectively. We used our molecular staging and typing model for neoadjuvant chemotherapy for 665 patients with locally advanced lung cancer. The 1-, 3-, 5- and 10-year survival rate were 79.35%, 51.46%, 27.39% and 20.34% of the patients, respectively. We used our molecular typing model to divide N2 lung cancer into invasive N2 and Non-invasive N2 group. We used our molecular models adenocarcinoma and squamous carcinoma to divide T4 lung cancer into high recurrence and low recurrence groups, and help postoperative adjuvant therapy. **Conclusion:** Our molecular staging and typing models can help us carry out individual precision surgery, predicting prognosis and cancer recurrence of the cancer for locally advancer no-small cell lung cancer.

Keywords: lung cancer,individual surgery,molecular staging

P2.01-123 TRANSLATIONAL MEDICINE OF LUNG CANCER METASTASIS: FROM BENCH TO BEDSIDE

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Background: Cancer invasion and metastasis is not only the malignant marker and characteristics, but also the main cause of failure to cure and lose their life of the patients with lung cancer.30% of the lung cancer patients had distant metastasis diagnosed with lung cancer. 80% to 90% of the patient dead of distant metastasis. In this study, we presented the results of individual translational medicine of lung cancer metastasis: from bench to bedside. **Method:** A pair of lung cancer cell lines (L9981 and NL9980) with same inherit background, different metastatic potential were screened and identified by Single Cell Limited Dilution Cloning. Several differential mi-RNA and gene profiles were screened and identified by mi-RNA array and gene chips from the cells, and peri-cancerous and cancer tissues of patients. Molecular model for early diagnosis and prediction of lung cancer metastasis, molecular typing model of N2 lung cancer were developed by molecular biostatics. 5 small molecular compounds inhibiting lung cancer metastasis were screened and identified based on the molecular targets related to lung cancer

metastasis. **Result:** We successfully established a pair of lung cancer cell lines with same inherit background, different metastatic potential. High-metastatic cell line L9981 with LOH of gene, deletion of mRNA and protein expression of nm23-H1and high metastasis potential, and low-metastatic cell line NL9980 with normal NM23-H1 and low metastasis potential. After knockdown the nm23-H1 gene in NL9980 cell, the Nl9980 cell was endowed the same biological property as L9981 cell has. We got a differential panel of mi-RNAs and gene signature. We found that the patient with LOH of gene, deletion of mRNA and protein expression of nm23-H1 more likely to have distance metastasis and poor prognosis. Based on these findings, we proposed a hypothesis of "Lung Cancer Metastatic Suppressive Cascade" and translate the hypothesis into clinical use in the patients. We got several molecular model for early diagnosis and prediction of lung cancer metastasis of lung cancer after operation; a molecular typing model of dividing N2 lung cancer into invasive N2 and Non-invasive N2. Finally, we use the molecular targets related to lung cancer metastasis to screen and identify 5 small molecular compound inhibiting lung cancer metastasis. **Conclusion:** A pair of lung cancer cell lines with same inherit background, different metastatic potential was successfully established. We established several molecular staging and typing models related to lung cancer metastasis and translated them into clinical application in lung cancer patients.

Keywords: lung cancer metastasis, translation medicine, indivial medicine, lung cancer,metastasisi, tanslational medicine

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-124 SIB-IMRT IN SYMPTOMATIC BRAIN METASTASES FOR NSCLC: A RANDOMIZED CONTROLLED STUDY OF WBRT COMPARING 25GY AND 30GY

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Background: Intensity Modulated Radiation Therapy with Simultaneous Integrated Boost (SIB-IMRT) can better control intracranial local control rate and even prolong overall survival in non-small cell lung cancer (NSCLC) patients with brain metastases. However, some patients suffer severe neurocognitive dysfunction largely due to whole brain radiation. The purpose of this study is to explore the appropriate dose of whole brain RT when SIB-IMRT is applied. **Method:** A total of 75 patients with symptomatic brain metastases in NSCLC were randomly divided into 25Gy and 30Gy groups with 10 fraction whole brain radiation therapy (WBRT). The tumor beds with 3 mm expansion (PGTV) were synchronously boosted to 50Gy in both groups. The primary endpoint of the study was intracranial progression-free survival (iPFS) and neurocognitive dysfunction. Secondary endpoints objective response ratio (ORR) of 1 month after treatment and overall survival (OS) were included. **Trial registration number:** ChiCTR-INR-17013204. **Result:** There were 38 and 37 patients in 25Gy and 30 Gy groups, respectively. There was not significant differences in age, gender, performance status and number of brain metastasis between these groups (all Ps>0.05). The median follow-up is 15 (range 2-39) months. The median iPFS was 11 months (95%CI:8.7-13.3) in the 25Gy Group and 8 months (95%CI:4.4-11.6) in the 30Gy Group (P=0.104). The median OS was 13 (95%CI:11.4-14.6) months in the 25Gy Group, which is significantly better than 8 (95%CI:4.4-11.6) months in the 30Gy Group (P=0.025). The mini-mental state examination(MMSE)of neurocognitive dysfunction found significant differences in the 25Gy Group vs. 30Gy Groups, 27.4±1.26 vs. 26.4±2.03 (P=0.027) at 12 months after radiotherapy (Table 1).

Table 1. MMSE score statement

	Treatment arms		P value
	25Gy group	30Gy group	
Before radiotherapy	28.03±1.57	27.56±2.55	0.322
1-month After radiotherapy	28.29±1.33	27.92±2.13	0.228
3-monthAfter radiotherapy	28.12±1.01	27.98±1.24	0.323
6-month After radiotherapy	27.47±1.55	27.29±1.49	0.061
12-month After radiotherapy	27.40±1.26	26.37±2.03	0.027

Abbreviations: MMSE = mini mental state examination.

Conclusion: Based on this small randomized study, the 25Gy group with SIB did not reduce iPFS, but significantly improved OS and decreased toxicity of neurocognitive dysfunction at 12 months after radiotherapy, compared to the 30Gy group with 10 fractions SIB-IMRT in patients with NSCLC with symptomatic brain metastases.

Keywords: brain metastases, Intensity Modulated Radiation Therapy with Simultaneous Integrated Boost (SIB-IMRT), non-small cell lung cancer (NSCLC)

P2.01 ADVANCED NSCLC
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P2.01-125 EGFR MUTATIONS BY NGS IN ADVANCED SQUAMOUS CELL LUNG CANCER

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Background: Targets for Squamous cell lung cancer are none as against adenocarcinomas.Also there is limited data available from ct DNA in these patients **Method:** This prospective observational study looked at patients with squamous cell carcinoma lung, either newly diagnosed or having a progressive disease on prior therapy were enrolled. cf-DNA was extracted from peripheral blood and analyzed for EGFR, KRAS, NRAS, BRAF mutations using NGS.20 ml of the blood sample was collected from the patient prior to the initiation of therapy or at progression. **Result:** Sixteen patients of squamous cell carcinoma lung were enrolled into the study. The mean circulating cell-free tumour DNA extracted from the plasma was 96.6 ng (Range, 15-200 ng). Genomic analysis by NGS on the extracted DNA revealed mutations in the EGFR pathway among 8 (50%) patients. The commonest mutation was Exon 21 Leu858Arg (4 patients). One patient had Exon 20 Thr790Met mutation. One patient had complex mutations with coexisting Exon 21 Leu858Arg and Exon18 Gly719Arg in the same sample. Two patients had KRAS Exon2 Gly12Cys mutation. Among the patients with Exon 21 mutation, two patients were treatment naïve and two patients were having a progressive disease (one post Gemcitabine/Carboplatin-based chemotherapy and another post Gemcitabine/Carboplatin and Docetaxel chemotherapy). Patient with complex mutations had progressive disease post Gemcitabine/Carboplatin. Patient with Exon 20 T790M mutation had a hyper-progressive disease post-Nivolumab based regimen. While one patient with KRAS mutation one patient was treatment naive while another had progressive disease post Gemcitabine/Carboplatin-based regimen (Table 2).

Table 2: Depth of Analysis and mutation allele frequency

Patient Number	DNA extracted (ng)	Hotspot region average sequencing depth	Depth of Mutation analysis	Mutant Allele (%)	First line regimen	Second Line regimen
1	92	128078X	18010X	1.9	Gemcitabine/Carboplatin	Docetaxel
2	100	870347X	32233X	1.2	Induction Chemotherapy and radiotherapy	Nivolumab
3	15	130773X	1946X	2.3	Gemcitabine/Carboplatin	-
4	32	137878X	8900X	8.5	Gemcitabine/Carboplatin	-
	-		22202X	1.5		-
5	95	167048X	15839X	1.6	Treatment naive	-
6	145	472744X	26229X	16	Treatment naive	-
7	190	161326X	22162X	1	Treatment naive	-
8	70	417686X	32255X	29	Gemcitabine/Carboplatin	-
9	70	793053X	-	-	Gemcitabine/Carboplatin	Docetaxel
10	25	349726X	-	-	Gemcitabine/Carboplatin	-
11	200	169027X	-	-	Gemcitabine/Carboplatin	-
12	45	228170X	-	-	Treatment naive	-
13	200	242459X	-	-	Treatment naive	-
14	130	164393X	-	-	Treatment naive	-
15	40	580006X	-	-	Treatment naive	-
16	95	155958X	-	-	Treatment naive	-

Two patients with Exon 21 mutations who progressed on earlier lines of treatment received Gefitinib. One patient had progressive disease at 3 months while the other patient succumbed to the disease two months after starting Gefitinib. Treatment Naïve patients with EGFR Exon 21 mutations (N=2) upfront received Gemcitabine and Carboplatin-based chemotherapy. Of this 1 patient is currently progression-free and another patient progressed 6 months post chemotherapy and at progression was started on Gefitinib. Patient has a stable disease after 3 months of treatment and still on gefitinib. Patient with Exon 20 T790M mutation was stated on nab-paclitaxel and succumbed to the illness 6 months later. Patient with complex mutations received Docetaxel as second-line

chemotherapy and had a progressive disease 4 months after the initiation of therapy and died. **Conclusion:** Treatment options for squamous cell carcinoma lung detection of EGFR mutations helps increase the treatment armamentarium for management of these patients. cf-DNA is a good technique for detecting relevant mutations

Keywords: Squamous cell lung cancer, NGS

P2.01 ADVANCED NSCLC
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P2.01-126 MICRORNA-330-3P MODULATES TUMOR VASCULAR NORMALIZATION AFTER HYPOFRACTIONATED RADIOTHERAPY BY TARGETING P-STAT3/ HIF-1 ALPHA PATHWAY

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Background: Our study aimed to explore the effect of microRNA-330-3p (miR-330-3p) on radiosensitivity of NSCLC on HFRT both *in vivo* and *in vitro*. **Method:** The miR-330-3p over-expressed H460 (H460-OE) and HCC827 (HCC827-OE) cell lines were established using lentivirus vector expressed miR-330-3p. Tumor-bearing nude mice and the dorsal skinfold window chamber (DSWC) models (divided into H460-OE, HCC827-OE, H460 and HCC827 groups) were established and received 0-Gy (control group) or 12-Gy (HFRT group) radiation respectively. At different time points after irradiation, the vasculature of DSMC was visualized by FITC-Dextran; co-immunofluorescence of α-SMA/CD34 staining was employed to detect the coverage rate of pericyte cells on tumor vessels; pimonidazole hydrochloride (PIM) was used to detect the hypoxia; Western blotting and RT-PCR were used to detect the expression levels of p-STAT3/HIF-1α/VEGFA signal pathway and downstream factors CXCL12/CXCR4. *In vitro*, after radiation, the colony formation assay was used to detect the radiosensitivity. The rate of apoptosis cells were detected by flow cytometry. Moreover, STAT3 inhibitor, S3I-201, was used to further verify the mechanism of miR-330-3p regulating HIF-1α and its downstream factor by Western blotting. **Result:** The curve of relative volume-time displayed that the radiosensitivity of miR-330-3p over-expressed xenografts decreased as compared to H460 and HCC827 xenografts. HFRT-induced decrease of MVD and hypoxia, increase of pericyte coverage on tumor vasculars in H460 and HCC827 xenografs were inhibited in H460-OE and HCC827-OE xenografts (P <0.05). Colony formation assay showed that the radiosensitivities in miR-330-3p over-expressed groups decreased and the flow cytometry assay showed that after HFRT, apoptosis rate was higher in H460-OE than H460 cell lines. Western blotting and RT-PCR displayed that, both on the 7th and 14th day after HFRT, the levels of p-STAT3, HIF-1α, VEGFA and CXCL12/CXCR4 in miR-330-3p over-expressed xenografts were higher than that in HCC827 and H460 xenografts (P <0.05). The *in vitro* studies showed that 2-28 hours after HFRT, the expression levels of p-STAT3, HIF-1α and VEGFA in H460-OE cells was up-regulated as compared to H460 cells (P<0.05). After adding S3I-201, the levels of p-STAT3/HIF-1α could not be inhibited in H460-OE, but could be inhibited in the H460 group (P<0.05). Also compared to the HCC827 cells after HFRT, the levels of p-STAT3 in HCC827-OE group could not inhibited by S3I-201 (P<0.05). **Conclusion:** miR-330-3p may decrease the HFRT-radiosensitivity of NSCLC via upregulating the p-STAT3/HIF-1α pathway and its downstream factors, VEGFA and CXCL12/CXCR4, therefore inhibiting vascular normalization effect of HFRT.

Keywords: miR-330-3p, vascular normalization, Hypofractionated radiotherapy

P2.01 ADVANCED NSCLC
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P2.01-127 EFFICACY OF ENDOSTAR COMBINED WITH WHOLE BRAIN RADIOTHERAPY IN PATIENTS WITH NSCLC BRAIN METASTASES

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Background: Brain metastasis (BM) is the leading cause of poor prognosis, recurrence, and death in non-small-cell lung cancer (NSCLC) patients. The effectiveness of whole-brain radiotherapy is unsatisfactory. Endostar was reported as an anti-angiogenic agent, which could promote vascular normalization in tumor. This study is to investigate the influence of endostar combined with cranial radiation to cerebral blood flow, immune status and survival of the patients. **Method:** 28 NSCLC patients with multiple brain metastasis(more than four)were randomly divided into two groups. The experimental group (n = 14) received WBRT (30Gy/10F) combined with Endostar (15mg/m^2, 7days), and the control group (n=14) received WBRT (30Gy/10F) alone. Magnetic resonance perfusion imaging was carried out pre- and one month post-radiation to detect regional cerebral blood volume (rCBV), regional cerebral blood flow (rCBF) and mean transit time (MTT) of the contrast medium. The changes of blood T lymphocyte subpopulation, the cognitive function and overall healthy level were evaluated pre- and post- radiation every two months against the MMSE, MoCA and EORTC QLQ-C30 scales. Moreover, Tumor progression was established by certified oncologists based on whole brain MRI scan. **Result:** In the endostar group, rCBV, rCBF and MTT had a 122%, 210% and 11% higher in the target lesion region one month post radiation, compared with baseline data, while in the control group, rCBV, rCBF and MTT had a 18%, 20% and 26% lower change. These results showed a significant improvement of the cerebral perfusion in the endostar group. The T lymphocyte subpopulation increased in the Endostar group, especially the CD8+ T lymphocyte with a significant difference compared with the control group(p=0.0233). At the same time, the intracranial PFS (iPFS) was 349 days *vs*. 287 days and the PFS was 229 days *vs*. undefined between the Endostar group *vs*. the control group, but neither with significant difference, may for the limit of sample size. After cranial radiation, the cognitive function, physical, role, social and emotional functions improved in the endostar group, while a small fluctuation in the control group. **Conclusion:** Our study showed that endostar could promote vessel normalization and improve cerebral perfusion, and ameliorate the immune status, cognitive function and quality of life of the patients, which may also improve the survival of the patients.

Keywords: Magnetic resonance perfusion imaging, Endostar, whole-brain radiotherapy

P2.01 ADVANCED NSCLC
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P2.01-128 LOW POSITIVITY RATE IN T790M DETECTION WITH CTDNA IN NSCLC AND POST EGFR-TKI PROGRESSION – TIMING OR SENSITIVITY?

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Background: The approval of Osimertinib in Brazil in 2016 for post EGFR-TKI progression T790M+ NSCLC treatment allowed offering to the patient the best available therapy, when, it is mandatory to identify the occurrence of T790M mutation before initiating the treatment. The prevalence of T790M mutation as resistance mechanism post EGFR-TKI treatment is estimated to be around 60%. Considering the limitations for tumor tissue biopsy in progressive disease setting, identifying molecular changes by using alternative tumor DNA sources, such as blood samples, serum, and plasma can become an interesting strategy in cases where a tissue specimen or acceptable quality biopsy is not available. However, the sensitivity of ctDNA analysis for T790M may be disappointingly low. **Method:** We performed a retrospective analysis of ctDNA samples database collected between June 2016 and December 2017 in Brazil. Blood samples of patients with post EGFR-TKI progression were submitted, at discretion of attending physicians, for EGFR mutation testing by cobas®. **Result:** 761 tests were included. The positivity rate was 43.9% for EGFRm and 10.4% for T790M. Considering EGFRm positive tests, the positivity rate for T790M among EGFRm positive was 23.7%. Data are shown in Table-1. This positive rate is lower than expected and may be explained by three factors: T790M ctDNA cobas® low sensitivity; test request before progression; or T790M prevalence lower in Brazilian population. Still, more detailed testing using tissue and/or more sensitive methods are needed before definitive conclusion. Tissue test should continue being recommended as gold standard in T790M detection on this patient setting. Table 1- Frequency and mutations detected by ctDNA cobas® test in Brazil.

(See next page)

Exon	18	19		20	21		19 + 20	21 + 20
Mutation	G719X	19Del	19Ins	T790M	L858R	L861Q	19Del + T790M	L858R + T790M
Number	9	183	1	9	60	2	53	17
Positivity rate (%)	1.2	24.1	0.1	1.2	7.9	0.3	7.0	2.2
% of EGFRm	2.7	54.8	0.3	2.7	18.0	0.6	15.9	5.1

Conclusion: Our findings suggest that ctDNA approach in post EGFR-TKI progression may not be the best diagnostic strategy to identify resistance T790M mutation as first option. When patient cannot be submitted to tissue biopsy at progression, ctDNA test is an acceptable alternative.

Keywords: advanced NSCLC, ctDNA, T970M frequency

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-129 POTENTIAL IMPACT OF KRAS MOLECULAR PROFILING OF NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC).

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Background: Several studies suggest that patients with KRAS-mutant (KRASmut) NSCLC fail to benefit from platinum-based systemic chemotherapy and are not likely to have targetable mutations. Molecular profiling has the potential to identify other potential targets that might provide novel therapy for KRASmut NSCLC. **Method:** In this study, we purified RNA from archived tumors of patients with stage I and II NSCLC wild-type (wt) and mutant (Mut) KRAS and from paired normal tissue from 20 and 17 patients, respectively, and assessed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) the expression of four genes involved in DNA synthesis and repair including thymidylate synthase (TS), BRCA1, ECCR1, RAP80, and the proto-oncogene, SRC. Additionally, we assessed expression of PD-L1 IHC 22C3 by immunohistochemistry using an antibody against PD-L1 IHC 22C3. **Result:** Our results show that in KRASmut tumors, ERCC1, TS, and SRC expression were increased in comparison to paired normal lung tissue ($p \leq 0.04$). Expression of BRCA1 and RAP80 were similar in both KRASmut tumor and the paired-normal tissue. Furthermore, expression of BRCA1, TS and SRC were significantly increased in KRASwt tumor relative to their expression in normal lung ($p \leq 0.044$). Expression of ERCC1 and RAP80 were similar in KRASwt tumors and paired normal tissue. Interestingly, SRC expression in KRASmut tumor was decreased in comparison to KRASwt tumor. There was a notable expression of PD-L1 (cut off level of 50%) in the tumor and surrounding stromal cells in 2 out of 20 KRASmut tumors. **Conclusion:** In conclusion, within the limitation of our retrospective study, KRASmut NSCLC would likely be platinum, taxane and pemetrexed resistant, having a low level of PD-L1 expression. KRAS wt BRCA1 positive tumors tend to be sensitive to taxane therapy and possibly platinum-based drugs. Our result suggests the need to develop targeted therapies for KRASmut NSCLC and other therapies specific to the molecular profile of the tumor.

	ERCC1	BRCA1	TS	SRC	PD-L1 (50%)
mt.Kras	+	-	+	-	10%
Wt.Kras	-	+	+	+	
Normal Lung Tissue	-	-	-	-	

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-130 DETECTION OF ACTIONABLE MUTATION STATUS IN ADVANCED NON-SMALL CELL LUNG CANCER BY NEXT-GENERATION SEQUENCING OF CIRCULATING TUMOR DNA

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Background: Genotype directed therapy has become increasingly important for personalized therapy of patients with advanced non-small cell lung cancer(NSCLC),but obtaining tumor tissue for genetyping remains a challenge.Plasma circulating tumor DNA(ctDNA) analysis by next-generation sequencing (NGS)may allow for noninvasive evaluation. We demonstrate the feasibility and clinical utility of ctDNA NGS in the management of advanced NSCLC. **Method:** A total of 114 plasma samples were detected by NGS to identify actionable oncogenic driver mutations or mechanisms of resistance in 108 patients with advanced NSCLC.Among those 108 patients,there were 79 paired tissue DNA (tDNA) detected using ARMS PCR,We also evaluated the concordance in detecting of EGFR between ctDNA and paired tDNA. **Result:** Of the 114 plasma ctDNA , 47(47/114,41%) actionable somatic mutations and 1 EGFR T790M germline mutation were dectected.EGFR variants were most common(39/114,34%).Among the 79 patients with matched tDNA and ctDNA, 32(32/79,41%)therapeutically targetable EGFR mutations were detected in tDNA and 30(30/79,38%) in ctDNA samples, yielding an overall concordance of 70%,the sensitivity and specificity of NGS were 59% and 77%.Of the 47patients with tDNA negative,11(11/47,23%) patients harbored EGFR mutation detected in ctDNA during the course of their disease.Of the 31 patients with brain metastases,22(71%) harbored an EGFR sensitive mutation(15,48%EGFR 19del and 7,23%EGFR L858R).Of the 40 patients who resistant to 1st and 2nd EGFR-TKI therapy,14(14/40,35%) showed the T790M acquired resistance mutation. the mean time of EGFR-TKI resistance was 11.5months.Patients with T790M mutations had significantly better PFS than those without T790M. **Conclusion:** CtDNA NGS can be adopted as a tool for providing precision genomic analysis and dynamic monitoring, thus improving patient management, and even,undertaking hereditary counseling.

Keywords: EGFR, NSCLC, ctDNA

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-131 APATINIB AS AN ALTERNATIVE FOR ADVANCED NON-SMALL CELL LUNG CANCER

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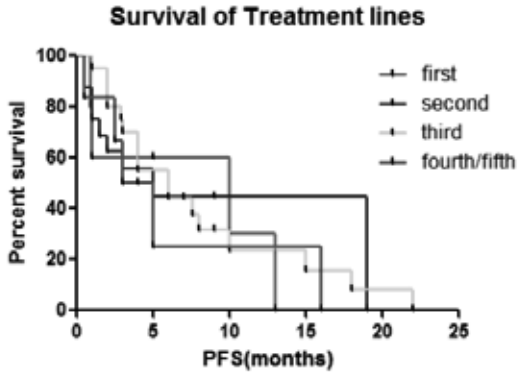
Background: Methylsulfonic apatinib showed promising efficacy for the treatment of non–small-cell lung cancer (NSCLC) as one of the TKIs which specifically inhibits VEGFR-2. We aimed to assess the efficacy of apatinib in each lines of treatment to patients with advanced/metastatic NSCLC. **Method:** We retrospectively analyzed variables and outcomes of patients with advanced NSCLC, who had received apatinib between January 1, 2016 and April 30, 2018, including: 5 patients of first line treatment, 16 second line treatment, 20 third line treatment and 6 fourth and fifth line

treatment. **Result:** The most frequent treatment-related adverse events were hypertension, proteinuria, hand-foot skin reaction and hemoptysis. Among the 47 cases included in the final analysis, the median progression-free survival among patients was 5.66 months specialized in: 0-24.0 months in first line treatment, 0-10.0 in second line treatment, 2.0-10.0 in third line treatment and 0.6-5.4 months in fourth and fifth line treatment. The median overall survival time for apatinib were 25.97 months, 21.4-28.5 months in third line treatment and 0-64.9 months in fourth and fifth line treatment. No significance was found in either PFS and OS among lines of treatment, histology and EGFR mutation status.

A



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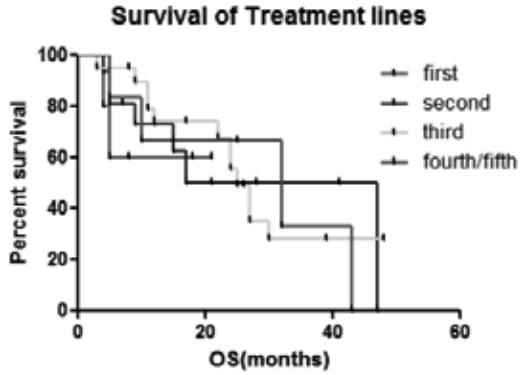

Figure 1 PFS and OS of apatinib in different lines of treatment **Conclusion:** The results indicate the administration of apatinib could be used as an alternative for advanced/metastatic NSCLC patients.

Keywords: Apatinib, advance NSCLC, VEGFR-2 inhibitors

P2.01 ADVANCED NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.01-132 COMPARISON MOLECULAR PROFILES IN NSCLC BY USING DIFFERENT NGS PLATFORMS AND DIFFERENT VARIANT FREQUENCY CUTOFF

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Background: There are several methods to detect molecular alterations in precision medicine era. This is a pilot study aimed to explore the concordance of molecular alterations testing using NGS different platforms and different cutoff allele frequency in NSCLC patients. **Method:** Ten NSCLC patients' FFPE were retrieved for DNA extraction. All qualified samples were analyzed using NGS on 45 cancer genes panel on Ion Torrent system NGS Gene read Qiagen Lung Cancer Panel. Variants from NGS with coverage of are higher than 1000X. The cutoff 1% and 3% of variant allele frequency were considered positive. *EGFR, BRAF, KRAS* were validated by Real-time PCR technique using the Amoy DX and Actionable Insights Tumor Panel in GeneReader NGS system. **Result:** We found 90%/30% *EGFR*-mutation, 40% *BRAF V600E*, 70%/30% *KRAS*-mutation by NGS using allele frequency cutoff at 1% and 3%, respectively. We validated by Real-Time PCR and Actionable GeneReader showed 70%/40% *EGFR*-mutation, 20%/10% *BRAF V600E*, and 0%/30% of *KRAS*-mutation (Table1). Regarding *EGFR*-mutation, 5 cases of discordance showed positive at 1% but negative at 3% cutoff allele frequency by NGS and validated by Real-Time showed positive all 5 cases. Two negative cases by Real-Time PCR show positive in NGS cutoff 1% (2/2) and 3% (1/2). In early stage (80%), there was 60% of *EGFR* 19 del detected by NGS cutoff 1%. The patients have continued follow-up at the clinic with the mDFS of 4.7 years. Two stage IV patients with exon19del were death and received EGFR-TKI as a second-line treatment with mOS at 1.1 and 1.2 years. Table 1

Number of 10 cases positive	NGS Ion-Torrent Cutt Off at 1%	NGS Ion Torrent Cutt Off at 3%	NGS Gene-Reader	Real-time PCR
EGFR Mutation	9	3	4	7
Exon 19 Del	6	2	2	5
L858R	1	0	2	2
>1 EGFR Mutations	2	1	0	0
No Mutation	1	7	6	3

Conclusion: Different platform of NGS and different cutoff variant allele frequency gave the different result of gene frequency. We need to explore the standard of NGS testing including the proper cutoff for allele frequency in order to establish the most efficient method and correlate with the clinical treatment outcomes.

Keywords: NSCLC, EGFR mutation, early stage

P2.03 BIOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.03-01 PREVALENCE OF EGFR ALTERATIONS IN CHILEAN LUNG CANCER PATIENTS: A RETROSPECTIVE STUDY

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Background: Recently, several countries in Latin America (LA) have entered into an epidemiological shift, switching the burden of disease from infectious to chronic non-transmittable disorders. In fact, many studies anticipate that Lung Cancer (LC) will soon emerge as the first cause of mortality in the region, possibly over the next decade. In Chile, LC is currently the second leading cause of cancer death and responsible for >2,500 deaths every year. Epidemiological data from Chilean LC patients is scarce and scattered. On the other hand, Tyrosine Kinase Inhibitor (TKI) drugs have been successfully used in a subset of LC patients that harbor alterations in the Epidermal Growth Factor Receptor (EGFR) gene. Here, we aimed to quantify the prevalence of EGFR alterations in the Chilean population **Method:** We performed a retrospective study that involved 1,405 biopsies from 1,385 Chilean LC patients. Then we selected patients with EGFR alterations and retrieve clinical data from these patients including age, gender, histological type, smoking habits and type of EGFR alteration. We also analyzed overall survival (OS) rates **Result:** We found that 300 out of 1,385 (21.7%) had clinically relevant EGFR alterations. Within this group median age at diagnosis was 65 yr. As expected, most patients were female (64%), and classified as Non-Small Cell Lung Cancer adenocarcinomas (94.5%). Also in patients with EGFR alterations, the majority were either non-smokers or light smokers (93.1%). Regarding the type of EGFR alterations the most prevalent was the exon 19 deletions (50.6%) followed by Leucine-to Arginine 858 (L858R, 28.9%). Further analyses indicated that OS within this group was 15 months. Also, information clinical follow-up and TKI treatment was available for 87 patients. As expected the use of TKIs in these patients significantly improved OS **Conclusion:** The prevalence of EGFR alterations in the Chilean population is 21.7%, a value between the Caucasian and Asian population, 18.6% and 57.1% respectively. This value is also comparable to other reports from countries within LA

such as Argentina (14.4%), Uruguay (18.3%), Colombia (24.7%) and Peru (37%). Similarly, OS was 15 months and the most frequent EGFR reported alteration was exon 19 deletions. Finally, the use of TKIs in these patients significantly improves OS.

Keywords: Lung cancer, overall survival, EGFR mutants

P2.03 BIOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.03-02 CELL-FREE DNA (CFDNA) TESTING IN LUNG ADENOCARCINOMA (LUAC) PATIENTS: SPANISH LUNG LIQUID VERSUS INVASIVE BIOPSY PROGRAM (SLLIP)

R. Palmero[1], A. Taus[2], S. Viteri[3], M. Majem[4], E. Carcereny[5], J. Garde-Noguera[6], E. Felip[7], M. Sampayo[8], L. Gomez[8], N. Lopez[8], S. Olsen[9], M. Jackson[9], I. Faull[10], D. Dix[9], N. Karachaliou[11], R. Rosell[12]

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Background: Liquid biopsies are a revolution in cancer diagnostics as a minimally invasive alternative to tissue biopsy. cfDNA is used for the detection of biomarkers in LUAC patients if a tumor tissue sample is not available. We conducted the SLLIP study to prospectively validate Guardant360 for the detection of 7 targetable activating alterations (EGFR, ALK, ROS1, BRAF, MET, RET, and ERBB2) in LUAC. **Method:** Blood samples from treatment-naïve stage IIIB-IV LUAC patients were analyzed using Guardant360, a next-generation sequencing panel covering 73 genes. The assay includes complete exon sequencing for 19 cancer genes, sequencing of critical exons in 54 genes, and detection of amplifications (18 genes), fusions (6 genes), and indels (23 genes) with high overall clinical sensitivity rates (85%) and ultra-high specificity (>99.9%). Indels and point mutations can be detected at a mutant allele fraction as low as 0.1%. Guardant360 was compared with tissue genotyping performed as standard of care, using a variety of "real life" techniques. The primary objective was to demonstrate the non-inferiority of Guardant360 versus tissue analysis for the detection of the 7 genetic alterations. The study is registered with ClinicalTrials.gov, number NCT03248089. **Result:** 186 LUAC patients were enrolled over a period of 11 months (August 2016-July 2017). Median age 64, 65% male, 72% smoker/ex-smokers, 85% ECOG performance status 0-1. Targetable activating alterations were detected by the Guardant360 assay and by tissue analysis in 25% (n=47) and 26% (n=49) of patients, respectively (non-inferiority P=0.268). Thirty patients (16%) had alterations identified by both modalities. None of the 186 patients was successfully tested in tissue for all 7 alterations. Of the 17 patients who were negative in tissue but for whom Guardant360 identified targetable alterations, 3 had BRAF V600E mutations. For none of these patients was BRAF tested in tissue. Clinical efficacy per biomarker and treatment modality are awaited. **Conclusion:** Guardant360 cfDNA and tissue analysis detect relevant somatic tumor alterations at similar rates in LUAC patients. Under-genotyping in tissue is common but can be mitigated by the use of cfDNA next generation sequencing assays.

Keywords: targeted sequencing, cell free DNA, NSCLC

P2.03 BIOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.03-03 UPFRONT NEXT GENERATION SEQUENCING IN NSCLC: A PUBLICLY FUNDED PERSPECTIVE

K. Perdrizet[1], T. Stockley[2], M. Tsao[1], J. Morganstein[3], S. Kamel-Reid[4], L. Ranich[5], F. Shepherd[6], P. Bradbury[3], G. Liu[7], D. Hwang[1], P. Pal[2], J. Schwock[4], S. Boerner[4], A. Sacher[8], J. Law[8], N. Leighl[7]

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Background: A growing number of targeted drug treatments in non-small cell lung cancer (NSCLC) have led to the need for molecular profiling beyond the standard of care (SOC) *EGFR/ALK*. Here we present actionable targets, impact on patient treatment, clinical trial opportunities and costs using the Illumina TruSight Tumor 15 panel (TST15) for NSCLC samples. **Method:** Tissue-based next generation sequencing using the TST15 was reflexively performed on all newly diagnosed cases of non-squamous NSCLC at the University Health Network (Toronto, Canada) from February 2017-February 2018. The panel identifies hot spot mutations in *KRAS*, *EGFR*, *TP53*, *PIK3CA*, *BRAF*, *ERBB2*, *FOXL2*, *GNA11*, *GNAQ*, *KIT*, *NRAS*, *PDGFRA*, *RET*, *AKT1* and *MET*, but not fusions, copy number variations (CNV) nor *MET* exon 14 skipping mutations. Patient age, stage, pathologic subtype, and genotyping results were collected prospectively. Treatment changes as a result of TST15 and clinical trial opportunities (clinicaltrials.gov) were identified. Incremental testing costs were based on direct laboratory costs, but not personnel and administration costs. **Result:** Testing included 342 samples from 336 patients. The TST15 panel identified 409 mutations from 342 samples. Sample demographics include: male: 53, and stage 1/2/3/4: 34/8/15/43%. Incremental actionable targets beyond *EGFR* and *ALK* were identified in 3.5% of patients (*ERBB2* 2.3%, *BRAF* V600E 1.2%). Most mutations occurred in *TP53* (43%), *EGFR* (24%) and *KRAS* (26%). Co-mutations occurred in 32% (*TP53*, *KRAS*, *EGFR*) of samples. To date, one patient has had a treatment change as a result of TST15 beyond targeting *EGFR*. Above SOC clinical trial options were identified for 88% of stage IV and 26% of stage III patients. 3.6 samples were needed to identify one actionable mutation, predominantly in *EGFR*, at an estimated cost of $1919 CAD per target. **Conclusion:** Extended genotyping with TST15 in NSCLC identifies an additional 3.5% of patients with actionable mutations above SOC and improves clinical trial options for patients. Despite this, impact on patient treatment beyond targeting *EGFR* is minimal. To enhance the number of targets and minimize costs, affordable population-based comprehensive testing with a panel that includes fusions/CNV is needed.

Keywords: Molecular, sequencing, cost effectiveness

P2.03 BIOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.03-04 NEXT GENERATION SEQUENCING IN LUNG CANCER USING THE ONCOMINE COMPREHENSIVE ASSAY: THE CANADIAN PUBLICLY FUNDED EXPERIENCE

K. Perdrizet[1], T. Stockley[2], J. Law[3], M. Shabir[3], L. Le[4], M. Tsao[5], S. Kamel-Reid[5], T. Zhang[5], M. Sawczak[3], D. Hwang[5], P. Pal[5], G. Liu[6], P. Bradbury[3], F. Shepherd[6], A. Sacher[3], N. Leighl[6]

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Background: Standard of care (SOC) diagnostics for patients with stage IV non-small cell lung cancer (NSCLC) in Canada includes *EGFR* and *ALK* testing. Other genomic alterations are not tested routinely; however, access to enhanced molecular testing may broaden treatment options, clinical trial access, and improve outcomes for patients. This study uses the Oncomine Comprehensive Assay (OCA) v3, a next generation sequencing (NGS) panel in NSCLC to evaluate actionable targets, clinical trial eligibility, treatment impact, costs, turnaround time, and patient preference. **Method:** Consecutive consenting stage IV NSCLC outpatients at the Princess Margaret Cancer Centre without *EGFR/ALK/KRAS/BRAF* derangement diagnosed at the University Health Network (UHN) in Toronto, Canada will be enrolled to undergo OCA testing on diagnostic samples. The selected platform (OCA v3, ThermoFisher) includes 161 genes including hotspots, fusions, and copy number variations. Patient age, pathologic subtype, genotyping results and treatment history will be collected. Primary endpoints include incremental actionable targets identified and clinical trial opportunities (clinicaltrials.gov) added through incremental testing beyond SOC. Secondary endpoints include treatment changes as a result of OCA testing, costs from the perspective of the Canadian public healthcare system, patient willingness-to pay, and test turnaround time. **Result:** The study activated in February 2018 with 7 patients enrolled as of April 2018. Results of the value of incremental OCA testing beyond standard of care in the Canadian public healthcare system will be presented at the meeting. **Conclusion:** While OCA testing in patients with advanced NSCLC may identify more actionable targets than selected genotyping, its cost effectiveness in the Canadian healthcare system is unknown and will be determined through this study.

Keywords: clinical trial, next generation sequencing

P2.03-05 BIOLOGIC PROFILING OF BRAIN METASTASIS FROM NON-SMALL CELL LUNG CANCER

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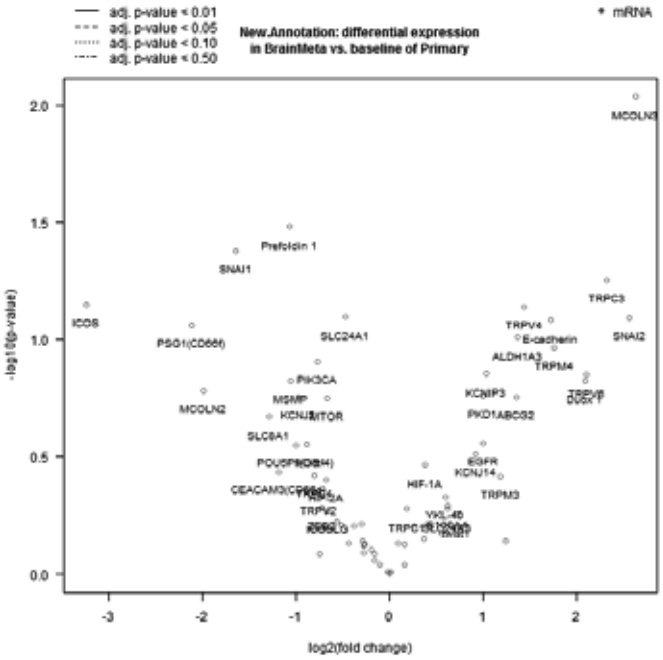
Background: Bain metastasis develops in approximately 50% of patients with non-small cell lung cancer (NSCLC), resulting in poor prognosis and low health-related quality of life. Immunological microenvironment and functions of ion channels have been indicated to play pertinent roles in epithelial-to-mesenchymal transition (EMT) and its reverse mesenchymal-to-epithelial transition (MET), crucial steps in distant metastasis, but their actual roles in brain metastasis of NSCLC remains unclear. The aim of this study is to investigate biologic profiles of brain metastasis of NSCLC. **Method:** Formalin-fixed paraffin-embedded (FFPE) samples of brain metastasis and paired primary sites were collected from 3 patients with NSCLC undergoing surgical resection between Jan. 2012 and Dec. 2017. Total RNA was extracted from the archived FFPE, of which integrity was briefly checked by Nanodrop. Gene expression was detected by nCounter (NanoString Technologies, WA, USA) with PanCancer Immune Profilling Panel and custom-made KMU IonChannel Panel that covered selected 100 genes. Detected data was analyzed by nCounter Advanced Analysis (version 2.0.115). Factors with unadjusted P-value < 0.01 were regarded as candidates for further investigation. **Result:** Brain metastasis showed upregulations of MCOLN3 and YTHDF2 (unadjusted P-value= 0.0093 and 0.0063, respectively) compared to the primary site. Conversely, primary site showed upregulations of IFNAR1, TNFRSF4, CXCL11, CT45A1, MAP3K5, TAL1, LAG3 and MARCO. In LATE-BREAKING ABSTRACT, we will report following data: 1) Immunohistochemistry results of the candidate proteins in resected brain metastasis and primary sites of NSCLC from larger population. In situ hybridization is also planned. 2) Additional data of expression profiles of the candidate genes in sphere cell line from brain metastasis and primary site of NSCLC.



Conclusion: Biologic profilings of brain metastasis from NSCLC may subsequently help to understand underlying mechanism and ultimately lead to novel targeted therapy. Futher details will be added in LATE-BREAKING ABSTRACT.

Keywords: Brain metastasis, ion channel, nCounter

P2.03-06 SERUM SYNDECHAN-1 LEVELS IN PATIENTS WITH NONSMALL CELL LUNG CANCER

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Background: Cytokines as polypeptide or glycopeptide molecules are the essential mediators of immune response and the inflammatory reactions in addition to numerous biological reaction they are involved in. Syndecans have an important role in a variety of cellular functions including cell proliferation and migration, and cell- /cell and cell-/ matrix interactions. Syndechan-1 is a transmembrane heparan sulphate proteoglycans that is present on most cell types. In this study we aimed to evaluate the levels of syndecan-1, levels in non-small cell lung cancer (NSCLC), and to evaluate their relationship with tumor progression. **Method:** Sixtysix patients (F=3, M=63) with non-small cell lung cancer and 22 healthy (F=3, M=19) subject were enrolled this study. Patients with infections or other systemic disease were not included in the study. Serum levels of syndecan-1 was measured by ELISA system. Serum samples were obtained from each patient before the initiation of any type cancer treatment. They were centrifuged at 3000 rpm for 10min, and then stored at -70°C. Unpaired t-test was used to compare continuous variables between the patient group and control group and within the patient group according to TNM classification. Correlation analysis between cytokines and tumor stage was performed using the Pearson correlation coefficient. Sensitivity, specificity, positive predictive value and negative predictive values for syndecan-1 were determined using receiver operator characteristic analysis (ROC). These analyses were done to define clinically valid cutoff points to predict distant metastasis. A two-sided p values less than 0.05 was considered to be statistically significant. **Result:** Serum levels of syndecan-1 in patients with NSCLC were significantly higher than those of controls (p<0.001). In addition, mean levels of synde- can-1 in stage IV disease were significantly higher than non-metastatic NSCLC (p<0.001). In the patients with only one distant metastasis, levels of syndecan- 1 were found to be lower than those of the patients with multiple distant metastases. Syndecan-1 has high sensitivity (78%), specificity (91%), positive (88%) and negative predictive (80%) values for prediction of metastasis. **Conclusion:** In conclusion, we found that syndecan-1 changes significantly in serum of patients with NSCLC. In our study, these changes correlated well with the stage of lung cancer. Syndecan-1 with a high sensitivity, specificity and positive predictive value may be used in predicting the presence and nature (single or multiple) of metastasis. The authors believe that the current findings will provide clinicians with new insights, allowing them to implement more individualized treatment strategies in patients with lung cancer.

Keywords: nonsmall lung cancer, syndecan-1, metastasis

P2.03-07 RADIOMIC SIGNATURES LINKED TO GENETIC ALTERATIONS AS DETECTED BY NEXT-GENERATION SEQUENCING: A RADIOGENOMICS ANALYSIS OF EARLY-STAGE NSCLC

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Background: Radiomics uses large-scale quantitative analysis of extracted image-based features to identify tumor phenotypes. Such frameworks based on computed tomography (CT) have identified informative features in lung cancer related to treatment response and prognosis. Molecular profiles have been increasingly recognized in non-small cell lung carcinoma (NSCLC) as predictors of clinical outcomes. The aim of this study is to isolate radiomic signatures which are associated with genomic alterations discoverable by extended panel testing. **Method:** Patients with early-stage NSCLC who received definitive local treatment and underwent next-generation sequencing were included for this analysis. 35 genomic alterations representing 32 genes were evaluated using SNaPshot (Life Technologies), TruSight (Illumina Inc), Guardant360 (Guardant Health) or a FISH panel of ALK, MET, ROS1 and RET. Regions of interest including each primary tumor volume were delineated on diagnostic CTs datasets; they were defined as either tumor only (TO), or tumor with a 1cm anatomically-modified anisotropic

margin (TM). Measures describing delineation and tumor appearance within each volume were extracted using in-house software, recording HU characteristics, inhomogeneity, and first and second-degree texture statistics. 91 structural, textural, and intensity features were extracted. Univariate logistic regression was performed to test the performance between each extracted feature and the presence of genomic alterations. **Result:** 40 patients with diagnostic CTs available for feature extraction were included for analysis. The rate of mutation prevalence in the most commonly altered genes were: TP53 (52.1%), cMET (34.5%), KRAS (27%), PTEN (13.8%), EGFR (13.2%), and MET (12.1%). 5 features were associated with TP53 mutations using TO-extracted features, and 4 using the TM-based approach. cMET was linked to Hounsfield minimum (odds ratio [OR] 1.01, p=0.027), and Sobel minimum (p=0.049) using the TO approach. Long run emphasis standard deviation (STD) [OR 0.36, p=0.04], and long run low grey level emphasis STD (OR 0.37, p=0.04) correlated with cMET mutations using the TM approach. Laplacian sharpening mean was associated with the presence of EGFR mutations using both extraction approaches; finding OR 1.10 (p=0.04, TO method) and OR 1.12 (p=0.02, TM method). No other features were linked to EGFR alterations. Gradient magnitude variance was associated with PTEN using tumor-with-margin volumes (OR 0.83, p=0.028). No features were significantly linked to KRAS mutations using either extraction approach. **Conclusion:** Multiple radiomic features were associated with TP53, cMET, EGFR, and PTEN mutations. Integration of such signatures may help inform prognosis for a heterogenous cohort of patients with early-stage non-small cell lung carcinoma.

Keywords: Genomics, non-small cell lung cancer, Radiomics

P2.03 BIOLOGY
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P2.03-08 MOLECULAR SPECTRUM OF PATIENTS WITH MSH2 MUTATIONS IN CHINESE NON-SMALL CELL LUNG CANCER

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Background: Although inactivation of MutS Homolog 2 (*MSH2*) genes may predict sensitivity to immunotherapy in non-small cell lung cancer. little is known about their etiology and prognosis in non-small-cell lung cancer (NSCLC). The aim of this study is to investigate mutations and prognosis of NSCLC harboring *MSH2* mutations. **Method:** A total of 326 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *MSH2* mutation or other genes were detected by next generation sequencing. **Result:** *MSH2* gene mutation rate was 9.51% (31/326) in non-small cell lung cancer, including H839R (5 patients), L390F (4 patients), E809K (3 patients), I169V (3 patients), I544M (1 patient), R217C (1 patient), T8M (1 patient), T552S (1 patient), A189S (1 patient), Q493P (1 patient), I735V (1 patient), A45T (1 patient), A573T (1 patient), R534L (1 patient), V712Sfs*5 (1 patient), F58L (1 patient), S676L (1 patient), N583S (1 patient), I766V plus A2V (1 patient) and Q419K plus Q629R (1 patient), and median overall survival (OS) for these patients was 16.0 months. Among them, all patients were *MSH2* gene with co-occurring mutation. Briefly, patients with (n=6) or without (n=25) co-occurring *EGFR* mutations had a median OS of 6.5 months and 17.0 months respectively (P=0.02); patients with (n=20) or without (n=11) co-occurring *TP53* mutations had a median OS of 14.0 months and 17.0 months respectively (P=0.85). **Conclusion:** *MSH2* is involved in MMR, controlling several aspects of genome stability. Immunotherapy may displayed moderated efficacy in patients with *MSH2* mutation. *EGFR* accompanied mutations might play a good prognosis in *MSH2* gene mutation NSCLC.

Keywords: MSH2 mutation, Non-small-cell lung cancer, Prognosis

P2.03 BIOLOGY
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P2.03-09 THE REAL WORLD OF NTRK FUSION DATA IN THE CHINESE LUNG CANCER POPULATIONS: A MULTICENTER STUDY

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Background: *NTRK* fusions have been recently identified as a therapeutic target in a rare fraction of Caucasian patients with lung cancer (3.3%). The aim of this study was to evaluate the prevalence of *NTRK* fusions in Chinese lung cancer populations, which had not been reported earlier, and to describe targeting potential in Chinese lung cancer populations. **Method:** A multicenter study in China was initiated from **February 2014**, and lung cancer patients have been enrolled as of December 2017. Capture-based comprehensive genomic profiling was performed on **2719 lung cancer** FFPE samples (non-squamous/squamous/small=**2061/349/309**) sequenced to a mean coverage depth of > 650X for up to 381 cancer-related genes. Genomic alterations (GA) included short variant (SV) base subs and insertions/deletions, copy number alterations, and rearrangements/fusions. Tumor mutational burden (TMB; mut/Mb) was calculated on up to 1.2 Mb of sequenced DNA. **Result:** Of this entire cohort, just one (**0.04**%) patient was identified with a *TPM3-NTRK1* fusion. The patient was diagnosed with **SCLC**. *TPM3-NTRK1* fusion was found by biopsy using NGS, the genes co-altered with *NTRK* fusion was no concurrent with *KRAS*, *EGFR*, *ALK*, *ROS1*, or other known drivers were identified in the study cohort cases. **Conclusion:** *NTRK* fusions are a rare molecular subtype in Chinese lung cancer populations. Given clinical evidence for the activity of targeted therapy approaches, molecular eligibility for clinical trials of larotrectinib or entrectinib should include these fusion subtypes. The clinical evidence for responsiveness of *NTRK* fusions driven lung cancer provides an opportunity to personalize treatments and improve clinical outcomes for patients.

Keywords: next-generation sequencing, lung cancer, NTRK fusion

P2.03 BIOLOGY
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P2.03-10 GENE MUTATIONAL PROFILING OF CHINESE TKI-SENSITIZING EGFR MUTATIONS NSCLC PATIENTS REQUIRED RESISTANCE TO ICOTINIB USING NGS

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Background: Icotinib is an oral first-generation epidermal receptor 1/epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor (TKI). Identification of actionable genetic alterations conferring drug-resistance can be helpful for guiding the subsequent treatment decision. One of the major resistant mechanisms is EGFR-T790M mutation. Other mechanisms, such as MET amplifications, BRAF mutations and PIK3CA mutations, were also reported. In this study, we performed gene mutational profiling in a cohort of 162 TKI-sensitizing EGFR mutations NSCLC patients and acquired resistance to icotinib using targeted NGS. **Method:** A total of 162 patients with stage IIIb-IV TKI-sensitizing EGFR mutations NSCLC were undergoing tumor biopsies, blood or serous effusions withdrawing by the time of acquiring resistance to icotinib. We used targeted NGS to detect genes status of patients. **Result:** In total, we identified 373 genetic alterations with a median of 2.3 mutations per patient. 64.20% (104/162) of patients still exhibit TKI-sensitizing EGFR mutations, and 46.30% (75/162) of patients acquired EGFR-T790M mutations. Besides other known resistance mechanisms, we identified MET amplification 6.17% (10/162) of patients, BRAF mutations in 3.09% (5/162) of patients, and PIK3CA mutations in 2.47% (4/162) of patients. Interestingly, we also observed RBM10, ASXL1 and BMX mutations in EGFR-T790M wild patients, which are restricted to icotinib treatment resistance. **Conclusion:** Our study uncovered mutational profiles of TKI-sensitizing EGFR mutations NSCLC patients with icotinib resistance with potential therapeutic implications. Our analysis strongly suggests that MET amplification, BRAF mutations and PIK3CA mutations may serve as bypass resistance mechanisms in patients who are EGFR T790M wild type.

Keywords: required resistant, EGFR T790M, Non-small-cell lung cancer

P2.03-11 PDGFRA DEFINES A UNIQUE MOLECULAR SUBTYPES OF CHINESE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Activation of the platelet-derived growth factor (PDGF) signaling system has been implicated in the development and malignant progression of non-small-cell lung cancer. Recently, the platelet-derived growth factor receptor A (*PDGFRA*) gene mutations are identified in non-small-cell lung cancer (NSCLC). While the genetic locus of *PDGFRA* mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *PDGFRA* mutations. **Method:** A total of 467 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *PDGFRA* mutation and other genes were detected by next generation sequencing. **Result:** *PDGFRA* gene mutation rate was 2.14% (10/467) in non-small cell lung cancer, including S716R (1 patient), L615* (1 patient), A916T (1 patient), H104R (1 patient), V536M (1 patient), N505K (1 patient), V421I (1 patient), V538M (1 patient), M578K (1 patient) and V544A (1 patient), and median overall survival (OS) for these patients was 24.0 months. Among them, all patients were *PDGFRA* gene with co-occurring mutation. Briefly, patients with (n=2) or without (n=8) co-occurring *EGFR* mutations had a median OS of 19.0 months and 24.0 months respectively (P=0.96); patients with (n=6) or without (n=4) co-occurring *TP53* mutations had a median OS of 24.0 months and 19.0 months respectively (P=0.99); patients with (n=2) or without (n=8) co-occurring *BRCA2* mutations had a median OS of 25.0 months and 19.0 months respectively (P=0.17); patients with (n=2) or without (n=8) co-occurring *IDH2* mutations had a median OS of 15.0 months and 24.0 months respectively (P=0.22). **Conclusion:** Mutation type of *PDGFRA* has a potential for predicting the course of the disease and might contribute to management individualization of NSCLC patients. *EGFR*, *TP53*, *BRCA2* and *IDH2* gene accompanied may have less correlation with *PDGFRA* mutation in NSCLC patients. Imatinib may displayed moderated efficacy in patients with *PDGFRA* mutation.

Keywords: Non-small-cell lung cancer, Prognosis, PDGFRA mutation

P2.03 BIOLOGY
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P2.03-12 EGFR AND ERBB2 GERMLINE MUTATIONS IN CHINESE LUNG CANCER PATIENTS AND THEIR ROLES IN GENETIC SUSCEPTIBILITY TO CANCER

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Background: Inherited genetic determinants of lung cancer risk remains relatively elusive. Rare germline mutations in *EGFR* and *ERBB2* have previously been reported in lung cancer patients, which may be associated with the genetic susceptibility to lung cancer. **Method:** We retrospectively analyzed the next-generation sequencing (NGS) results targeting 416 cancer-relevant genes, including the whole exons of *EGFR* and *ERBB2*, in a cohort of 9091 Chinese lung cancer patients. **Result:** Of the 9091 Chinese lung cancer patients, nine germline mutations from 12 patients were identified within or adjacent to the kinase domain of EGFR: K757R (two patients), D1014N (two patients), I646S, G724S, V786M, T790M, L792F, R831H, and L844V, and one germline mutation was identified adjacent to the kinase domain of *ERBB2*: V1128I. The incidence of *EGFR* T790M germline mutation is much lower compared with the reported frequency in the Caucasian patients. Somatic mutations detected in the 12 patients carrying rare EGFR/ERBB2 germline mutations were most commonly *EGFR* exon19 deletion, L858R, and G719S mutations, and rare *EGFR:* S768I mutation and a novel D770delinsDNPH indel mutation. The superior response to afatinib of the patient carrying only *EGFR* L844V germline mutation suggests that this germline mutation might be sensitive to TKI treatment. **Conclusion:** Here we indentified eight novel *EGFR* germline mutations and the *ERBB2*: V1128I germline mutation were linked to the genetic susceptibility of lung cancer in Chinese population.

Keywords: germline mutation, EGFR, ERBB2

P2.03 BIOLOGY
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P2.03-13 SWATH MS ANALYSIS OF SERINE HYDROLASE ACTIVITY IN HUMAN LUNG ADENOCARCINOMA FOR BIOMARKER DISCOVERY

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Background: Serine hydrolases (SHs), one of the largest enzyme families, have previously been shown to be implicated in the development of lung cancers. Activity-based protein profiling (ABPP) is a proteomic method that uses active site-directed chemical probes to selectively target the active form of the subsets of the enzymes in question, and then by a combination of a streptavidin-biotin enrichment step and mass spectrometry quantifies the catalytically active amount of the enzyme molecule. In this project, we monitored both forms of serine hydrolase, the "catalytically active" and "inactive", in a distinct patient cohort of lung adenocarcinoma biopsies. For this purpose, we combined the activity-based proteomics for serine hydrolase and SWATH mass spectrometry (MS), which ensures highly reproducible protein quantification in a large panel of clinical samples. **Method:** Twenty four lung biopsies of long- and short surviving patients with stage IIIA adenocarcinomas and their normal tissue counterparts were available as OCT-embedded tissue. The common OCT sample clean-up by organic solvents is not compatible with the ABPP protocol since organic solvents can inactivate the molecular structure of the enzymes. The additional challenge of the ABPP protocol includes a streptavidin-biotin enrichment step of the active enzymes, which also leads to sample contamination by streptavidin peptides, and negatively influences MS spectra analysis and, consequently, biomarker discovery. Therefore, we proceeded with optimizations of sample preparation in ABPP experiments and developed an OCT clean-up protocol compatible with "enzyme-substrate binding" of activity-based chemical probes and the targeted portion of the active enzyme. To prevent digestion on streptavidin beads and MS spectra contamination, we used the reproducible and accurate SWATH MS to indirectly measure the active enzyme form in the biopsy-extract solution. **Result:** We identified over 4000 lung tissue proteins from a few milligrams of OCT-embedded biopsies, and confirmed good data quality for further SH enzyme quantification. In addition to the analysis of total proteome, 278 distinct proteins were identified on the parallel streptavidin bead samples, with chemical probes being used to deplete the active enzyme from the biopsy-extract. Each SWATH experiment reported the percentage of "active" enzyme form through the indirectly measured ratio between the "inactive SHs" (sample depleted for active SHs) and the "total" SHs (non-depleted sample). We detected around 80 enzymes with the "active" form comparably measured in three independent experiments, which amount generally accounted for between 5–55% of the total enzyme concentration. **Conclusion:** Combination of ABPP and SWATH MS enables highly reproducible protein quantification in biomarker discovery.

Keywords: biomarker discovery, activity based protein profiling, mass spectrometry

P2.03 BIOLOGY
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P2.03-14 PKCι-PAK1 PATHWAY MODULATES SENSITIVITY TO THERAPY IN EGFR, KRAS MUTANT AND SQUAMOUS CELL NON-SMALL CELL LUNG CANCER (NSCLC)

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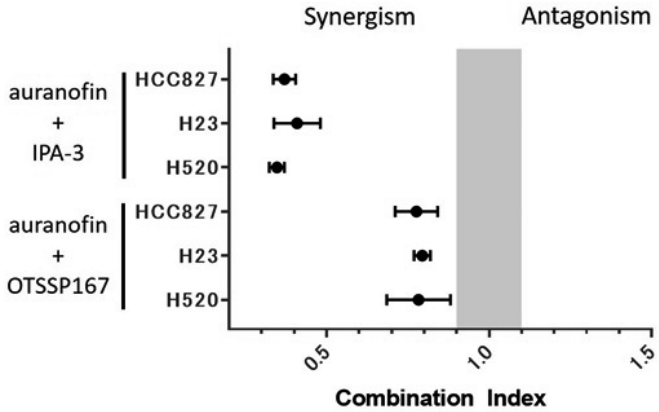
Background: To understand intrinsic and acquired resistance to different MAPK signaling inhibitors, we explored PKCι-PAK1 signaling in EGFR, KRAS and Squamous cell carcinoma (SCC) cell lines. **Method:** Three lung cancer cell lines were used: HCC827 and H23 lung adenocarcinoma cells that carry EGFR and KRAS mutations, respectively, and H520 PAK1 amplified squamous NSCLC cells. Cell viability assays and western blotting were applied to evaluate the effect of auranofin (PKCi inhibitor) plus IPA-3 (PAK1 inhibitor). Since IPA-3 is only for laboratory use, we also tested auranofin in combination with OTSSP167 (a MELK inhibitor in phase I trials), which, in our experience, inhibits pPAK1 (Thr423 and

Thr212 in the HCC827 cell line). **Result:** Auranofin plus IPA-3 was highly synergistic (CI less than 0.4) in EGFR mutant (HCC827), KRAS mutant (H23) and SCC with PAK1 amplification (H520 cells). Similar synergism was found with the combination of auranofin plus OTSSP167 in the 3 cell lines (Figure). the combination of auranofin with either IPA-3 or OTSSP167 ablated EGFR phosphorylation and downstream signaling pathways: ERK, AKT, STAT3, YAP1 and inhibited the expression of RTKs: AXL, MET and CDCP1. We created EGFR mutant gefitinib and osimertinib resistant cell lines (PC9-GR3, GR4, OR2, OR4). Auranofin plus IPA-3 was highly synergistic in all cell lines. **Conclusion:** These observations suggest that the combination of auranofin with OTSSP167 can be used for treatment of different subclasses NSCLC with driver EGFR or KRAS mutations, as well as SCC with PAK1 amplification.



Keywords: Auranofin, IPA-3, OTSSP167

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P2.03-15 INTEGRIN-LINKED KINASE (ILK), PROTEIN TYROSINE PHOSPHATASE SHP2 AND B LYMPHOMA MO-MLV INSERTION REGION 1 HOMOLOG (BMI-1) IN EGFR-MUTANT NSCLC

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Background: The clinical efficacy of EGFR tyrosine kinase inhibitors (TKIs) in EGFR-mutant non-small cell lung cancer (NSCLC) is jeopardized by the activation of multiple signaling pathways. ILK regulates the expression of Bmi-1, a well-known epithelial mesenchymal transition-inducing transcription factor. SHP2 function is required for MAPK pathway activation, and also plays a role in receptor tyrosine kinase signaling pathways. **Method:** Clinical data were assessed in accordance with the protocol approved by the institutional review board and de-identified for patient confidentiality. Pretreatment tumor specimens from advanced EGFR-mutant NSCLC patients (pts) were collected from eight sites in Spain, France, Italy and Colombia. mRNA gene expression analysis was performed by TaqMan (qRT-PCR). We examined the mRNA levels of ILK, SHP2 and Bmi-1. **Result:** With a median follow-up of 26.7 months, median progression-free survival (PFS) was 9.3 (95% CI, 7.6-14.2) and 15.7 months (95%CI, 12.3-30.1) for pts with high and low ILK mRNA, respectively (P=0.0002), (HR for disease progression, 2.4; 95% CI, 1.3-4.5; P=0.002). Median PFS was 11.4 (95% CI, 8.2-14) and 24.1 months (95% CI, 8.2-30.9) for pts with high and low SHP2 mRNA, respectively (P=0.009), (HR, 2.4; 95% CI, 1.2-4.7; P=0.01). Median PFS was 8.2 (95% CI, 4.8-13.1) and 24.1 months (95% CI, 14.2-36.5) for pts with high and low SHP2 mRNA, respectively (P=0.001), (HR, 2.9; 95% CI, 1.4-5.9; P=0.002). Median overall survival (OS) was 17.9 (95% CI, 13.2-33) and 34.4 months (95% CI, 18.5-44.2) for pts with high and low ILK mRNA, respectively (P=0.200), (HR, 1.5; 95% CI, 0.79-3; P=0.200). Median OS was 18.5 (95% CI, 14-33) and 36.7 months (95% CI, 16.7-47.1) for pts with high and low SHP2 mRNA, respectively (P=0.018), (HR, 2.5; 95% CI, 1.1-5.8; P=0.020). Median OS was 17.6 (95% CI, 8.6-39.1) and 36.7 months (95% CI, 19.1-64.1) for pts with high and low Bmi-1 mRNA, respectively (P=0.004), (HR, 2.2; 95% CI, 1.0-5.1; P=0.040). **Conclusion:** The disturbance of RTKs, including ILK-SHP2-Bmi-1 axis, occurs frequently in EGFR mutant NSCLC patients, significantly limiting the PFS and OS. The levels of ILK, SHP2 and Bmi-1 could be predictive for upfront combinatory therapy of EGFR TKI plus a MAPK pathway inhibitor (SHP2 or MEK inhibitors).

Keywords: Bmi-1, ILK, SHP2

P2.03 BIOLOGY
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P2.03-16 TGF-β INDUCED EMT AND STEMNESS CHARACTERISTICS ARE ASSOCIATED WITH EPIGENETIC REGULATION IN LUNG CANCER

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Background: Transforming growth factor-β (TGF-β) promotes tumor invasion and metastasis by inducing an epithelial-mesenchymal transition (EMT). EMT is often associated with acquisition of stem-like characteristics. In this study, we investigated whether EMT and stem-like characteristics induced by TGF-β could associated with epigenetic regulation in lung cancer. **Method:** Human normal epithelial (BEAS-2B) and cancer (A549, H292, H226 and H460) cell lines were incubated with 10 ng/ml of TGF-β for 3 days. Transcriptome analysis of BEAS-2B and A549 cells treated with TGF-β were performed by using next-generation sequencing (HiSeq 2500 system). Western blotting was performed to analyze the expression of epithelial marker (E-cadherin) and mesenchymal markers (N-cadherin, fibronectin, vimentin and α-SMA). Wound healing assay, Matrigel invasion assay, sphere formation assay and in vivo mice tumor model were used to assess functional characteristics of EMT and stemness acquisition. TGF-β induced DNA demethylation was identified by methylation-specific PCR and bisulfite sequencing. **Result:** Next-generation sequencing revealed significant changes in the expression of stem cell markers, CD44, CD87 and CD90 in both BEAS-2B and A549 cells. Functional analysis revealed increased wound healing, Matrigel invasion, sphere formation and in vivo mice tumor formation after TGF-β treatment. TGF-β induced EMT was associated with acquisition of stem-like characteristics. CD44, CD87 and CD90 were activated by either TGF-β and treatment with AZA. MSP showed decreased CD44, CD87 and CD90 promoter methylation after TGF-β treatment. **Conclusion:** These results suggest that TGF-β induces stem cell characteristics which are related with CD44, CD87 and CD90 reactivation by promoter demethylation.

Keywords: TGF-β, stemness characteristics, epigenetic regulation

P2.03 BIOLOGY
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P2.03-17 EGFR T790M MUTATION MAY NOT BE GENERATED THROUGH SELECTION BY EGFR-TKI FROM RANDOMLY OCCURRING MUTATIONS IN VITRO USING ENU

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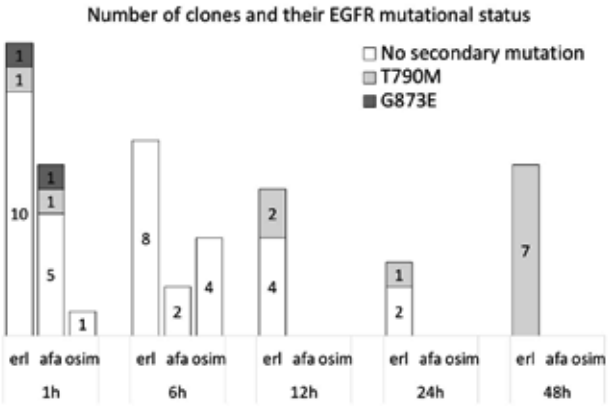
Background: It is postulated that T790M resistant mutation is a result of selection by EGFR-TKI from clones that have randomly generated mutations. If so, it would be possible to detect the process of convergence from random mutations to T790M, depending on exposure time for EGFR-TKI. **Method:** After exposure of Ba/F3 cells expressing EGFR Del19 to ENU (N-ethyl-N-nitrosourea) for 24 hours, they were cultured with various concentrations of 3 EGFR-TKIs at trough concentrations (Fig.). At 1, 6, 12, 24, and 48 hours, cell viability was evaluated and single cell cloning was performed. EGFR exons 18 to 21 were analyzed by Sanger sequencing. **Result:** Percentages of viable cells exposed to TKI were approximately 80%, 50%, < 20%, and < 3% at 1, 6, 12, 48 hours, respectively. These ratios were almost similar among 3 TKIs. Of 50 clones that had survived TKI treatment, T790M was detected in 12 (24%) (Fig.). Notably, two were detected in cells exposed to erlotinib or afatinib only for one hour (Fig.). In addition, we found 2 G873E (c.2876G>A) mutations, known to be oncogenic, with the same

TKI treatment. In contrast, 36 clones (72%) with TKI or additional 19 clones without TKIs that had been exposed to only ENU did not harbor any secondary EGFR mutations.



*drug concentrations: erlotinib 1000nM, afatinib 100nM, osimertinib 500nM

Conclusion: It is unlikely that EGFR T790M mutation is generated through selection by EGFR-TKI from randomly occurring mutations. Rather, it appears that T790 is the preferred target of mutagenesis through yet an unknown mechanism which occurs after only one-hour treatment.

Keywords: EGFR, Acquired resistance, T790M

P2.03 BIOLOGY
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P2.03-18 X-INACTIVATION SPECIFIC TRANSCRIPT (XIST)-MEDIATED MIRNA SEQUESTRATION IN NSCLC

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Background: Long non-coding RNA (lncRNA; >200nt) transcripts have been recently recognized as crucial regulators of gene expression. XIST is a prototypical lncRNA involved in cis-silencing of an X chromosome in females; however, there are conflicting reports of lncRNA-mediated regulation in cancer biology and therapeutics through "sponging" of single miRNAs that cause upregulation of canonical miRNA-target genes. XIST-associated sex-specific differences afford the opportunity to study lncRNA sponging systems within a cancer type. Existing studies considering one miRNA in singular cancer types do not account for important biological considerations, including sex and localization of miRNA and XIST transcripts. Here, we detail an in-depth and unbiased pipeline for the discovery of candidate miRNA and gene targets in lncRNA sponging, and validate the miRNA that may be mediating these interactions in XIST. **Method:** We performed a comprehensive analysis of the role of XIST in the positive regulation of protein-coding genes using male and female lung adenocarcinoma (LUAD) samples as a model. To find genes regulated by XIST-mediated miRNA sponging, we correlated all Ensembl-annotated genes with XIST expression in female LUAD (n=307; rho>0.4, p<0.05). Using a specialized algorithm based on binding energies and sequence homology, we assessed the potential binding of all miRNAs against target genes and XIST. We then determine the best candidates for sponging by XIST using XIST-high (female and male) and XIST-low (male) systems, and validate the presence of these candidate miRNAs in the nucleus. **Result:** Our analysis yielded 543 genes that may be defended from miRNAs by XIST (DMX), with a predicted 804 miRNAs targeting both DMX genes and XIST. We compared the changes in miRNA-DMX relationships in XIST-high and XIST-low systems and discovera high-confidence set of 13 miRNA-DMX gene pairs. Interestingly, 5 of these miRNA-DMX gene pairs involve miRNA with validated nuclear localization. **Conclusion:** A massive number of lncRNA sponging studies exist, but most only consider one miRNA in a singular type of cancer, are biased in their selection of this target, and limited in biological context. By analyzing the transcriptome of female and male LUAD, we show that the XIST-miRNA-DMX sponging axis is affected by expression of sex-specific genes and number of shared miRNA binding sites on DMX genes. Importantly, we identify that the miRNAs that mediate the XIST-DMX gene axis are enriched in the nucleus, co-localizing with XIST. In summary, our analysis provides both a comprehensive methodology for studying cancer-related miRNA sponge lncRNAs, and suggests the relevance of XIST in lung cancer.

Keywords: long non-coding RNA, microRNA

P2.03 BIOLOGY
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P2.03-19 RET-MEDIATED ACTIVATION OF EZRIN IS ASSOCIATED WITH CELL MOTILITY AND SURVIVAL IN A SUBSET OF LUNG ADENOCARCINOMAS

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Background: Lung cancer is the leading cause of cancer mortality worldwide with 40% of cases diagnosed as lung adenocarcinoma (LADC). Increased expression of RET has been reported in 10-20% of LADCs and is associated with metastasis and reduced survival. Alternative gene splicing of RET generates two co-expressed isoforms; RET9 and RET51, with unique C-terminal tails. The tails confer distinct protein binding opportunities with signaling proteins, known as scaffolds, to promote different signaling events and cell processes. RET9 interacts with the SHANK family scaffolds at a PDZ-binding motif and Enigma at tyrosine (Y) 1062, whereas, RET51 interacts with Grb2 at the unique Y1096. RET9 and RET51 are associated with distinct functions in thyroid cancer, where RET51plays a predominant role in cancer metastasis. Ezrin is a scaffold protein and tyrosine kinase substrate that bridges the plasma membrane to the actin cytoskeleton to promote adhesion, organization and migration. Overexpression of ezrin is associated with invasion and metastasis of osteosarcoma and pancreatic cancer cells. The roles of RET isoform-scaffold interactions in the progression of LADC has never been investigated. **Method:** HEK-293 cells were co-transfected with RET isoform or mutant constructs and Ezrin and/or Grb2 dominant negative (DN) constructs. A549 LADC cells were transfected with RET51 construct. SH-SY5Y neuroblastoma and HCC1833 LADC cells endogenously express Ezrin and RET. Cells were treated with RET/ Ezrin inhibitors and/ or stimulated with glial-derived neurotrophic factor (GDNF) then fixed or harvested. Co-immunoprecipitation (Co-IP) or pull-down assays coupled to western blotting were used to investigate binding domains required for RET interaction with and activation of Ezrin or downstream effectors. Immunofluorescence confocal imaging was used to determine co-localization of RET and Ezrin and changes to cell morphology. GDNF-impregnated agarose bead live-cell fluorescence assays were used to measure cell growth, survival, spread and motility. SynTarget (cancer gene expression analysis tool) was used to assess co-expression of RET and Ezrin with respect to clinicopathological parameters and survival outcomes in LADC. **Result:** Ezrin binds kinase active RET51 with Grb2. GDNF-stimulation promotes the formation of cytoskeletal outgrowths with increased co-localization of Ezrin and RET. GDNF-activation of RET results in scaffold-mediated activation of Rho-family GTPases to promote cell motility. Like RET, overexpression of Ezrin is associated with poor overall survival in LADC patients and overexpression of both RET and Ezrin has a negative synergistic effect on overall survival in a subset of LADC patients. **Conclusion:** RET interaction with Ezrin identifies a distinct functional role of RET as an oncogenic driver in lung adenocarcinoma.

Keywords: Cancer metastasis, RET Receptor Tyrosine Kinase, Scaffold Protein

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P2.03-20 FACTOR XIIIA-EXPRESSING INFLAMMATORY MONOCYTES PROMOTE LUNG SQUAMOUS CANCER THROUGH FIBRIN CROSS-LINKING

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Background: Lung cancer is the leading cause of cancer-related deaths worldwide, and lung squamous carcinomas (LUSC) represent about 30% of cases. Molecular aberrations in lung adenocarcinomas have allowed for effective targeted treatments, but corresponding therapeutic advances in LUSC have not materialized. However, immune checkpoint inhibitors in sub-populations of LUSC patients have led to exciting responses. **Method:** See results **Result:** Using computational analyses of The Cancer Genome Atlas(TCGA) dataset, we identified a subset of LUSC tumors characterized by dense infiltration of inflammatory monocytes (IMs) and poor survival. Multiplex immunohistochemistry for CD14/CCR2/pan-cytokeratin revealed that dual-positive CD14+/CCR2+ cells predominately reside in the stromal LUSC compartment and not cancer cell islets. Using immunogenomics, we found that amongst 9 immune subsets expressing CD14, IMs had the strongest relationship with CD14 expression and poor LUSC survival. With novel, immunocompetent metastasis models, we demonstrated that tumor cell derived CCL2-mediated recruitment of IMs is driven by TNFa-mediated activation of the NFkB pathway. Furthermore, tumor production of CCL2 isnecessary and sufficient for LUSC metastasis.

Pharmacologic inhibition of IM recruitment with a potent CCR2 inhibitor (PF-04136309) had substantial anti-metastatic effects, which was not due to inhibition of tumor-associated macrophages (TAMs) but rather by blockade of IMs in the blood and tumor microenvironment. Notably, in contrast to TAMs, we show that IMs express high levels of Factor XIIIA (FXIIIA). We demonstrate that FXIIIA is packaged into podosome-like structures in IMs, and when in contact with fibrin the IMs are capable of rapidly creating fibrin cross-linkages. We show that FXIIIA-mediated IM fibrin cross-linking creates a scaffold for LUSC cell invasion, migration and metastases. Consist with this observation, we found clinical LUSC samples containing extensive cross-linked fibrin in the microenvironment correlated with poor relapse-free survival. **Conclusion:** Given the rapidly evolving landscape of precision immune-oncology, these findings identify IMs as a novel context-specific vulnerability of LUSC and provide an important insight into the mechanisms through which this immune cell type determines a poor prognosis.

Keywords: Inflammatory Monocytes, metastasis, Lung Squamous Cancer

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P2.03-21 MECHANISTIC INVESTIGATION OF DRD1 IN LUNG CANCER

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Background: The D1 dopamine receptor (DRD1) is a G protein-coupled receptor (GPCR) for the catecholamine dopamine (DA). Historically, DA was thought to function mainly within the central nervous system (CNS), and there have been no prior reports linking the DA pathway (DAP) to lung cancer biology. Our group previously discovered an epidemiological association between a *DRD1* gene polymorphism and risk of developing lung cancer. Since this association was observed in never smokers,it suggested that DRD1 may play a direct role in the pathogenesis of lung cancer. We have been investigating this novel function of DRD1. **Method:** The DAP has never been fully characterized in lung. We therefore examined the presence of DAP-related proteins, including dopamine receptors, metabolizing and synthesizing enzymes, and dopamine transporter in normal human lung tissue. To understand the mechanistic role of DRD1 in lung cancer, we generated stable lung cancer cell lines in which DRD1 was overexpressed or knocked down and performed proliferation, transcriptome, and kinome analysis. **Result:** We found that dopamine-related proteins are expressed throughout the respiratory tract in normal human tissue. Further, we observed that DRD1 expression is significantly downregulated in lung cancer using samples from the on NCI-MD case control study and replicated this with TCGA. Methylation analyses in NCI-MD and TCGA showed that DRD1 is hyper-methylated in lung cancer and that there is a negative correlation between DRD1 mRNA and methylation. DRD1 methylation and methylation are associated with patient outcome. Modulation of DRD1 in multiple cell line model systems affects cell proliferation. Transcriptome and kinome profiling revealed that this modulation is mediated through EGFR and downstream MAPK and AKT signaling. Immunofluorescent staining shows that EGFR and DRD1 colocalize at the cell membrane. Ongoing work is aimed at establishing the exact nature of the DRD1/EGR interaction. **Conclusion:** Collectively, this work suggests that DRD1 acts like a tumor suppressor in lung cancer, that inherited susceptibility in the DRD1 gene contributes to lung cancer and agents that modulate the bioavailability of dopamine could modulate patient survival. Understanding the possible crosstalk between DRD1, EGFR and MAPK signaling may be very valuable for lung cancer therapeutic strategy. The majority of patients receiving EGFR inhibitors eventually develop resistance. Using DRD1 agonists as combinatorial agents may help bypassing anti-EGFR resistance.

Keywords: Lung cancer, Dopamine receptor, EGFR-MAPK

P2.03 BIOLOGY
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P2.03-22 OCT4&SOX2 SPECIFIC CTLS PLUS PD-1 INHIBITOR HAD SYNERGISTIC EFFECT ON KILLING CSC AND TREATING DRUG-RESISTANT LUNG CANCER MICE

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Background: This study aimed to investigate the synergistic effect of OCT4&SOX2 specific cytotoxic T lymphocytes (CTLs) and PD-1 inhibitor on killing lung cancer stem-like cells (LCSCs) and their efficacy in treating drug-resistant lung cancer (DRLC) mice. **Method:** OCT4&SOX2 specific CTLs and PD-1 inhibitor with differed doses were applied to treat PC9 cells and PC9 LCSCs. CCK8 assay and flow cytometry (FCM) assay with CFSE staining target cells before treatment and PE staining died cells after treatment were conducted to detect the cytotoxic activity. DRLC mice were constructed by injection of PC9 LCSCs suspension and Matrigel into left lung of SD mice. DRLC mice was randomly divided into 5 group: Control group, CMV pp65 CTLs group, OCT4&SOX2 CTLs group, PD-1 inhibitor group and OCT4&SOX2 CTLs+PD-1 inhibitor group. **Result:** *In vitro*, Both CCK8 assay and FCM assay disclosed that OCT4&SOX2 specific CTLs plus PD-1 inhibitor presented with elevated cytotoxic activity on PC9 cells and PC9 LCSCs. *In vivo*, tumor volume and tumor weight were decreased, while tumor necrosis and tumor apoptosis were increased in OCT4&SOX2 CTLs group than CMV pp65 CTLs group and control group, and in OCT4&SOX2 CTLs+PD-1 inhibitor group than OCT4&SOX2 CTLs group and PD-1 inhibitor group. In addition, CD8 expression was increased while OCT4 and SOX2 expressions were decreased in OCT4&SOX2 CTLs+PD-1 inhibitor group than OCT4&SOX2 CTLs group and PD-1 inhibitor group. **Conclusion:** In conclusion, OCT4&SOX2 specific CTLs and PD-1 inhibitor presented with synergistic effect on killing LCSCs *in vitro* and treating DRLC mice *in vivo*.

Keywords: PD-1 inhibitor, Cytotoxic T lymphocytes, Synergistic effect

P2.03 BIOLOGY
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P2.03-23 MICRORNA-30E INHIBITS CELL PROLIFERATION AND INVASION IN NON-SMALL CELL LUNG CANCER VIA DIRECTLY TARGETING SOX9

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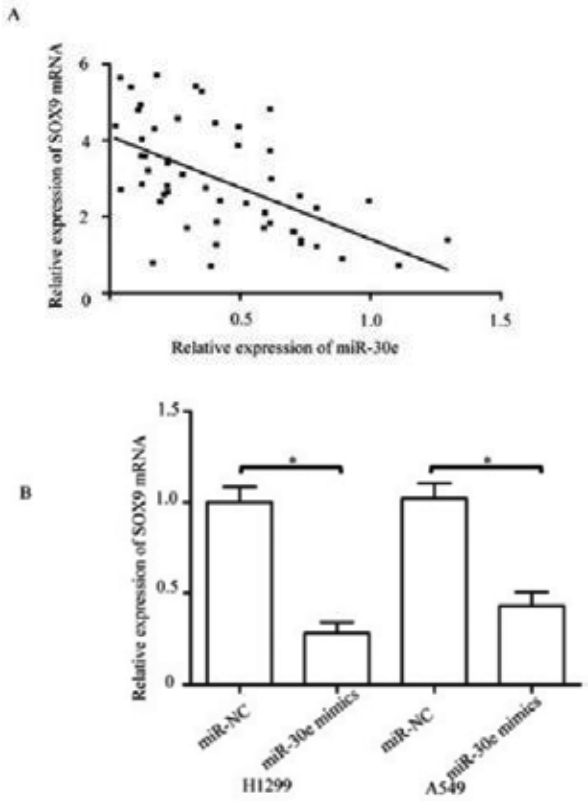
Background: Previous studies reported that microRNA-30e (miR-30e) was dysregulation in multiple human cancers. However, the expression, functions and molecular mechanism of miR-30e in NSCLC remains unknown. In this study, we found that miR-30e expressed at low levels in NSCLC tissues and NSCLC cell lines. **Method:** The miR-30e expression was texted in NSCLC tissues and cell lines by RT-qPCR. We then overexpressed miR-30e expression in NSCLC cells to evaluate its effects in regulating NSCLC proliferation and invasion in vitro. Moreover, the mechanisms underlying the biological roles of miR-30e in NSCLC were investigated using luciferase reporter assay.



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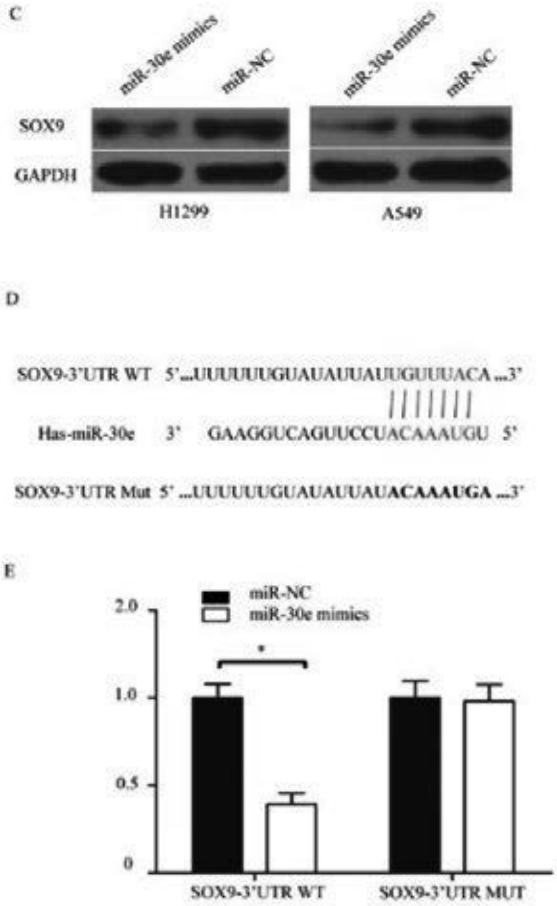

Result: In NSCLC cell lines, enforced expression of miR-30e inhibited cell proliferation and invasion *in vitro*. In addition, miR-30e negatively regulated SOX9 expression through directly binding to the 3'UTR of SOX9, and an inverse correlation was found between miR-30e and SOX9 mRNA expression level in NSCLC tissues. Moreover, SOX9 knockdown led to decreased proliferation and invasion of NSCLC cells. **Conclusion:** miR-30e is downregulated in NSCLC and inhibits cell proliferation and invasion, possibly by directly targeting SOX9.

Keywords: non-small cell lung cancer, microRNA-30e, SOX9

P2.03 BIOLOGY
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P2.03-24 CD90 ENHANCES METASTASIS BY EPITHELIAL-MESENCHYMAL TRANSDIFFERENTIATION IN LUNG ADENOCACINOMA

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Background: The specific mechanism of lung cancer remains unclear. The existence of cancer stem cells(CSCs) reflects the cellular heterogeneity within tumors,and we presume that CD90^{pos} lung adenocarcinoma(LA) cells play the role of CSCs. The epithelial-to-mesenchymal transition (EMT) is a de-differentiation process that has been implicated in metastasis and generation.In this study, CD90^{pos} CSC were isolated and characterized from LA cell line A549, and we discovered that the specific subtype displayed CSCs and epithelial-mesenchymal transition phenotypes. **Method:** Section not applicable **Result:** 1. CD90^{pos} CSC was isolated and characterized from LA cell line A549. 1)FACS assay was utilized to isolated CD90^{pos} cells from LA cell line A549 ,we found that adherent A549 cells possess much lower proportion of CD90 than A549 sphere cells, indicating that CD90 maybe the potential CSCs marker. 2) CD90^{pos} cells expressed higher stemness genes Oct4 and Nanog via Western blot analysis. Also the clonal formation and sphere formation assay by CD90^{pos} and CD90^{neg} cells was performed, and the former highly expressed proliferation capability. 3) The tumorigenicity assay in nude mice showed CD90^{pos} cells highly expressed tumorigenicity in vivo, which possessed shorter latency stage and formed larger xenograft nodes. 2. CD90^{pos} cells possessed highly metastasis and invasiveness associated with epithelial mesenchymal transition. 1) Migrative and invasive ability of CD90^{pos} cells was measured by migration and Transwell invasion assay, and we found that CD90^{pos} cells with higher migrative and invasive ability in vitro compared with CD90^{neg} cells. 2) To further confirm upper observation, an experimental tail vein metastasis model was performed in vivo,and CD90^{pos} cells displayed a superior ability to metastasize to the lung. 3) RT-PCR measurement of gene expression related with EMT showed same tendency compared with Western blot analysis and immunofluorescence assay.MMP2 was higher expression in CD90^{pos} cells, also transcription factors Twist increased significantly, in which mould be involved in the EMT phenotype maintaining. 3. CD90 expression has important clinical significance for patients with LA. **Conclusion:** CD90 is a effective marker for isolation and enrichment of LCSCs. CD90^{pos} cells highly expressed stem cell related genes, self-renewal capability in vitro, showed stronger tumorigenicity in vivo. Furthermore, CD90^{pos} cells possesse higher metastasis and invasiveness, which is associated with EMT.CD90^{pos} cells are endowed with EMT phenotype and show an decreased expression of E-cadherin, and increased expression of N-cadherin, vimentin, MMP2, which would be associated with Twist. Expression of CD90 is negatively correlated with survival time in the metastatic sites instead of primary sites.

Keywords: CD90, lung cancer, epithelial-mesenchymal transition

P2.03 BIOLOGY
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P2.03-25 LOSS OF EXPRESSION RATHER THAN CYTOPLASMIC MISLOCALIZATION OF RUNX3 PREDICTS WORSE OUTCOME IN NON-SMALL CELL LUNG CANCER

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Background: Functional inactivation of RUNX3 through epigenetic silencing was well-documented in many cancers. Added to gene mutation and promoter hypermethylation, cytoplasmic mislocalization was another major manifestation of RUNX3 dysfunction in malignancies like gastric cancer. We aimed to investigate whether NSCLC patients with different RUNX3 expression patterns would have differrent OS, and the associations of different patterns with clinicopathologic parameters and clinical outcome. **Method:** Expressions of RUNX3 and Ki-67 were immunohistochemically detected in normal lung tissue (n=5) and surgically resected NSCLC patients (n=188). The optimal cutoff of RUNX3 was determined by X-tile software related to their survival. Apoptotic index in cancerous tissue was evaluated by TdT mediated dUTP-biotin nick end labelling (TUNEL) method. The prognostic significance of different expression patterns of RUNX3 was determined by means of Kaplan-Meier survival estimates and log-rank tests. **Result:** Loss of RUNX3 expression in NSCLC was correlated with low cancerous apoptotic index ($P<0.001$), shorter OS and worse prognosis ($P=0.0142$), while no statistical difference of apoptotic index ($P=0.73$) or survival ($P=0.3781$) had been determined between patient subgroups with different localization of RUNX3 expression.

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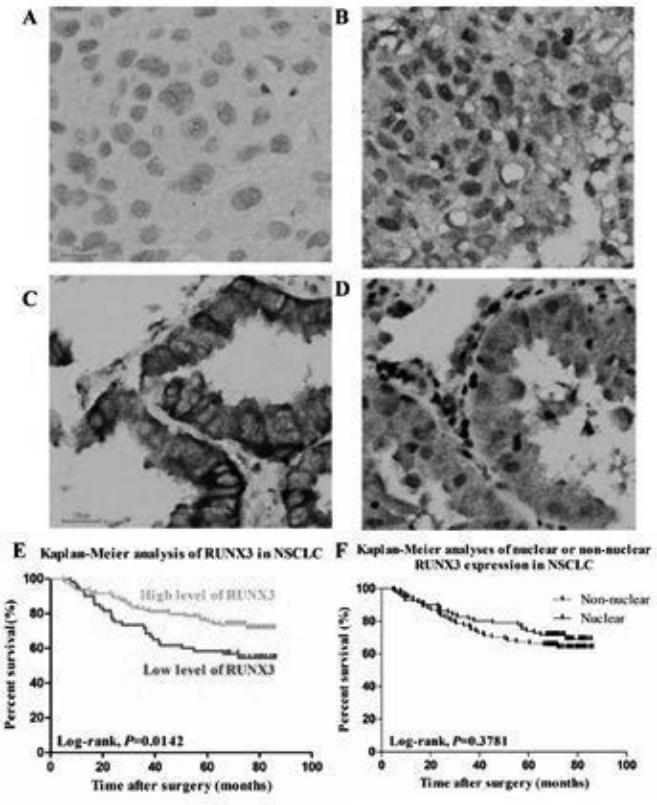

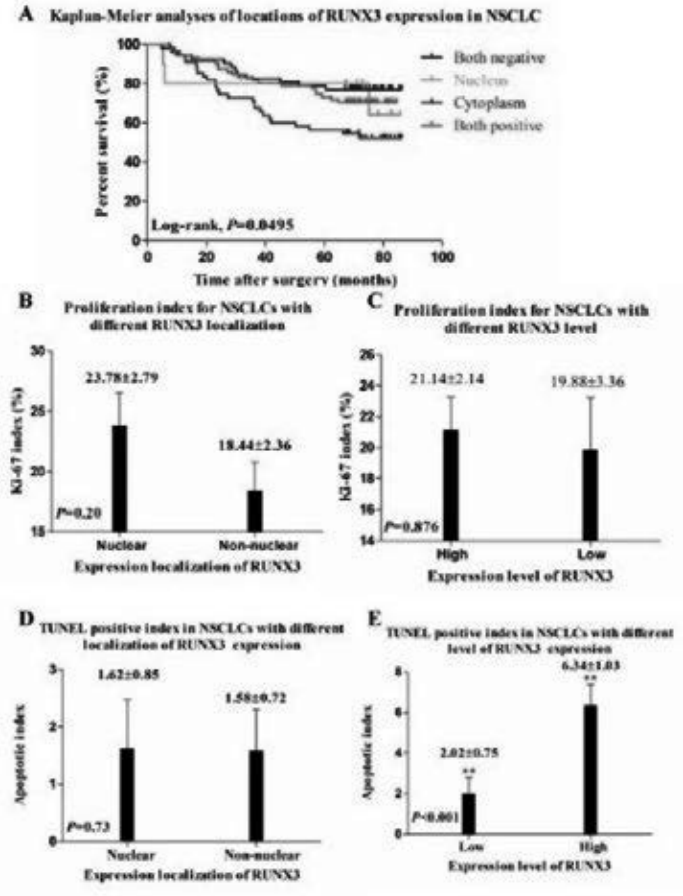

Conclusion: Loss of expression rather than cytoplasmic mislocalization of RUNX3 predicted worse outcome in NSCLC, which was quite different from what it manifested in other cancer types.

Keywords: RUNX3, cytoplasmic mislocalization, non-small cell lung cancer

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P2.03-26 A PROSPECTIVE COHORT STUDY OF TMB AND DETERMINANTS OF CTDNA DETECTION BY COMPREHENSIVE GENOMIC PROFILING IN STAGE I LUNG ADENOCARCINOMAS

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Background: Plasma tumor mutational burden (TMB) is a predictor of immune checkpoint inhibitors treatment in advanced lung cancer patients. A preliminary study has shown the feasibility of PD-1 treatment in resectable lung cancer. However, few studies investigated TMB and plasma circulating tumor DNA detection in stage I lung adenocarcinomas. **Method:** We prospectively enrolled 67 consecutive patients with pulmonary nodule who intended to undergo curative lung resection (NCT03320044). Comprehensive genomic profiling were used to identify somatic variants in both tissue and matched blood samples. Tissue clonal mutations were defined if mutations were in the cluster with the highest mean variated allele frequency with PyClone. **Result:** Mean effective depth of coverage of 1045x and 27410x were obtained in tissue and plasma samples, respectively. Resected stage I lung adenocarcinoma patients were included (4 IA1, 20 IA2, 9 IA3, 12 IB)(Fig.1). An increasing tissue TMB was detected in Stage IA1, Stage IA2, Stage IA3 (1.5mut/Mb, 3mut/Mb, 4mut/Mb, p<0.05). Mixed invasive subtype appeared the highest TMB, followed by invasive adenocarcinoma and minimally invasive adenocarcinoma (4mut/Mb, 3mut/Mb, 1mut/Mb, p<0.05). A significant rise of TMB was identified in pure ground-glass nodule, subsolid nodule and solid nodule (1.5mut/Mb, 2 mut/Mb, 4 mut/Mb, p<0.05). 30.3 % (10/33) patients were demonstrated to be ctDNA-positive with a mean ctDNA abundance of 0.0415% (ranged from 0.012 to 0.119%). A series of factors such as gender, pleural invasion and solid tumor size affected ctDNA detection. 50% patients detected clonal alterations in plasma. Unlike tissue, blood TMB showed no relation with clinical-pathological characteristics.

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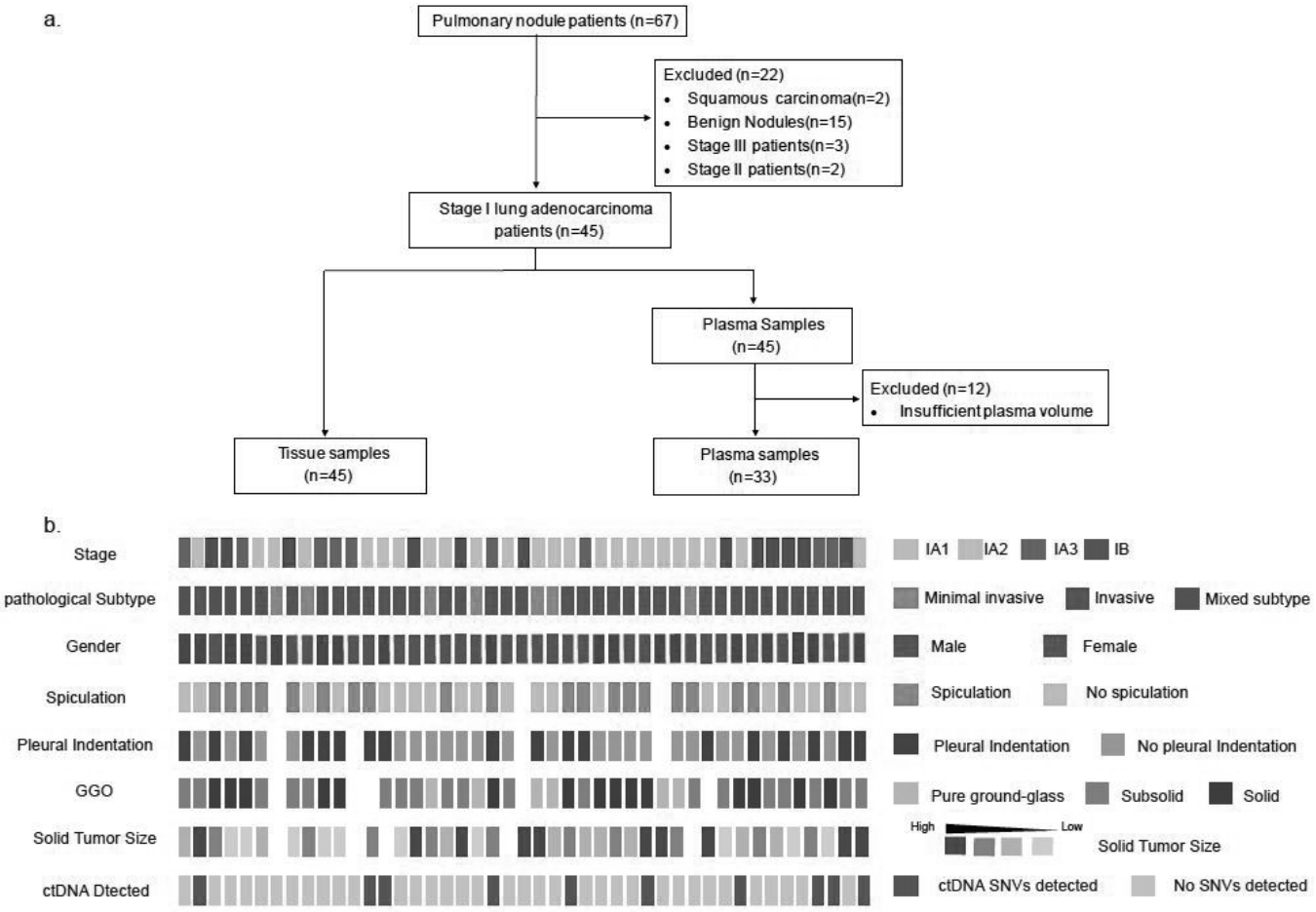

Figure 1. a) Flowchart of the research. b) Clinical features and ctDNA detection of 45 enrolled patients.

Conclusion: We evaluated the feasibility of TMB and determinants of ctDNA detection in stage I lung adenocarcinomas. TMB was related to the invasiveness of tumor, while no such correlation were found in ctDNA. Improving the sensitivity of ctDNA detection, such as incorporated methylation or cancer-related antibodies detection, may be necessary in early stage patients.

Keywords: Circulating Tumor DNA, Tumor mutation burden, early stage

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P2.03-27 POLYMORPHISMS IN FOLATE METABOLISM RELATED GENES AFFECT THE SURVIVAL OUTCOMES OF EARLY-STAGE NON-SMALL CELL LUNG CANCER

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Background: Cellular folate status influences the DNA stability and integrity, and many epidemiologic, animal and human studies suggest that folate status modulates carcinogenesis. This study was conducted to investigate the association between single nucleotide polymorphisms (SNPs) in genes involved in folate metabolism and survival outcomes of surgically resected non-small cell lung cancer (NSCLC). **Method:** We genotyped 182 potentially functional SNPs in folate metabolism pathway in a discovery study involving 354 NSCLC patients who underwent curative surgery. A replication study was performed in an independent cohort of 428 patients. **Result:** In the discovery set, 38 SNPs were significantly associated with survival outcomes in multivariate analyses. Among these, two SNPs (*ALPL* rs2242421G>A, *MTHFD1L* rs9397033A>T) were replicated in the replication set. In combined analysis, *ALPL* rs2242421G>A was significantly associated with better overall survival under a codominant model (adjusted hazard ratio [aHR] = 0.72, 95% confidence interval [CI] = 0.59-0.88, P = 0.002). *MTHFD1L* rs9397033A>T was significantly associated with worse disease-free survival under a recessive model (aHR = 1.45, 95% CI = 1.13–1.87, P = 0.004). In a luciferase assay, the rs2242421A allele showed significantly higher luciferase activity than the rs2242421G allele (P = 0.02) in H1299 cell lines. Consistently, the level of *ALPL* mRNA expression in tumor tissues increased as the number of A allele increased (P trend = 0.05). **Conclusion:** Our results suggest that the 2 SNPs, especially ALPL rs2242421G>A could be used as a biomarker for predicting the clinical outcomes of patients with early stage NSCLC.

Keywords: non-small cell lung cancer, polymorphisms, folate

P2.03 BIOLOGY
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P2.03-28 WHOLE EXOME SEQUENCING TO DISCOVER LUNG TUMOR PREDISPOSITION IN WOMEN WITH PREVIOUS BREAST CANCER

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Background: During their life, women treated for breast cancer (BC) are at risk to develop lung cancer (LC); this risk is increased in smokers and if adjuvant radiation (aRT) was administered for BC. The relative risk of LC after treated BC ranges from 1.38 to 5.05. We hypothesized that genetic variants might predispose patients (Pts) to develop LC after BC. Our aim was to perform whole exome sequencing (WES) to identify genes associated with such predisposition. **Method:** 28 women who developed LC after BC (Study Population, SP) and 32 women treated for BC and with no secondary cancer after a follow-up ≥10 years (control population; CP) were enrolled. DNA was extracted from tumors and normal tissue samples from both SP and CP. Libraries were prepared with Agilent SureSelect All Exon kit and sequenced on Illumina HiSeq2500. Variant calling was performed with FreeBayes software. **Result:** The median age of SP at BC diagnosis was 63.5 years (range: 47-76); the median interval between diagnosis of BC and occurrence of LC was 4.5 years (range: 0-11). 13 Pts (46%) were never-smokers and, among the 21 Pts who had received aRT, 13 (62%) developed ipsilateral LC. At somatic analysis, no common mutation among known driver genes was shared between each BC and LC pair. WES performed on BC and LC samples identified two mutational signatures (S1 and S2). S1 (C>T substitutions) was observed in all BC samples and 16/28 (57%) LC samples and was more frequent in never-smokers (11 vs. 5 Pts) and among Pts who developed ipsilateral LC after aRT (10 vs. 6 Pts). S2 (C>A transversions) was observed in 12/28 LC samples (43%) and was strongly associated with smoking habit (10 vs. 2 Pts). When compared to COSMIC libraries, S2 resulted similar to COSMIC 4, common in LC samples collected from smokers. Since S1 was largely shared between paired BC and LC samples, we explored the eventuality of a genetic predisposition to S1-related malignancies with a gene-based burden test over rare germline variants in normal tissue of S1-LC Pts compared to CP Pts; 249 candidate genes were identified (FDR<0.05). **Conclusion:** Our data identify two mutational S underlying the LC development. Germline analysis suggests that genetic variants may contribute to increase the risk of LC after BC.

Keywords: lung cancer, Breast cancer, Whole exome sequencing

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P2.03-29 PROGNOSTIC SIGNIFICANCE OF PHOSPHORYLATED FYN IN PATIENTS WITH LUNG ADENOCARCINOMA

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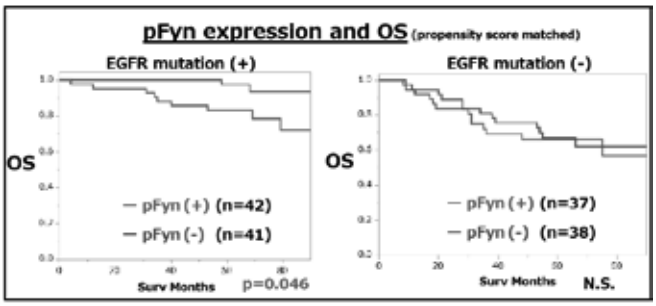
Background: Src family tyrosine kinases, including Fyn, are non-receptor tyrosine kinases and they are known to drive malignancy in various kinds of cancers. Some papers have reported that Fyn is an effector of EGFR signaling. Additionally, Fyn is recognized as an additional therapeutic target. However, little is known about the clinical importance of phosphorylated Fyn (pFyn) in lung adenocarcinoma. The purpose of the present study is to clarify the prognostic significance of pFyn in lung adenocarcinoma. **Method:** A total of 251 lung adenocarcinoma specimens were collected from patients who underwent surgery in our institute. Tissue microarrays (TMA) were assembled from paraffin-embedded tumor blocks. We analyzed pFyn expression through immunostaining of TMA and classified them as 0, +1, +2, +3. The association between pFyn expression as well as the patients' clinical information was statistically analyzed. Correlations were compared using Pearson's chi-square test and overall survival (OS) were compared using the log-rank test after propensity score matching (age, gender, smoking history, pathological stage, EGFR mutation status, and p53 mutation status). The Institutional Review Board approved this study and informed consent for tumor tissue usage was obtained pre-operatively. **Result:** Unadjusted pathologic stage distributions by TNM classification (WHO, 7th edition) were as follows: Stage 1A: 128 patients, Stage 1B: 73, Stage 2A: 23, Stage 2B: 4, Stage 3A: 23. pFyn was positive in 118 cases (47.6%). There was a significant correlation between pFyn expression and gender, pathological stage, p53 mutation status, and poor OS. The propensity score adjusted analysis revealed that the prognosis of pFyn positive group was significantly worse compared to the pFyn negative group (p=0.046), which was observed only in the patients with mutant EGFR.



Conclusion: pFyn expression may affect the prognosis of patients with lung adenocarcinoma in a EGFR mutation dependent manner.

Keywords: phosphorylated Fyn, Adenocarcinoma, EGFR mutation

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P2.03-30 PROTEINS INVOLVED IN NECROPTOSIS AND DNA DAMAGE REPAIR AND SURVIVAL OF STAGE I NON-SMALL-CELL LUNG CANCER PATIENTS

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Background: Survival of patients with stage I non-small-cell lung cancer (NSCLC) was indicative of significant variability with biological complexity. In addition to repairing DNA damage, understanding for necroptosis as new mechanism of cell death is rapidly growing as one of the hallmark of cancer. Therefore, the development of a prognostic biomarker focusing on necroptosis and DNA damage is an intriguing issue. **Method:** Expression of eight proteins (RIPK3, MLKL, PELI1, P53, ATM, gH2AX, Chk2, and BRCA1) and overall survival were investigated in 394 pathological stage I NSCLC patients. **Result:** The proteins involved in necroptosis or DNA damage repair exhibited differential expression between squamous cell carcinoma and other histology. Low expression of RIPK3 showed a trend for having worse survival in the entire cohort. Analysis performed based on histology revealed that expression of RIPK3, PELI1, P53, or BRCA1 was an independent prognostic factor in squamous cell carcinoma patients (aHR, Cox *P*: 2.292, 0.008 for RIPK3; 2.007, 0.033 for PELI1; 0.391, 0.003 for P53; 2.088, 0.018 for BRCA1). When combined effect of RIPK3 or PELI1 with P53 or DNA damage repair proteins analyzed, the effect on survival is was markedly strengthened in squamous cell carcinoma patients. However, these effects were not detected in adenocarcinoma patients. **Conclusion:** Expression or their combination of proteins involved in necroptosis and DNA damage repair is an important determinant of survival in stage I squamous cell carcinoma patients.

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P2.03-31 LNCRNA RGMB-AS1 AFFECTS LUNG ADENOCARCINOMA PROGNOSIS BY REGULATING MICROTUBE ASSOCIATED GENES: A GENOME-WIDE ANALYSIS IN SILICON

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Background: To analyze the co-expression network of long non-coding RNA RGMB-AS1 in lung adenocarcinoma (LUAD) and to investigate its impact on prognosis by mining the molecular mechanisms and prognostic signature in silicon. **Method:** We performed a co-expression analysis of RGMB-AS1 by integrating sixty thousand public Affymetrix microarrays data to reveal its associated signal pathways. QPCR and Western blot were performed to validate the significant genes. Furthermore, survival analysis of data in the Cancer Genome Atlas (TCGA) was applied to seek the prognostic value of RGMB-AS1 and its co-expressed genes. **Result:** The most enriched signal pathways of RGMB-AS1 co-expressed genes

were pathogenic Escherichia coli infection, gap junction and ubiquitin mediated proteolysis. Among the 30 validated genes, we found that a sixteen microtube-associated genes signature is an independent prognostic marker of OS of LUAD patients and demonstrates good performance for predicting 5-year OS.

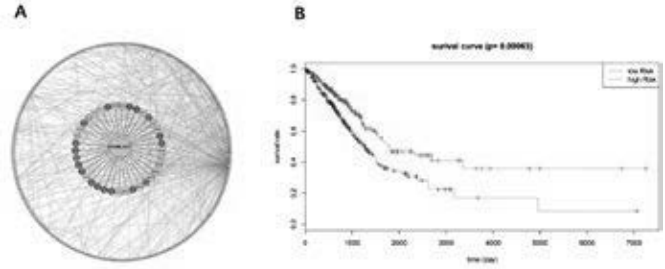

Figure 1 lncRNA RGMB-AS1 Associates With microtube associated proteins (MAPs) which Correlates with LUAD survival. (a) Protein-Protein Interaction (PPI) network of RGMB-AS1 co-expression genes. (B) The sixteen microtube associated proteins signature is an independent prognostic marker of OS of LUAD patients and demonstrates good performance for predicting 5-year OS

Conclusion: Our results suggest that RGMB-AS1 may serve as a novel prognosis indicator and therapeutic target for LUAD patients.

Keywords: lung adenocarcinoma, microtube, RGMB-AS1

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P2.03-32 GENOME-WIDE ANALYSIS OF M6A-MODIFIED RNA BINDING PROTEINS ASSOCIATED WITH LUNG CANCER SURVIVAL

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Background: N6-Methyladenosine (m6A) is a type of RNA modification involved in a variety of biological processes. RNA-binding proteins (RBPs) play a crucial role in post-transcriptional regulation in gene expression. However, no research reveals how m6A-modified RNA binding proteins affect lung cancer survival systematically. **Method:** RNA-seq data were downloaded from NCBI GEO via accession number GSE62944 including both lung adenocarcinoma and squamous lung cancer. The differentiated analysis run by limma bioinformatic package and fold-change more than 1,5 with FDR<0.05 was considered as significant. The optimal cut-off value of low and high expression was defined by X-tile. Cox regression model and log-rank test was applied for survival analysis. **Result:** Eleven out of twenty-nine m6A-modified RNA binding proteins are differently expressed(FC>1.5,FDR<0.05,Figure 1). Furthermore, five RBPs are associated with lung cancer survival. Kaplan-Meier analysis indicated that higher IGF2BP1 or IGF2BP3 expression is associated with poor survival of lung adenocarcinoma (P= 0.00058 and P=0.005171, respectively). Subgroup analysis show that high GNL3 expression is associated with poor prognosis of young and male patients, while its high expression is an indicator of good prognosis in female patients.

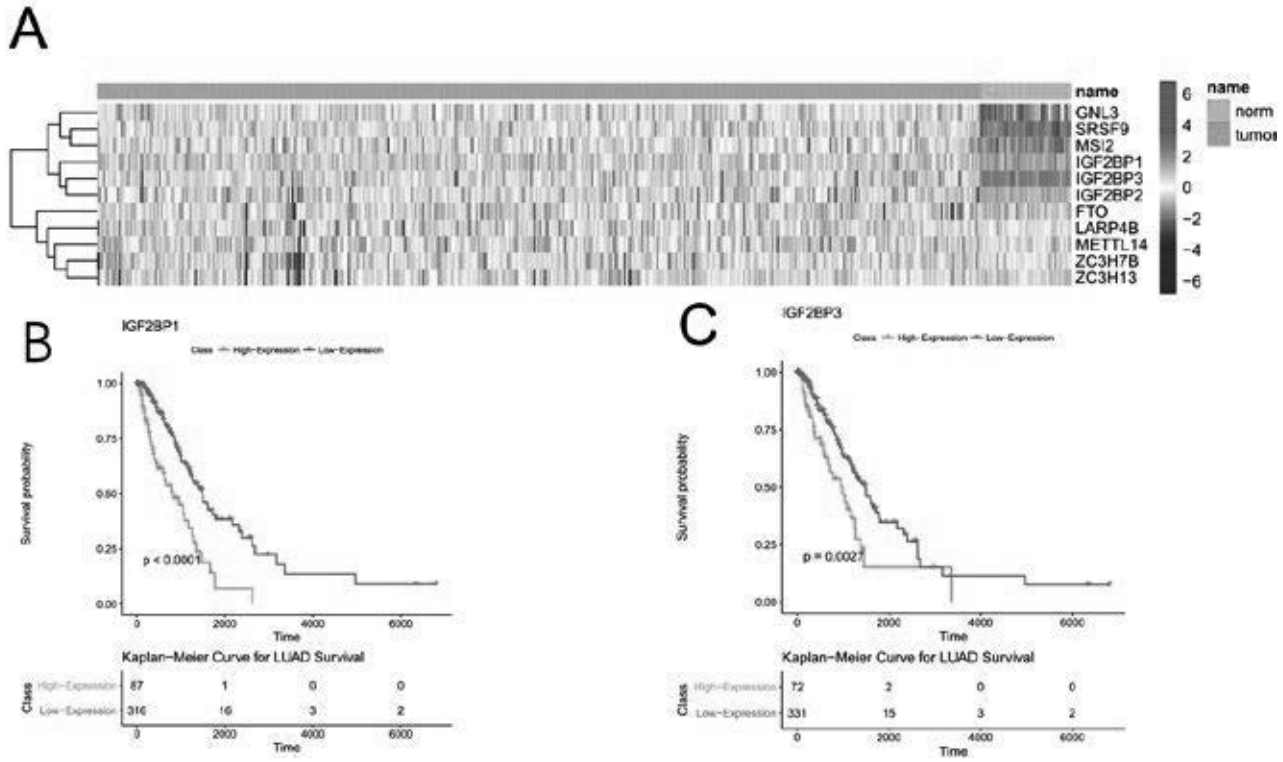

Figure1 Identification of lung cancer survival associated m6A-modified RNA binding proteins. (A) Heatmap shows the deferentially expreesed m6A-modified RNA binding proteins. (B) IGF2BP1 expression is associated with poor survival of lung adenocarcinoma (P= 0.00058). (C) IGF2BP3 expression is associated with poor survival of lung adenocarcinoma (P=0.005171). **Conclusion:** In this analysis, we revealed that IGF2BP1 and IGF2BP3 are potential m6A targets which may affect lung adenocarcinoma survival. Further biomolecular experiments are warranted.

Keywords: lung adenocarcinoma, m6A, survival

P2.03-33 ANTI-AGING GENE, KLOTHO IS A PREDICTIVE FACTOR OF PEMETREXED FOR LUNG CANCER TREATMENT

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Background: Adjuvant chemotherapy of lung cancer including cisplatin is recommended for patients with lung cancer p-stage IB-IIIA, who were received surgical resection completely. In order to improve the prognosis of the patients with lung cancers, we need to find a new predictive factor for anti-cancer agents and establish a new adjuvant chemotherapy. We reported that anti-aging gene Klotho expression was a prognostic factor for small cell lung cancer and LCNEC so far. In this study, we evaluated that the expression of Klotho was a prognostic factor and predictive factor for lung cancer treatment. **Method:** We established a cell line, A549/Klotho, which stably overexpress Klotho. Next, we checked expression of Epithelial-Mesenchymal Transition related protein such as N-cadherin, E-cadherin, Snail, Vimentin, etc, by Western blot analysis. Finally, We examined the sensitivity test for various anticancer agents including pemetrexed, CDDP, paclitaxel, gefitinib, etc, using A549 cells and A549/Klotho cells. **Result:** In Western blot analysis, no expression of N-cadherin was observed. This result indicated that overexpressing Klotho inhibit the expression of N-cadherin, and suggest that Klotho can regulate the EMT. Secondly, we performed sensitivity test by MTT assay. A549/Klotho cells were more sensitive seven times against pemetrexed compared to A549 cells (IC50; 0.1 micro M). There is no difference of sensitivity between A549/Klotho cells and A549 cells against molecular target drugs such as gefitinib. **Conclusion:** From these result, we conclude that overexpression of Klotho may regulate the sensitivity against pemetrexed through the inhibition of N-cadherin. In the future, we may establish a new strategy of adjuvant chemotherapy for lung cancer based on the expression of anti-aging gene Klotho.

Keywords: pemetrexed, lung cancer, Klotho

P2.03-34 THE RELATIONSHIP BETWEEN TREATMENT RESPONSE AND SERUM EGFR LEVEL IN NONSMALL CELL LUNG CANCER

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Background: Early diagnosis and the improvement in the treatment options in cancer patients can prolong the survival in the majority of malignancies, although they add no benefit to the survival of patients with non-small cell lung cancer (NSCLC). Some patients with NSCLC respond to the treatment well while others do not. Therefore, new prognostic factors and biomarkers other than the stage of disease should be explored in NSCLC. The management of NSCLC may be different according to those biomarkers. The new biomarkers may help to the clinicians to identify who patients have poor prognosis and respond to the specific treatment. **Method:** The aim of this study is to investigate whether there is a relationship between the response to treatment and serum level of active EGFR or not. Thirty-three patients with locally advanced, metastatic or recurrent non-small cell lung cancer were enrolled into this study. Cisplatin docetaxel treatment was planned for those patients. Baseline and at the end of second and forth cycle of the treatment, serum EGFR were measured. Patients were divided into 2 groups according to their response to the treatment.SPSS7.0 was used to analyse patient data. Student t test and Mann-Withney U tests were used for the comparison between the groups' averages. Spearmann rho and Ki square tests were used to evaluate the relationships between parameters. Kaplan-Meier method was used for the survival analysis. **Result:** Of 33 patients, 4 were female and 29 were male. The average of age of patients was 52. 12 patients were stage III, 21 were relapsed or stage IV. Objective response rate and overall response rate were found 15.6%, 34.4% respectively. Progression occurred 34.4% among patients in the study. When serum EGFR level cut off is 0.080 fmol/ml, while in patients who didn't respond, the positivity of serum EGFR level was 55.6%, it was 80% in patients who responded. Baseline serum EGFR levels were higher in patients with stage III disease compared to those of patients with relapsed and stage IV disease. In patients who responded to the therapy, baseline serum EGFR levels were found higher than those of the patients who didn't respond regardless of the stage. Following two cycles of treatment, if serum EGFR level is found high, then the probability to respond to the treatment increases significantly. **Conclusion:** In conclusion, the serum level of EGFR seems to be a useful biomarker for predicting and monitoring the response to the treatment in patients with NSCLC.

Keywords: Serum EGFR level, non-small cell lung cancer, Prognosis

P2.03-35 NON-SMALL-CELL LUNG CANCER WITH SMO GENE VARIANTS OF UNCERTAIN SIGNIFICANCE SHARE DISTINCT MOLECULAR FEATURES

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Background: Recently, alterations of the Smoothened (*SMO*) gene (mutation, amplification, mRNA overexpression) were found in 12.2% of tumors of The Cancer Genome Atlas (TCGA) lung adenocarcinomas by whole-exome sequencing. While the genetic locus of *SMO* mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *SMO* mutations. **Method:** A total of 423 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *SMO* mutation and other genes were detected by next generation sequencing. **Result:** *SMO* gene mutation rate was 2.60% (11/423) in non-small cell lung cancer, including T179M (4 patients), S566R (1 patient), P694Lfs*82 (1 patient), S590T (1 patient), P693S (1 patient), P60L (1 patient), E211D plus G212C (1 patient) and M230I plus A289T (1 patient), and median overall survival (OS) for these patients was 24.0 months. Among them, all patients were *SMO* gene with co-occurring mutation. Briefly, patients with (n=6) or without (n=5) co-occurring *EGFR* mutations had a median OS of 19.0 months and 25.0 months respectively (P=0.23); patients with (n=2) or without (n=9) co-occurring *TP53* mutations had a median OS of 19.0 months and 25.0 months respectively (P=0.36); patients with (n=3) or without (n=8) co-occurring *KRAS* mutations had a median OS of 23.0 months and 24.0 months respectively (P=0.75); patients with (n=4) or without (n=7) co-occurring *BRCA2* mutations had a median OS of 16.0 months and 24.0 months respectively (P=0.01). **Conclusion:** *SMO* mutations may be a potential novel mechanism of acquired resistance in *EGFR*-mutated NSCLC patients. *EGFR*, *TP53* and *KRAS* gene accompanied may have less correlation with *SMO* mutation in NSCLC patients. *BRCA2* accompanied mutations might play a worse prognosis in *SMO* gene mutation NSCLC. Screening of *SMO* alteration by the role of the Hh pathway suggests new opportunities to design new treatment strategies in NSCLC.

Keywords: SMO mutation, Non-small-cell lung cancer, Prognosis

P2.03-36 DNA METHYLATION: A MORE SENSITIVE MARKER FOR TREATMENT MONITORING?

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Background: Detection of genomic aberrations in cell-free DNA (cfDNA), requiring ultra-deep sequencing due to the low allelic frequencies (AF) of mutation, has been utilized to monitor treatment response. However, 20%-30% of patients yield no mutation from plasma genotyping despite deep sequencing depth, thus necessitating alternative monitoring method. The role of aberrant DNA methylation in the process of tumorigenesis both at individual genes and a genome-wide scale has been well elucidated. We investigated the potential of DNA methylation as a biomarker for treatment monitoring. **Method:** We investigated the performance of mutation and DNA methylation as biomarkers to evaluate response to osimertinib using a DNA methylation panel consisting of 100,000 CpG sites and a targeted panel for mutation detection consisting of 168 lung cancer related genes with an average sequencing depth of 1,000x and 10,000x, respectively. Longitudinal plasma samples from 6 patients undergoing osimertinib were collected prior to treatment and at regular interval until disease progression, ranged from 6 to 9 times. Methylation level of a given sample was reflected by the percentage of significantly methylated blocks, which were significantly hypermethylated blocks comparing to healthy individuals. **Result:** All patients had *EGFR* sensitizing mutation and T790M at baseline. Four patients had additional concurrent mutations, including *TP53*, *RB1*, *OR6F1* and *BRCA2*. At PD,

all patients had detectable mutations except for one and 3 developed *EFGR* C797S. Four patients had at least two times of no detectable mutation during treatment. Among them, P05 and P06 had 5 and 6 times of no detectable mutation, respectively. In contrast, all patients had significantly methylated blocks detected at every point. In general, the trend of changes in mutation AF corresponds to the changes in the percentage of significantly methylated blocks in all patients except for one, who only had mutations detected at baseline and had consistently detectable DNA methylation at every point. Collectively, DNA methylation reached nadir at best response and gradually increased thereafter. An elevation of mutation AF or the emergence of new mutation(s) (molecular PD) was observed in 4 patients prior to PD assessed by imaging. In all patients, an elevation of DNA methylation was observed prior to PD assessed by imaging; among them, 3 had changes in DNA methylation prior to molecular PD, suggesting DNA methylation may be a more sensitive biomarker. **Conclusion:** Collectively, our study demonstrates DNA methylation, continuously increasing from the nadir (best response), can be utilized as a biomarker for treatment monitoring.

Keywords: DNA methylation, osimertinib, cfDNA

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P2.03-37 THE EFFICIENCY OF OCTAMER-4 SPECIFIC CYTOTOXIC T CELLS INDUCE BY CD40-B CELLS IN KILLING LUNG CANCER STEM-LIKE CELLS

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Background: This study aimed to investigate the correlation of Octamer-4 (OCT4) expression with clinicopathological features and prognosis in lung adenocarcinoma patients, and to further explore the killing effect of OCT4 specific cytotoxic T cells (CTLs) on lung cancer stem cells (LCSCs). **Method:** 257 lung adenocarcinoma patients underwent thoracic surgery were enrolled in this study and tissue samples were obtained during the operation. OCT4 expression was detected by immunofluorescence staining assay. CD154$^+$ feeder cells were constructed to transfect CD40-B cells, and then mixed with OCT4 antigen peptides and CD8$^+$ T lymphocytes extracted from peripheral blood of lung adenocarcinoma patients, subsequently the OCT4 specific CTLs were co-cultured with PC9 LCSCs to detect the killing efficacy. OCT4$^+$ phenotype was illuminated to be associated with poor differentiation, worse disease free survival (DFS) and overall survival (OS). And Cox's analysis revealed OCT4$^+$ was an independent predictive factor for shorter DFS and OS. **Result:** CD40-B-cells with antigen presenting capacity was successfully constructed indicated by elevated CD86$^+$, human leukocyte antigens (HLA)-A$^+$ and CD80$^+$ cells percentage, and OCT4 specific CTLs was successfully activated suggested by increased CD3$^+$, CD4$^+$ and CD8$^+$ cells percentage as well as elevated interleukin (IL-2) and interferon (IFN)-γ expressions. OCT4 specific CTLs presented an elevated cytotoxic activity on LCSCs at percentage 75.5% ± 8.2% compared with CMV pp65 CTLs (25.6% ± 5.1%) and blank control CTLs (20% ± 4.7%). **Conclusion:** In conclusion, OCT4 expression could be served as a convincing risk biomarker for prognosis in lung adenocarcinoma patients and potential target of CTLs as immuntherapy in killing LCSCs.

Keywords: Octamer-4 (OCT4), lung adenocarcinoma, Prognosis

P2.04 IMMUNOONCOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.04-01 ASSOCIATIONS HISTOLOGICAL SUBTYPE OF LUNG ADENOCARCINOMA AND PROGRAMMED DEATH LIGAND 1 (PD-L1) EXPRESSION IN TUMOR CELLS.

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Background: The analysis by immunohistochemistry (IHC) of the programmed cell death-ligand 1 (PD-L1) protein expression is the most extensively explored biomarker for response to immunotherapy in non-small cell lung cancer (NSCLC). However, there are differences concerning diverse IHC assays and cut-off criteria: Pembrolizumab with the 22C3 assay with cut-off ranges of >1%, 1-49% and >50%; and Nivolumab with the 28-8 assay and ranges of <1%, 1-5%, 5 -10% and >10%. Furthermore, there is lack of information regarding the association between the histological subtype of adenocarcinoma and PD-L1 expression. In this work, we assessed the frequency of PD-L1 expression according with to histological subtype of adenocarcinoma. **Method:** PD-L1 expression was assessed using the PD-L1 IHC 22C3 pharmDx immunohistochemistry assay (Dako North America, Inc.). We correlated histological subtype of adenocarcinoma with the frequency and intensity of PD-L1 expression, smoking history, *EGFR* and *ALK* status. **Result:** Tissue samples from one hundred and sixty-two were analyzed, of which 33 (20.4%) were excluded due to insufficient material for PD-L1asessment. Among them, 106 patients (71,55%) were female, the median age was 63 years (range 31-86 years), 69 (53.5%) were never-smokers with no exposition to wood smoke or asbestos (79,61.2% and 117, 90.7% respectively). Among the 129 adenocarcinomas, 31.0% were acinar histological subtype; 27.1% solid, 17.1% papillary, 3.9% lepidic, 1.6% micropapillary and 54.3% had a moderated tumor differentiation grade. According to PD-L1 score, 49 (38%) of the patients were classified as negative (PD-L1<1%), 71(55%) as poor PD-L1 expression (1 - 49%), and 9 (7%) as strong PD-L1 expression (≥50%). According to the IASLC/ATS adenocarcinoma histological subtype was associated with PD-L1 expression (p=0.003). Solid and acinar adenocarcinomas were more likely to present strong PD-L1 expression (55.6% & 33.3%, respectively) compared to lepidic, papillary, micropapillary and unspecified tumors, which presented a strong PD-L1 expression in up to 11.1%. Median PFS to first line therapy was 10.3 (95% CI: 6.1–14.5) months. Tobacco exposure was the only factor independently associated with an increase in the hazard of progression to first line therapy (either CT or TKI) from any cause among NSCLC patients (HR, 95% CI: 1.56-12.1). The median OS was 41.9 (95% CI: 10.9–72.9) months. Median OS differences were not found among PD-L1 (negative vs. positive: 60.6 vs. 31.3 months, p=0.685). **Conclusion:** Patients with adenocarcinoma tumors, solid histological subtype and poor differentiation grade can be more benefited with a PD-1 based immunotherapy. PD-L1 score can be a predictor factor for the response to first line chemotherapy.

Keywords: Programmed-death receptor ligand 1, Immunotherapy, NSCLC

P2.04 IMMUNOONCOLOGY
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P2.04-02 PREDICTIVE VALUE OF CIRCULATING TUMOR CELLS AND CIRCULATING FREE DNA IN NSCLC PATIENTS TREATED WITH NIVOLUMAB

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Background: Immunotherapy represents a dramatic change in the treatment of non small cell lung cancer (NSCLC), but nowadays prognostic and predictive factors of response to immune checkpoint inhibitors (ICIs) are still under debate. It has been observed that circulating biomarkers might have a prognostic role in lung cancer. The aim of this study was to determine whether circulating tumor cells (CTCs) as well as circulating free DNA (cfDNA) might predict the outcome of patients with advanced NSCLC treated with Nivolumab. **Method:** From May 2015 to April 2017 89 NSCLC patients were treated with Nivolumab as a second or further line of therapy. All patients underwent blood sample collection before the start of treatment (baseline) and after 4 and 7 cycles of Nivolumab to evaluate both biomarkers. CTCs were isolated from 3mL of blood by the filtration-based device ScreenCell Cyto (ScreenCell) according to manufacturer's protocol. cfDNA was extracted from plasma using the QIAamp DNA Blood Mini Kit (Qiagen) and quantified (ng/mL) by qPCR method, using *hTERT* single copy gene. The median baseline CTC number and cfDNA content were used as cut-off values to discriminate patients with different outcomes. An univariate analysis was done to evaluate the overall survival (OS) in the study population based on CTC and cfDNA using the Kaplan Meyer method. **Result:** The median CTC number and cfDNA at baseline were 2/3mL and 836.5 ng/mL, respectively. Median OS was 8.8 and 6.2 months for patients with baseline CTC ≤2 and >2, respectively (HR 1.53, 95% CI 0.96-2.42; *p*=0.072). Similarly, patients with high level of cfDNA > 836.5 ng/ml showed a worse OS as compared with those having lower cfDNA: 5.1 vs 9.4 months (HR 1.63, 95% CI 1.02-2-59; *p*=0.040). **Conclusion:** A statistically significant advantage in terms of OS was observed in the group of patients with baseline cfDNA below the median value. Similarly, a longer survival, although of borderline significance, was observed in the group of patients with baseline CTC ≤2. Longitudinal change evaluations of both circulating biomarkers compared to radiological tumor size are currently ongoing.

Keywords: circulating free DNA, Circulating tumor cells, Immunotherapy

P2.04-03 NF-κB AND HIF-1α PLAY IMPORTANT ROLES IN REGULATING PD-L1 EXPRESSION BY EGFR OR KRAS MUTANTS IN NON-SMALL CELL LUNG CANCER CELLS

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Background: Programmed death ligand 1 (PD-L1) is expressed in various human tumors and is of critical importance for the immune escape of tumor cells. Some driver gene mutations including EGFR and KRAS have been reported to be involved in PD-L1 expression regulation. However, the potential role and precise mechanism of EGFR and KRAS mutants in PD-L1 expression regulation in non-small cell lung cancer (NSCLC) remain obscure. **Method:** The expression levels of PD-L1 and key molecules of EGFR and KRAS signaling pathways were examined in 11 NSCLC cells with wild-type or mutant EGFR and KRAS genes. Additionally, ectopic expression or depletion of EGFR or KRAS mutants and pharmacological inhibitors of MEK/ERK, PI3K/AKT, IκBα, and HIF-1α were employed to elucidate the effects of activation or inhibition of EGFR or KRAS pathway on PD-L1 expression regulation in NSCLC cells. The effects of pathway inhibitors on tumorigenesis and PD-L1 expression of EGFR or KRAS-mutated NSCLC cells were also examined using xenograft mouse model, Furthermore, the correlations between EGFR and KRAS status and protein levels of HIF-1α and PD-L1 were analyzed in 97 NSCLC tissues. **Result:** Examination of the EGFR and KRAS signaling cascades in NSCLC cells revealed an apparent association of PD-L1 overexpression with activation of MEK/ERK and PI3K/AKT pathways, especially with increased protein levels of p-IκBα and HIF-1α. Notably, ectopic expression or depletion of EGFR or KRAS mutants and administration of EGFR or KRAS pathway inhibitors showed important interplay and cooperation between NF-κB and HIF-1α in PD-L1 expression regulation in NSCLC cells. Furthermore, administration of EGFR or KRAS pathway inhibitors significantly inhibited xenograft tumor growth and PD-L1 expression of NSCLC cells in nude mice. Moreover, NSCLC tissues with positive HIF-1α staining presented significantly increased positive rate of PD-L1 expression compared with tissues scored HIF-1α negative (49.1% vs. 20.5%, $P = 0.003$). NSCLC tissues with EGFR or KRAS mutants showed obviously elevated expression levels of HIF-1α and PD-L1 compared with tissues carrying wild-type EGFR and KRAS genes (68.4% vs. 43.4%, $P = 0.018$ and 50.0% vs. 28.3%, $P = 0.035$, respectively). **Conclusion:** Taken together, both EGFR and KRAS mutants were identified to regulate PD-L1 expression via signaling effectors, NF-κB and HIF-1α, suggesting the correlation between driver gene mutations and tumor immune escape in NSCLC.

Keywords: EGFR, KRAS, PD-L1, NF-κB, HIF-1α, NSCLC.

P2.04-04 EXPRESSION OF INTRATUMORAL PROGRAMMED CELL DEATH-LIGAND 1 (PD-L1) AND INTRATUMORAL CD4⁺T CELL, CD8⁺T CELL AND FOXP3⁺T CELL IN LUNG CANCER

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Background: Overexpression of PD-1 and PD-L1 induces immune evasion by cancer cells. Blockade of this immune checkpoint could reverse the tumor immune system and activate the anti-cancer response. Nivolumab and pembrolizumab, anti-PD-1 antibodies, were recently approved for the treatment of advanced NSCLC. A PD-L1 positive expression status by immunohistochemistry (IHC) has been associated with a favorable response. However responses to these drugs are limited, with the objective response rate ranging between 20%-30%. These results suggest that individual tumor microenvironments vary according to the immune evasion process of each cancer tissue. Consequently, the introduction of biomarkers, which predict the responders to the immune checkpoint blockades are necessary in clinical practice. $FOXP3^+CD4^+$ regulatory T cells recognizing tumor-specific shared antigens maintain the immunological self-tolerance and suppress the activation of T cells in cancer tissue. Moreover, anti-CTLA-4 monoclonal antibody therapy reduces $FOXP3^+CD4^+$ expression in cancer tissue. However, the precise conditions and diagnostic value of these immunological factors remain uncertain and specific biomarkers predictive of response have not yet been identified. **Method:** PD-L1, CD4, CD8 and FOXP3 expression in tumor cells and tumor infiltrating lymphocytes (TILs) were examined by IHC in 45 cases (including 32 cases of adenocarcinoma and 13 cases of squamous cell carcinoma) with advanced lung cancer treated with nivolumab or pembrolizumab. Histologic subtypes, tumor stage and other clinicopathologic conditions were compared with the level of their expression. **Result:** Expression of PD-L1 expression in tumor cells was detected in 75.6% of the cases. The objective response rate was 46.7%, and it was significantly correlated PD-L1 positivity with CD8 TILs ($p<0.0001$). Eleven cases having driver gene mutations did not show a tendency towards favorable response. Cases with PD-L1 overexpression showed consistently dense $CD8^+$ TILs, even in subgroup analyses according to histological subtype, stage, age and smoking status. In cancer-associated stroma, $CD4^+$ cells and $FOXP3^+$ positive cells were detected, and cases with PD-L1-, low $CD8^+$, and $FOXP3^+$ status were also detected. **Conclusion:** Overexpression of PD-L1 with $CD8^+$ TILs was associated with a favorable response to treatment with nivolumab and pembrolizumab. In contrast, PD-L1- with low $CD8^+$ TILs and $FOXP3^+$ TILs was not associated with favorable response. Therefore, assessment of PD-L1, $CD8^+$ TILs and $FOXP3^+$ TILs by IHC may be valuable for predicting response to treatment with nivolumab and pembrolizumab. PD-L1- and $CD8^+$ TILs and $FOXP3^+$ TILs may be indicative of a combination with other therapeutic agents. Investigation of novel combinations of immunotherapy according to individual tumor microenvironments is warranted.

Keywords: PD-L1, CD8+ T cell, FOXP3+ T cell

P2.04-05 CORRELATION BETWEEN PD-L1 GENE PROMOTER POLYMORPHISMS AND EXPRESSION OF PD-L1 MRNA AND PROTEIN IN NSCLC PATIENTS.

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Background: Immunotherapy, the most novel approach to cancer treatment, gives a promising option for non-small cell lung cancer (NSCLC) patients. Most drugs targeting PD-1 or PD-L1 have been proven to be effective when cancer tissue expresses PD-1 or PD-L1 protein on its surface. The promoter region of *PD-L1* gene is responsible for regulating the gene expression, thus in effect the expression of the protein. We decided to check whether single nucleotide polymorphisms (SNPs) in *PD-L1* gene promoter region may affect this expression. **Method:** The study included 47 NSCLC patients (20 male, 27 female; median age 65±7.6). PD-L1 protein expression was analysed using two IHC assays with SP142 and 22C3 antibodies, on corresponding analysis platforms. mRNA was analysed using qRT-PCR method. *PD-L1* gene promoter region polymorphisms [rs822335(C/T) and rs822335(C/G)] were analysed using real-time PCR method, on Illumina Eco platform. The analysis was performed in histological (resected tissue) and cytological (cellblocks from bronchoscopy biopsies) material (FFPE blocks). **Result:** There were significant positive correlations between expression of mRNA of *PD-L1* gene and the percentage of PD-L1 protein positive cells: tumor cells in the reaction with 22C3 antibody ($R=+0.39, p=0.025$), tumor cells in the reaction with SP142 antibody ($R=+0.45, p=0.009$) as well as infiltrating immune cells in the reaction with SP142 antibody ($R=+0.49, p=0.006$). The studied group consisted of 21 CC homozygotes, 23 CT heterozygotes and 3 TT homozygotes in rs822335, and 12 CC homozygotes, 24 CG heterozygotes and 11 GG homozygotes in rs822336 polymorphic sites. Slightly higher ($p=0.08$) percentage of tumor cells with PD-L1 expression was observed in patients with CC genotype compared to patients with CT and TT genotypes in rs822335 polymorphism. We observed significantly higher expression of mRNA for *PD-L1* gene in patients with GG genotype compared to patients with CG genotype ($p=0.05$) in rs822336 polymorphism. Additionally, odds ratio analysis showed that a higher chance of high mRNA expression of *PD-L1* gene occurred in patients with GG genotype as compared to patients with CC genotype ($OR=7.0$, $ch^2=4.46$, $p=0.035$). **Conclusion:** Analysis of PD-L1 expression on tumor cells presents numerous problems – availability of material, tumor heterogeneity, different methods of detection. We have presented that analysis of *PD-L1* gene promoter polymorphisms may be useful in determination of PD-L1 expression. It might be carried out in blood samples, when surgical material is not available. The usefulness of *PD-L1* gene polymorphism, as a predictor of immunotherapy, should be investigated in clinical trials.

Keywords: PD-L1, gene polymorphisms, non-small cell lung cancer

P2.04-06 INCREASED PLASMA CELL % AND DECREASED B-CELLS IN TUMOR IMMUNE INFILTRATES ARE ASSOCIATED WITH WORSE PROGNOSIS IN LUNG ADENOCARCINOMAS

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Background: Clinical significance of tumor-infiltrating plasma cells and B-cells in lung adenocarcinoma is not well known. **Method:** CD3, CD20 and MUM1 immunostains were performed on representative tumor blocks selected from 120 consecutive lung adenocarcinoma cases resected. CD3-positive T-cells, CD20-positive B-cells, and MUM1-positive plasma cells were separately enumerated in the intraepithelial (IE) compartment and the stroma (ST) by digital image analyses. Distribution of measured tumor-infiltrating cells was systematically evaluated and their associations with patient's overall survival (OS) modeled using Cox proportional hazards analysis. **Result:** Median age of patients was 69 years (range, 46-91 years) and 52 patients were male. Eighty-two, 17, and 21 patients were tumor stage I, II, and III/IV, respectively. Ninety patients had surgery only; 30 had surgery with adjuvant chemotherapy and/or radiation therapy. Median numbers (interquartile range) of CD20-positive B-cells per $1mm^2$ in the tumor area (IE plus ST) and in IE compartment were 590 (224-1276) and 101 (38-109), respectively; the corresponding numbers of MUM1-positive plasma cells were 298 (180-605), and 67 (22-145), respectively. The percent of MUM1-positive plasma cells among all tumor immune infiltrate (i.e. MUM1-positive cells/ [CD3-positive cells + CD20-positive cells + MUM1- positive cells] x 100) ranged from 0 to 60% (median 10%) in the tumor area and showed a significant association with OS by univariate Cox analysis (continuous variable; negative correlation with HR=12.50 [95% confidence interval [CI], 1.75-89.27]). There was a significant association between IE CD20-positive B-cells and the patient's OS in univariate analysis (continuous variable; positive correlation with hazard ratio [HR]=0.81 (95% CI, 0.68-0.96). Both parameters remained significant by multivariate analysis. Cut-off points (low vs high) showing significant associations with patient's OS were found by log-rank test (Table 1).

Table 1. Summary of Cox proportional hazards analysis for overall survival

CD20 cells, intraepithelial			MUM1/(CD3+CD20+MUM1), intraepithelial and stromal		
Cut-offs (number)	HR (95% CI)	p	Cut-offs (%)	HR (95% CI)	p
>72.13	0.63 (0.37-0.04)	0.070	>20.4%	1.65(0.98-2.79)	0.063
<72.13	--		<20.4%		
>75.49	0.59(0.36-0.99)	0.045	>21.1%	1.71(1.01-2.90)	0.047
<75.49	--		<21.1%	--	
>85.66	0.49 (0.29,0.83)	0.007	>24.79%	2.29 (1.33,3.94)	0.003
<85.66	--		<24.79%	--	
>101.55	0.57 (0.34,0.96)	0.034	>26.0%	2.00(1.07-3.75)	0.031
<101.55	--		<26.0%	--	
>101.80	0.65 (0.39,1.09)	0.105	>26.4%	1.83(0.97-3.45)	0.064
<101.80	--		<26.4%	--	

Conclusion: High plasma cell % among immune infiltrate in the tumor area and low IE B-cell count were associated with worse prognosis in lung adenocarcinoma patients.

Keywords: Tumor-infiltrating immune cells, lung adenocarcinoma, plasma cells

P2.04-07 EFFECTS OF NEOADJUVANT CHEMOTHERAPY ON THE EXPRESSION OF PROGRAMMED DEATH LIGAND-1 AND TUMOR INFILTRATING LYMPHOCYTES IN LUNG CANCER TISSUES

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Background: Immune checkpoints programmed death 1(PD1)and its ligand PD-L1,PD-L2 pathways can mediate negative synergistic stimulation signals.Immunotherapy combined with chemotherapy can increase the objective response rate of cancer patients,but the mechanism of combination therapy is not clear.This study aims to analyze the changes of PD-L1,PD-L2 in lung cancer tissues and the changes of TILs (CD4+,CD8+,CD28+,and CD56+ lymphocytes) surrounding the tumor before and after neoadjuvant chemotherapy(platinum-based),in order to provide a theoretical basis for relevant clinical studies. **Method:** Tumor samples were obtained from 26 patients who confirmed primary lung cancer before and after NAC from 2009 to 2016 in the First Hospital of Jilin University. The expression of PD-L1, PD-L2 in lung cancer specimens were assessed by IHC. 5%,10%,20%,30%,50% expression thresholds were used to define PD-L1, PD-L2 positive status, respectively. Of 16 patients (since the biopsy tissue specimens were limited, only 16 cases of biopsy and postoperative tissue specimens were collected), the expression of TILs around the tumor before and after NAC were assessed by IHC. We analyze the changes of PD-L1 and PD-L2 in lung cancer tissues before and after NAC, the correlation between the changes of PD-L1 in lung cancer tissues and tumor shrink rate, the interval from the end of NAC to operation, pathological type, gender and smoking status. Of 16 patients, the changes of TILs around the tumor before and after NAC were also evaluated. $P<0.05$ was considered statistically significant. **Result:** 1. When using 5%, 10%, and 20% as expression threshold to define PD-L1 positive status, PD-L1 was up-regulated after NAC (P=0.008,P=0.016,P=0.016). However, there were no obviously statistical significance about the expression of PD-L1 when using 30%, 50% expression threshold. The expression of PD-L2 were not show any statistical significance before and after NAC. 2. Of 16 patients, the expression of CD4+, CD8+ and CD28+ lymphocytes increased after NAC (P=0.014,P=0.038,P=0.021), whereas the change of CD56+ lymphocytes was not statistical significant. 3. There were no significant difference between the changes of PD-L1 and tumor shrink rate, interval from the end of NAC to operation, pathological type, gender and smoking status . **Conclusion:** 1. NAC up-regulates the expression of PD-L1 in lung cancer tissues when the expression thresholds are 5%, 10%, and 20%. 2. NAC up-regulates the expression of CD4+, CD8+, and CD28+ lymphocytes. 3. No correlation exists between the variation of PD-L1 and tumor shrink rate, interval from the end of NAC to operation, pathological type, gender and smoking status.

Keywords: lung cancer, neoadjuvant chemotherapy, programmed death ligand-1 (PD-L1)

P2.04-08 PLATINUM-BASED CHEMOTHERAPY IS ASSOCIATED WITH ALTERED PD-L1 EXPRESSION IN LUNG CANCER

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Background: While the predictive value of programmed cell death ligand-1 (PD-L1) protein expression for immune checkpoint inhibitor therapy of lung cancer has been extensively studied, the impact of standard platinum-based chemotherapy on PD-L1 or programmed cell death-1 (PD-1) expression is unknown. The aim of this study was to determine the changes in PD-L1 expression of tumor cells (TC) and immune cells (IC), in PD-1 expression of IC, and in the amount of stromal mononuclear cell infiltration after platinum-based chemotherapy in patients with lung cancer. **Method:** We determined the amount of stromal mononuclear cells and PD-L1/PD-1 expressions by immunohistochemistry in bronchoscopic biopsy samples including 20 adenocarcinomas (ADC), 15 squamous cell carcinomas (SCC), 2 other types of non-small cell lung cancer (NSCLC), and 4 small cell lung cancers (SCLC) together with their corresponding surgical resection tissues after platinum-based chemotherapy. **Result:** PD-L1 expression of TC decreased in 10 patients (24.4%) and increased in 3 patients (7.32%) after neoadjuvant chemotherapy (p=0.051). The decrease in PD-L1 expression, however, was significant only in patients who received cisplatin-gemcitabine combination (p=0.020), while in the carboplatin-paclitaxel group no similar tendency could be observed (p=0.432). There was no difference between ADC and SCC groups. Neither PD-1 expression nor the amount of stromal IC infiltration showed significant changes after chemotherapy. **Conclusion:** This is the first study, in which both PD-L1 and PD-1 expression were analyzed together with the amount of stromal IC infiltration in different histological subtypes of lung cancer before and after platinum-based chemotherapy. Our results confirm that chemotherapy decreases PD-L1 expression of TC in a subset of patients, therefore rebiopsy and re-evaluation of PD-L1 expression may be necessary for the indication of immune checkpoint inhibitor therapy.

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P2.04-09 DRIVER MUTATIONS ARE ASSOCIATED WITH DISTINCT PATTERNS OF RESPONSE TO IMMUNE CHECKPOINT BLOCKADE IN NON-SMALL CELL LUNG CANCER

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Background: Immune checkpoint blockade (IO) has demonstrated durable clinical benefit in metastatic non-small cell lung cancer (NSCLC). Tumors with driver mutations such as EGFR exon 19 and 21 mutations and ALK translocation tend to have low response rates to IO. However, IO response in NSCLC patients with rare driver mutations, such as EGFR exon 20 (~2%), HER-2 (~2%) and BRAF (~3%), representing approximately 7% of lung adenocarcinomas, has been poorly addressed. **Method:** We queried GEMINI (MD Anderson Lung Cancer Moon Shot funded database for prospective collection of clinical information on NSCLC) for patients with mutations in EGFR exon 19, 20, 21, HER-2 and BRAF treated with PD-1/PD-L1 checkpoint inhibitors. We assessed progression-free survival (PFS), overall response rate (ORR) and overall survival (OS) in each molecular group. **Result:** Between 2014-2018, 108 patients with classic EGFR mutations (exon 19 del + exon 21 L858R, n=37), EGFR exon 20 mutations (n=36; no T790M included), HER-2 mutations (n=22) and BRAF mutations (n=13; V600E: 3pts; non-V600E: 10pts) had been treated with PD-1/PD-L1 inhibitors. EGFR exon 20 mutants and BRAF mutants demonstrated significantly higher PFS (EGFR exon 20: HR 0.4, p<0.001; BRAF: HR 0.2, p<0.001), higher disease control rate at 6 and 12 months as well as higher ORR when compared to classic EGFR mutants (Table). These differences remained significant in multivariate analysis after adjusting for age, smoking, PD-L1 status, radiation prior to treatment initiation, treatment with concurrent agents and prior treatment with TKIs. HER-2 mutants had similar PFS compared to EGFR classic mutants (HR 0.8, p=0.35) (Table).

	EGFR exon 20 N=36	Classic EGFR N=37	HER-2 N=21	BRAF N=13
Disease control – N (%)				
6 months	13 (36)	3 (8)	2 (10)	6 (46)
12 months	3 (8)	0 (0)	0 (0)	2 (15)
Response rate – N (%)				
ORR	7 (20)	0 (0)	2 (10)	3 (23)
SD	12 (33)	6 (16)	4 (19)	7 (54)
PD	17 (47)	31 (84)	15 (71)	3 (23)
Survival – median				
PFS	4.0	1.9	1.9	5.3
OS	26.6	11.4	31.7	23.5

Conclusion: EGFR exon 20 and BRAF mutations are associated with superior outcome from PD-1/PD-L1 checkpoint inhibitors compared to classic EGFR and HER-2 mutations. Further studies on co-mutational status and tumor mutation burden in these molecularly-defined groups are ongoing to address potential underlying mechanisms associated with these findings.

Keywords: Immunotherapy, Driver Mutations

P2.04 IMMUNOONCOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.04-10 EARLY MONITORING OF BLOOD BIOMARKERS TO PREDICT NIVOLUMAB EFFICACY IN NSCLC PATIENTS

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Background: In the present study we investigated whether early dynamic changes of circulating free (cf) DNA levels as well as peripheral blood cells count could predict resistance to nivolumab in pre-treated patients with advanced non-small cell lung cancer (NSCLC). **Method:** From September 2015 to January 2018, 45 NSCLC patients receiving i.v nivolumab 3 mg/kg every two weeks were included within a translational study. All the patients underwent CT-scan every 6 cycles and responses were evaluated by Response Evaluation Criteria in Solid Tumors (RECIST). Peripheral blood samples were obtained from the patients at baseline and at fourth cycle of therapy. The quantification of cfDNA (ng/µL plasma) was performed by qubit dsDNA HS assay and confirmed by qPCR evaluating a 115 bp fragment of ALU repeat. The median cfDNA level as well as the median neutrophil to lymphocyte ratio (NLR) value were calculated at the first and the fourth infusion of nivolumab. Time to progression (TTP) and overall survival (OS) were determined. **Result:** Elevated baseline cfDNA level was associated with inferior OS (7.2 vs 13.5 months, p=0.04) while high pre-treatment NLR predicted inferior TTP (4.5 vs 9.7 months, p=0.006). Patients with increased median cfDNA level >20% at fourth cycle reported significantly worse OS and TTP (OS: 5.7 vs 14.2 months, p<0.001; TTP: 3.3 vs 10.2 months, p<0.001). Patients with increased median NLR >20% at fourth cycle of therapy showed significantly worse OS and TTP (OS: 8.7 vs 14.6 months, p=0.035; TTP: 5.2 vs 10.3 months, p=0.039). Patients with a simultaneous increase >20% of both cfDNA level and NLR value showed significant worse survival outcomes as compared to patients with only one increased parameter or not increase of both parameters (OS: 5.8 vs 11.1 vs 11.5 vs 15.4 months, p=0.012; TTP: 3.2 vs 6.5 vs 7.33 vs 11.9, p= 0.028). **Conclusion:** Early increase of both cfDNA level and NLR value is a marker of resistance to nivolumab and predict worse survival outcomes in pre-treated patients with advanced NSCLC, suggesting a potential role in the real time monitoring of immunotherapy efficacy.

Keywords: NLR, cfDNA, Nivolumab

P2.04 IMMUNOONCOLOGY
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P2.04-11 AN IL-8/IFN-GAMMMA/NLR PLASMA SCORE TO PREDICT NIVOLUMAB EFFICACY IN PATIENTS WITH NSCLC

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Background: In the present study we investigated whether baseline plasma cytokines as well as neutrophil to lymphocyte ratio (NLR) could predict resistance to nivolumab in pre-treated patients with advanced non-small cell lung cancer (NSCLC). **Method:** From September 2015 to January 2018, 42 NSCLC patients receiving i.v. nivolumab 3 mg/kg every two weeks were included within a translational study. All the patients underwent CT-scan every 6 cycles and responses were evaluated by Response Evaluation Criteria in Solid Tumors (RECIST). Peripheral blood samples were obtained from the patients at baseline. A panel of cytokines and chemokines (IL-6, IL-8, CXCL10, CX3CL1, CCL2, VEGF, and IFN-gamma) were quantified in plasma by Cytokine Bead Array and their association with OS and TTP was assessed by Adaptive Index Modeling multivariable analysis. NLR in blood cell counts was also assessed for potential association with clinical outcomes. **Result:** An Index Score was identified clustering patients into 4 groups with progressively worsening TTP and OS. The score was composed by higher IL-8 and NLR (above the cut-offs of 10.76 pg/ml and 5.4, respectively) and lower IFN-gamma level (below cut-off of 11 pg/ml). Patients with score 0-1 (i.e. with none or 1 altered parameter; n= 17) displayed a median TTP of 11 months (95% IC= 5-NA) and median OS of 16 months (95% IC= 12-NA); in contrast, patients with score 2-3 (2 or 3 altered parameters; n=23) showed a median TTP of 3 months (95% IC= 2-5) and median OS of 5 months (95% IC= 2-8). The divergences among both TTP and OS Kaplan Meyers curves were statistically significant (P<0.0001). NLR alone showed instead either a borderline association with OS (p=0.048) and no ability to predict TTP (p=0.23). **Conclusion:** Baseline plasma levels of IL-8 and IFN-gamma potentiate the ability of NLR to predict resistance to nivolumab in pre-treated patients with advanced NSCLC. These data suggest that the systemic balance between neutrophil-related inflammation and lymphocyte anti-tumor immunity may condition response to immunotherapy in lung cancer.

Keywords: Nivolumab, NLR, cytokines

P2.04 IMMUNOONCOLOGY
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P2.04-12 A GENOMIC SIGNATURE [JAK2, JAK3, PIAS4, PTPN2, STAT3, IFNAR2] PREDICTS BASELINE RESISTANCE TO NIVOLUMAB IN ADVANCED NSCLC.

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Background: With the exception of PD-L1 expression for pembrolizumab, no biomarkers allow to maximize the benefit of immunotherapy in advanced pretreated non-small-cell lung cancer (AP-NSCLC). The genomic abnormalities of genes involved in immune-escape/editing are suggested as baseline mechanisms of resistance. **Method:** A retrospective series of AP-NSCLC patients (pts) undergone Nivolumab (NIVO) was collected. FFPE-tumor blocks were analyzed to identity somatic mutations (SMs)/ copy number variations (CNVs) with a Ampliseq CGS panel (17 genes: APLNR, B2M, IFNAR1, IFNAR2, IFNGR1, IFNGR2, IRF9, JAK1, JAK2, JAK3, PIAS4, PTPN2, SOCS1, STAT1, STAT2, STAT3 and TYK2). End-points were overall-, progression-free-survival (OS/PFS) and objective response rate (ORR). **Result:** Data from 24 consecutive AP-NSCLC pts who received NIVO were gathered (median age 69.5 yrs, median number of previous lines 3 [2-5], 2nd line NIVO [70.8%], median follow-up 6.8 months [range 1-23], deaths 14 [58.3%], male/female 79.2/20.8%, squamous/non-squamous 41.7/58.3%, EGFR mutant 5 [20.8%]). ORR (partial) was obtained in 4 pts (16.6%, 95% CI 1.7-31.6%), with stable- and progressive-disease in 5 (20.8%, 95% CI 4.5-37.1%) and 15 (62.5, 95% CI 43.1-81.8%) pts, respectively. JAK3/JAK2 (6/3 pts, 25/12.5%) CNVs, and IFNAR2/STAT3 SMs (2 pts, 8.3%) were the most frequent (>1 pts) abnormalities. The 12 pts with JAK3, PIAS4, PTPN2, STAT3, IFNAR2 and JAK2/3 SMs/CNVs had a significantly lower median OS (4 months, 95% CI 1-8) and PFS (3 months, 95% CI 2-3.5) than the other 12 pts wild-type/other alterations (median OS 13 months, n.e.; median PFS 6 months 95% CI 5-9) [p=0.046 for OS, p=0.002 for PFS]. No objective responses were observed in the pts' subgroup harboring the gene signature (p=0.09). At multivariate analysis, the genomic signature was independently associated with shorter OS (HR 2.20 95% CI 1.21-4.06, p=0.01) and PFS (HR 6.1 95% CI 2-18.7, p=0.001). No significant correlation between EGFR mutations and outcome was found. **Conclusion:** Despite the small sample, the customized gene sequencing of few genes involved in immune-escape/editing is able to identify a pts' subgroup of AP-NSCLC who appears to derive a lower benefit from NIVO, supporting intrinsic resistance. A larger prospective validation is planned.

Keywords: Genomic signature, advanced NSCLC, Immunotherapy resistance

P2.04 IMMUNOONCOLOGY
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P2.04-13 THE IMMUNE CHECKPOINT, HVEM CONTRIBUTE TO IMMUNE ESCAPE IN NON SMALL CELL LUNG CANCER OF LACKING PDL1 EXPRESSION

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Background: Herpes Virus Entry Mediator (HVEM) is an important immune checkpoint in cancer recognition. HVEM expressed on tumor cell membranes activates immune cell signaling pathways leading to either inhibition of activity (BTLA) or activation of immune activity (LIGHT). The aim of this study is to investigate the prevalence of HVEM expression and its association with PDL1 expression in NSCLC. **Method: A** TMA of 527 resected NSCLC samples and 53 NSCLC cell lines were evaluated for HVEM and PD-L1 expression. The IHC assay for HVEM was optimized on the Dako Link48 autostainer using a polyclonal antibody from R&D Systems(AF356). PD-L1 IHC was performed on the Dako Link48 autostainer using the PD-L1 22C3 pharmDx kit. Scoring HVEM employed the H-score system while for PD-L1 the tumor proportion score (TPS) was used. **Result:** HVEM expression in the NSCLC resected samples and cell lines revealed a positive H-score more than 1 was18.6%(77/415) and 45.3%(24/53) respectively. HVEM expression was significantly higher in patients with lymph node N2 metastasis (25.5% vs 7.9% vs 17.5%, P=0.046) when comparing with N1 or no lymph node metastasis, and was marginally significantly higher in patients with stage III/IV disease (24.5% vs 16.4%, P=0.059). Subgroup analysis showed that HVEM (median 45 vs 36 months, p=0.706) and PD-L1 expression (median 45 vs 48 months, p=0.178) status was not predictive of overall survival. HVEM was found to have a significant negative correlation with PD-L1 expression (r=-0.232, p=0.002, Figure 1A) in patients with NSCLC and also have a negative correlation in NSCLC cell lines(r=-0.055, p=0.764,Figure 1B).

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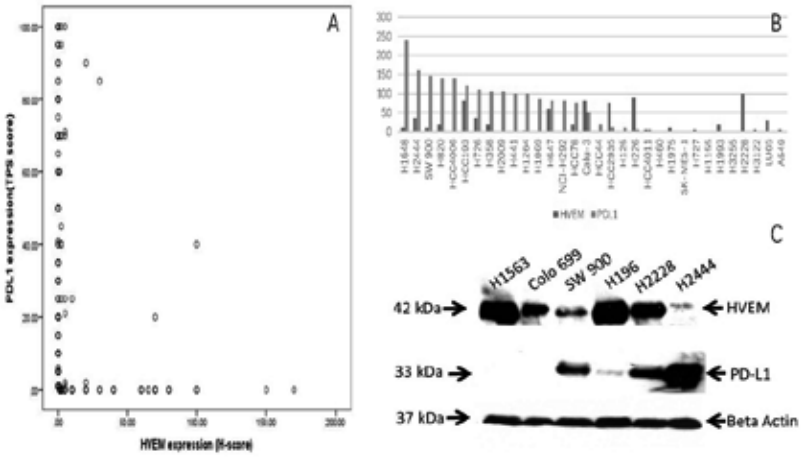

Figure 1. HVEM has a negative correlation with PD-L1 expression in NSCLC. Figure 1A, a significant negative correlation in 527 NSCLC patient cohort (r=-0.274, p<0.001). Figure 1B, HVEM has a negative correlation with PDL1 expression in NSCLC cell lines(r=-0.055, p=0.764). Figure 1C, Western blot with the HVEM and PDL1 antibody on 6 selected cell lines.

Conclusion: HVEM was found to be overexpressed in patients of NSCLC with advanced disease or lymph node metastasis and has a negative co-relationship with PD-L1 expression, while, it did not have a prognostic role in patients with NSCLC.

Keywords: Herpes Virus Entry Mediator, non small cell lung cancer, PDL1

P2.04 IMMUNOONCOLOGY
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P2.04-14 TUMOR MUTATIONAL BURDEN ASSESSED BY A TARGETED NGS ASSAY PREDICTS BENEFIT FROM IMMUNE CHECKPOINT INHIBITORS IN NON-SMALL CELL LUNG CANCER

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Background: Immune checkpoint inhibitors (ICI) improve overall survival in non-small cell lung cancer (NSCLC) in the 2nd-line setting and lead to prolonged disease control in a subgroup of patients (pts). Robust predictive biomarkers for ICI are highly desired. In an exploratory analysis of the CheckMate 026 study, high tumor mutation burden (TMB) assessed by whole-exome sequencing was associated with improved outcome of pts treated with nivolumab. **Method:** From our institutional database, 41 pts with metastatic NSCLC were included in this study and identified as either having clinical benefit (CB; defined as complete/partial response (CR/PR) or stable disease (SD)) or having no clinical benefit. TMB was assessed using a targeted NGS assay that simultaneously detects variants in all coding regions / sequences of 409 cancer-related genes (Oncomine Tumor Mutation Load Assay, Thermo Fisher Scientific, Waltham, MA, USA). TMB values were normalized to tumor cell content. The correlation between TMB and CB rate was assessed. Mann-Whitney test was used and differences were considered significant at a p-value <0.05. **Result:** Of 41 pts (mean age 63.7 years), 73% were male, 87.8% smokers and 71% had adenocarcinoma histology. Nivolumab was the most frequently used ICI (70.7%), and it was most commonly used in the 2nd-line setting (61.0%). PR was observed in 29.2% of patients, and SD in 14.6%. CB rate was 43.8%. The median number of genomic mutations per Megabase (Mb) was 8.81. In pts with CB, median TMB with 11.52 mutations per Mb was significantly higher than in pts without response to therapy (7.71 mutations per Mb; p=0.02). **Conclusion:** TMB as determined by a targeted NGS panel comprising the coding regions of 409 cancer-related genes can reliably predict clinical benefit from ICI. These results need further confirmation due to limited sample size of this study. We are currently analyzing a second independent cohort, and results will be presented during the meeting.

Keywords: Predictive biomarker, tumor mutational burden, immune checkpoint inhibitor

P2.04 IMMUNOONCOLOGY
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P2.04-15 HETEROGENEITY AND CORRELATION BETWEEN IMMUNE MARKERS IN LUNG CANCERS: ANALYSIS OF TREATMENT-NAÏVE LESIONS

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Background: Immunotherapies are becoming a new standard of care for patients with lung cancers. Although a few immune-checkpoints are currently used as therapeutic targets and/or as predictive biomarkers, the complex correlation between immune-checkpoints is not well understood. Expression level of immune-checkpoint molecules is affected by numerous factors including tumor cells themselves, patients' immunological characteristics, tumor microenvironment (metastatic sites), and previous treatments. To effectively investigate correlations of immune-checkpoints across multiple lesions, we analyzed gene expression data obtained from treatment-naïve autopsied patients. **Method:** Our cohort of 5 lung cancer patients included thirty specimens of both primary and metastatic lesions. RNA sequencing reads were mapped to the hg19 reference genome using the TopHat/Cufflinks workflow and transcripts were quantified using the FPKM method. Expression data for immune-checkpoints and total numbers of detected mutations were compared. **Result:** We observed substantial inter-tumor heterogeneity in immune-checkpoint expression between lesions obtained from each patient. No consistent correlation was found by comparison of primary vs. metastatic lesions or between primary vs. specific metastatic sites. Evaluation of immune-checkpoints expressed by tumor cells and/or antigen presenting cells revealed a positive correlation between GAL9 and PD-L2 (R = 0.79) and GAL9 and HVEM (R = 0.69; Figure 1A). We also observed a strong correlation between these markers when lesions obtained from each patient were correlated to each other (Figure 1B and C). Comparisons between immune-checkpoints expressed by immune cells identified a positive correlation between PD-1 and LAG3 (R = 0.77). No correlation was found between immune-checkpoint expression and mutation burden.

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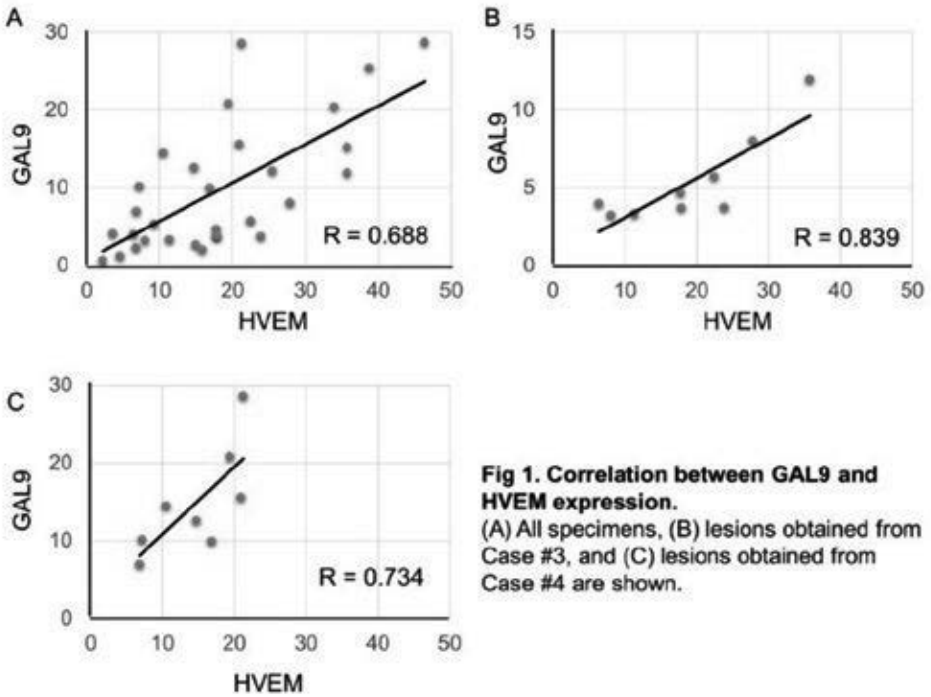

Fig 1. Correlation between GAL9 and HVEM expression.
(A) All specimens, (B) lesions obtained from Case #3, and (C) lesions obtained from Case #4 are shown.

Conclusion: We observed substantial inter-tumor heterogeneity in immune-checkpoints expression in each patient. We also found several positive correlations between immune-checkpoints which were consistent within the small cohort of patients. Further functional evaluation is warranted.

Keywords: biomarker, Immune checkpoint molecules, GAL9

P2.04 IMMUNOONCOLOGY
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P2.04-16 CORRELATION BETWEEN PROGRAMMED DEATH LIGAND 1(PD-L1) EXPRESSION AND SOLID COMPONENT ON HRCT IN STAGE I LUNG CANCER PATIENTS

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Background: Programmed death ligand 1(PD-L1) expression on lung cancer cell is one of the predictors of treatment response to immune checkpoint inhibitors. However, little has been reported about PD-L1 expression in patients with early stage lung cancer because previous clinical trials were mostly focused on advanced stage, and little has been also reported about association PD-L1 expression with high-resolution computed tomography (HRCT) findings. The purposes of this study were to describe PD-L1 expression in early stage lung cancer and to evaluate correlation with solid component on HRCT. **Method:** We evaluated patients with non-small cell lung carcinoma (NSCLC) who had been performed surgical resection between March 2017 and 2018, and resulted in pathological stage were stage I. Adenocarcinoma in situ was excluded. PD-L1 expression was assessed by means of the PD-L1 immunohistochemistry(IHC) 22C3 pharmDx assay (Agilent). PD-L1 expression was classified into three categories, negative group (PD-L1 expression less than 1%), low expression group (over 1% and less than 50%) and high expression group (over 50%). We also described HRCT findings of the tumor by solid/ground glass nodule (GGN)-ratio, calculating by the ratio of the solid component and GGN component area. The ratio was defined 0% in pure GGN cases and 100% in solid nodule cases. **Result:** During study period, 60 patients were evaluated. The mean age (±SD) was 67 (±10) years old, 28 patients (46.7%) were female. 47 patients (78.3%) were adenocarcinoma and, of these, 10 patients were minimally invasive adenocarcinoma. In radiological classification, 8 patients (13.3%) were pure GGN, 24 (40.0%) were part solid nodules and 28 (46.7%) were solid nodules. In PD-L1 expression, 33 (55.0%) patients were negative group, 23 (38.3%) were low expression group and 4 (6.7%) were high expression group. The mean PD-L1 expression (±SD) was 7.82 (±18.6)% and the mean solid/GGN-ratio (±SD) was 58.8 (±40.9)%. A Spearman's correlation test showed significant correlation between PD-L1 expression and solid/GGN-ratio. (rho=0.43, p<0.001) **Conclusion:** There was a positive correlation between PD-L1 expression and solid component on HRCT in stage I NSCLC patients.

Keywords: PD-L1 expression, early stage lung cancer, HRCT

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P2.04-17 PRE-THERAPY RADIOMIC FEATURES CAN DISTINGUISH HYPERPROGRESSION FROM OTHER RESPONSE PATTERNS TO PD1/PD-L1 INHIBITORS IN NSCLC

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Background: Immune checkpoint inhibitors (ICIs) can lead to durable responses in a fraction of patients with advanced non-small cell lung cancer (NSCLC), however a majority of patients do not respond to these agents. Of the non-responders, a subset of patients who have a dramatic increase in their tumor growth rates after ICI therapy have been previously described in the literature. There are currently no clinically validated biomarkers to identify these hyperprogressors (HPs). We sought to evaluate whether radiomic features of the tumor on baseline CT scans from patients with advanced NSCLC treated with ICIs could distinguish hyperprogressors from non-responders (NRs) and responders (Rs). **Method:** We retrospectively reviewed the charts of 336 patients with advanced NSCLC who received monotherapy with a PD1/PD-L1 inhibitor. For patients who developed progressive disease within 3 cycles of ICI therapy, pre-baseline, baseline and post treatment

scans were used to calculate tumor growth kinetics (TGK). TGK pre and post ICI was calculated by dividing the sum of the largest diameters of target lesions per RECIST criteria by the interval time between scans. The ratio of post- treatment TGK and pre-treatment TGK was used to identify hyperprogressors (ratio ≥2, N=28). Intratumoral and peritumoral radiomic features using annular 2 mm rings up to 10 mm from the center of the tumor on the baseline CT were extracted for hyperprogressors (N=28), responders (N=28) and non-responders (N=29). In the training cohorts, a total of 925 features that were differentially expressed in hyperprogressors vs responders (N=28) and hyperprogressors vs non-responders (N=28) were investigated. **Result:** Top 5 predictive radiomic features (from the Haralick, Laws and Gabor texture families) were identified using a minimum redundancy maximum relevance (mRMR) feature selection algorithm and their performance was validated using an independent test set of hyperprogressors vs responders (N=28) and hyperprogressors vs non-responders (N=29). Linear Discriminant Analysis (LDA) classifier was able to distinguish hyperprogressors vs non-responders with an area under the receiver operating curve (AUC) of 0.85 and a sensitivity of 0.92. The same classifier separated hyperprogressors and responders with an AUC and sensitivity of 0.58 and 0.85 respectively. **Conclusion:** Intratumoral and peritumoral radiomic textural features on baseline CT scans were able to distinguish hyperprogressors from those with other patterns of response to ICIs, particularly other non-responders. These radiomic features may serve as a predictive marker for patients who develop accelerated disease progression with ICIs. Further validation of these results in multi institutional cohorts is warranted.

Keywords: hyperprogression, Radiomic, Immune checkpoint inhibitors

P2.04 IMMUNOONCOLOGY
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P2.04-18 THE ASSOCIATION BETWEEN IDO ACTIVITY AND CLINICAL PROGNOSIS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER AFTER RADIOTHERAPY

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Background: Immunity affects the efficacy of radiotherapy and prognosis of patients. indoleamine 2,3-dioxygenase (IDO), a limiting enzyme in the IDO/kynurenine pathway, could converts the tryptophan (T) into kynurenine (K), which promotes immune suppression and assist tumor cells in immune evasion. The aim of this study was to investigate the association between the IDO activity and kynurenine and clinical outcome in non-small cell lung cancer (NSCLC) patients who received radiotherapy. **Method:** Blood serum K and T in 114 NSCLC patients were measured by high performance liquid chromatography and mass spectrometer in time before and after radiotherapy. The ratio of K: T represents the activity of IDO. Kaplan-Meier curve and log-rank test were performed to evaluated the correlation with Overall survival (OS) or progression-free survival (PFS) and IDO activity. The Cox proportional hazards model was used for univariate and multivariate analyses. **Result:** On average, both the K and the ratio of K: T were increased after radiotherapy (P<0.001 and P=0.006). The patients with reduced K: T after radiotherapy had better OS than who with increased K: T (not reached vs. 20.2 months,P=0.004). In subgroup of patients who received Stereotactic Body Radiation Therapy (SBRT), patients with reduced K: T after radiotherapy had better OS and PFS than who with increased K: T (median OS: not reached vs. 20.2 months,P=0.008 and median PFS: not reached vs. 10.9 months,P=0.006, respectively). Multivariate analysis also showed that IDO activity was a factor for OS and PFS (HR=6.667,95%CI: 1.515~29.411,P=0.012 and HR=5.348,95%CI: 1.427~20.000,P=0.013, respectively). **Conclusion:** The change of IDO activity after radiotherapy is associated with prognosis in NSCLC. The patients with reduced IDO activity after radiotherapy had better OS than who with increased. Especially for patients who received SBRT, patients with reduced IDO activity had better OS and PFS than those increased after radiotherapy. IDO is a potential molecular marker of NSCLC to evaluated the prognosis after radiotherapy.

Keywords: non-small cell lung cancer, Radiotherapy, IDO

P2.04 IMMUNOONCOLOGY
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P2.04-19 CORRELATION OF CLINICOPATHOLOGICAL CHARACTERISTICS WITH TUMOR MUTATION BURDEN IN CHINESE PATIENTS WITH NSCLC

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Background: Higher tumor mutation burden(TMB) has been associated with improved immune checkpoint inhibitor objective response, progression-free survival and over survival in non-small cell lung cancer(NSCLC). But the correlation of clinicopathological characteristics with tumor mutation burden(TMB) in Chinese patients with NSCLC remains unknown. **Method:** 266 lung adenocarcinoma (LUAD) and 66 lung squamous cell carcinoma (LUSC) patients from 18 hospitals across 11 provinces in China were recruited and the clinical whole exome of paired tumor/normal samples of each patient were sequenced. **Result:** Among the 332 prospectively enrolled NSCLC patients, 81.3% patients were recommended at least one FDA approved targeted/immunotherapy drug and 88.5% were matched at least one ongoing clinical trials. The median TMB of Chinese NSCLC patients was 5.62 mutations/Mb and upper tertilewas 7.87 mutations/Mb. TMB in Chinese LUSC cohort was slightly higher than the TCGA cohort (median: 10.6 mutations/Mb vs.9.0 mutations/Mb).WhileTMB in Chinese LUAD patients was slightly lower than the Caucasian cohort (median: 5.14 mutations/Mb vs. 6.3 mutations/Mb).Chinese LUAD patients with EGFR-mutant status (122/266) had significantly lower TMB compared with patients with EGFR wild-type (median: 4.90 mutations/Mb vs. 5.53 mutations/Mb, P=0.0013). This may help to explain why in EGFR-mutant advanced NSCLC, immune checkpoint inhibitors do not improve OS over that with docetaxel in secondline setting. However LUAD patients with KRAS-mutant status (31/266) had significantly higher TMB compared with patients with KRAS wild-type (median: 9.94 mutations/Mb vs. 4.84 mutations/Mb, P=0.021).A small subset (8/266) of NSCLC patients with CDKN2A-mutant possessed high TMB, although it did not reach statistical significance (P=0.0588). Consistent with previous research, mutant POLE/POLD1 (LUAD: 15/266 and LUSC: 8/66)was significantly associated with increased TMB. For all NSCLC in our study, patients with mutant POLE/POLD1 had significantly higher TMB compared with patients with wild-type POLE/POLD1 (Median: 10.18 mutations/Mb vs. 5.59 mutations/Mb; P=5.16e-7).TP53 and PTEN mutations were not enriched in NSCLC patients with high TMB. One EGFR (p.L858R) mutant LUAD patient with CTNNB1 (p.S33F) co-mutation developed to be innate PD-1 and EGFR-TKI resistance. Increased β-catenin signaling led to poor T cells infiltration into tumors and promoted epithelial-mesenchymal transition (EMT) as well. This case represented a novel genomic predictor of de-novo resistance to immune checkpoint blockade in EGFR-mutant LUAD. **Conclusion:** High TMB caused by DNA repair deficiency such as POLE/POLD1 mutation is common in Chinese NSCLC patient, and clinical evidence ssuggest thatTMB status and cancer driver mutations can help to establish clinically available tool to identify patients who are most likely to benefit from immunotherapies or targeted therapies.

Keywords: Non-small-cell lung cancer, Immunotherapy, Tumor mutation burden

P2.04 IMMUNOONCOLOGY
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P2.04-20 IMMUNOLOGIC CHARACTERIZATION OF FIBRINOUS PERICARDITIS AS AN IMMUNE CHECKPOINT BLOCKADE TOXICITY IN NSCLC

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Background: Immune checkpoint inhibitors have revolutionized the treatment paradigm in number of cancers including Non-Small Cell Lung Cancer (NSCLC) but unrestrained modulation of the immune system remains a challenge. Here, we characterized the immune infiltration in the toxicity site and compared immune profile in primary tumor in three patients treated with PD-1/PD-L1 axis inhibitors and developed fibrinous pericarditis (FP) **Method:** We used the AQUA method of quantitative immunofluorescence (QIF) to assess multiplexed panels identifying immune cell populations and their activation status in pre-treatment,

post-treatment primary tumor, post-treatment metastatic tumor and the toxicity sites (including pericardial tissue) from 3 NSCLC patients. We also compared the expression of 730 immune-related genes across sites from the 3 patients with FP and 2 NSCLC patients with different toxicity sites after immunotherapy (hypophysitis and myocarditis) using Nanostring Sprint platform. **Result:** In immune infiltration assessment, TILs markers' expression (CD4, CD8 and CD20) did not differ between primary tumor and toxicity site. There was a trend towards higher CD3+ expression in the toxicity samples but T-cell activation markers expression, Granzyme B and Ki67, was significantly lower in the pericarditis samples. Interestingly, high Granzyme B expression in CD3- cells and CD56+ cells were seen in the pericarditis samples. CD68+ expression, as well as PD-L1 expression in macrophages, was significantly higher (p<0.0001) in the pericarditis samples. mRNA analysis confirmed the QIF findings, with the chemokine profile indicating an M1 macrophage polarization. Additionally, there was a trend towards higher NCR1, perforin1 and Granzyme B gene expression in the toxicity samples, further supporting a possible role of Natural Killer (NK) cells in the development of toxicity. **Conclusion:** Our findings suggest that macrophages and possibly NK cells contribute to inflammatory tissue damage in immune related adverse events. Conversely, T-cells that were infiltrating the toxicity sites had low expression of activation markers, further indicating that toxicity may be mediated by other cellular pathways.

Keywords: fibrinous pericarditis, Immunotherapy, NK cells

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P2.04-21 REAL WORLD EXPERIENCE OF IMMUNE CHECKPOINT INHIBITORS IN NSCLC: OUR FIRST 10 MONTHS EXPERIENCE AT LEEDS CANCER CENTRE, UK

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Background: Pembrolizumab and Nivolumab are monoclonal antibodies to the PD-1 receptor and have shown significant overall survival(OS) and progression free survival(PFS) in the second line setting compared to chemotherapy in non-small cell lung cancer(NSCLC). Pembrolizumab has shown significant OS and PFS in the first line setting in high PD-1 expressors(>50%). In January 2017, immune checkpoint inhibitors became standard of care in the UK initially in the second line setting and subsequently first line later that year. Studies report fewer treatment-related adverse events in the checkpoint inhibitor arm Vs chemotherapy (10-20% Vs 54%). We report our first 10 months experience with routine use of checkpoint inhibitors in NSCLC at Leeds Cancer Centre(LCC), UK. **Method:** All patients receiving pembrolizumab and nivolumb between 1/1/17 and 31/10/17 at LCC, UK were included. Retrospective review of medical notes was performed and outcomes recorded including: checkpoint inhibitor received; time to response; OS and treatment-related adverse effects. Kaplan-Meier survival curves were used to assess survival outcomes. **Result:** Thirty-six patients received checkpoint inhibitors during this period. Median age was 68 years. Eleven patients received first line therapy with a response rate of 90% (n=10). Twenty-five patients received second line therapy with a response rate of 32% (n=8). For the whole cohort, median time to response was 52days. Median time to progression in responding patients was not reached. Median PFS was 152days (95%CI 57-232). Median OS was 467days (95% CI 194-not reached). Pseudoprogression occurred in one patient. Treatment-related adverse effects occurred in 58% (n=21). Of these, 57% (n=12) were non-autoimmune and 43% (n=9) were autoimmune. Grade 3-5 toxicities occurred in 8% (n=3), all were autoimmune mediated on pembrolizumab. In all cases, treatment was stopped. Thirty-one percent (n=11) remain on check-point inhibitors. **Conclusion:** Overall response rate to immune checkpoint inhibitors in this small cohort was better than reported data in both the first and second line setting (90% Vs 45% and 32% Vs 19% respectively). Time to response was comparable to previous trials (1.7months Vs 2.1months). Median PFS and OS were in keeping with large randomised controlled trials (PFS - 5months Vs 2.3-10.3months and OS - 15months Vs 12.2months). Frequency of treatment-related adverse effects and grade 3-5 effects were lower in this cohort at 58% and 8% respectively, compared to 69-73.4% and 10-26.6% in trials. In conclusion, our initial results in this real world cohort show immune checkpoint inhibitors are a safe, effective treatment in this group of patients.

Keywords: Immunotherapy, Checkpoint Inhibitor

P2.04 IMMUNOONCOLOGY
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P2.04-22 DENDRITIC CELL BASED IMMUNOTHERAPY IN STAGE IIB-IIIA NON-SMALL CELL LUNG CANCER PATIENTS: 10-YEARS EXPERIENCE.

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Background: Current immunotherapy options for non-small cell lung cancer **(**NSCLC) patients include tumor vaccines, cellular immunotherapies and immune checkpoint inhibition therapy, but which of them is most efficacious is unknown. Here, we represent a data of 10-years follow-up study of DC-vaccine immunotherapy effectiveness in stage IIB-IIIA NSCLC patients. **Method:** Two hundred fifty-three eligible patients with stage IIB-IIIA NSCLC were enrolled into the study. Patients were randomly allocated into two groups: 1 st – patients received DC based immunotherapy as adjuvant treatment option, 2nd - control group of patients who received surgery only. DC in amount 4,62±0,37x106 per injection were injected intravenously in 1-3 courses (6 months interval). One course consisted of 5 injections with one-month interval. Patients were monitored for immune function measures before and 1 month after each DC administration. Correlation between EGFR and KRAS mutation and clinical outcome was investigated. **Result:** Log-rank test revealed that the DC based immunotherapy contributes to significant increase in 5- and 10-years overall survival (OS) and event free survival (EFS) of NSCLC patients. Thus, the 5-years OS rate was 44,4% vs. 30,4% and the 10-years OS rate – 30,3% vs. 13,8% in DC-immunotherapy and control groups respectively (p=0,009); HR=0,60; 95: CI = 0,43-0,85, For patients in DC- immunotherapy group, the 5-years EFS rate was 42,8 % in contrast to 23,5 % in patients of control group (p=0,0085). At 10-years follow-up, we could observe that the difference in EFS rates between two groups decreases, but remains statistically significant: 22,6 % vs 10,5 % (p=0,0032); HR=0,58; 95: CI = 0,42-0,80. DCs based immunotherapy is effective modulator of the immune system of NSCLC patients. After the 3rd DC administration, changes in the balance between Th1- and Th2-type of immune response have been occurred. Prognostic significance of immunological parameters - TGF-β mRNA expression level, the number of CD4+CD45RO+ cells in circulation, the ratio of CD3 +IFN-γ+/CD3+IL-4+ after incubation with autologous tumor cells lysate has been revealed. According to proportional hazard Cox regression, EGFR and K-RAS mutations were not found to be associated with DC vaccine efficacy in NSCLC patients. **Conclusion:** DC based cellular immunotherapy enhanced 10-years OS and EFS in stage IIB-IIIA NSCLC patients. EGFR and KRAS mutation positivity was not predictive of survival benefit from DC based immunotherapy.

Keywords: dendritic cells, immunotherapy, non-small cell lung cancer

P2.04 IMMUNOONCOLOGY
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P2.04-23 IMMUNE-RELATED ADVERSE EVENTS: THE GROWING PAINS OF IMMUNOONCOLOGY

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Background: Immune checkpoint inhibitors (ICI) are associated with a distinct spectrum of toxicities, generally characterized as immune-related adverse events (irAEs). Despite increased recognition and improved management (mgmt), life-threatening toxicity affects a subset of pts. The Massachusetts General Hospital has created a novel inpatient oncology service, the severe ICI toxicity service (SIC), which aims to refine treatment of these irAEs. **Method:** We retrospectively identified pts with advanced thoracic malignancies who had received standard ICI (anti-PD(L)-1+/-CTLA-4 inhibition) and had been hospitalized for a grade ≥3 irAE. Demographic and clinical data were extracted from the medical chart and a descriptive analysis was performed. **Result:** We identified 32 pts who required admission for toxicity mgmt. (**Table 1**). Average age on admission was 67yo (53-86) with an equal distribution between genders. Toxicity onset occurred at 101days (2-579) after the 1st ICI dose with 93.5% receiving anti-PD-(L)1 monotherapy. The most common irAEs were pneumonitis (35%), hepatitis (22%) and colitis (19%). 84% of pts received high-dose corticosteroids (1mg/kg) with 15% requiring a 2L immunosuppressant. In pts who completed a steroid taper, duration of use was 81d (42-192). The average length of stay was 8d (2-24) with 7pts requiring re-admission for toxicity flare. Eight pts (25%) experienced a

grade 5 event (6 pneumonitis, 1 myocarditis, 1 hepatitis). Median PFS and OS were 6.3mths and 8.2mths, respectively.

Table 1:

Patient Characteristics	Outcome
Age at treatment initiation (average)	67yo (53,86)
Gender	
Male	16 (50%)
Female	16 (50%)
Type of lung ca	
Adenocarcinoma	23 (72)
Squamous	7 (22)
Small cell lung cancer	2 (6
PD-L1 expression	
>50%	11 (34)
<50%	3 (10)
unknown	18 (56)
Type of irAE	
Pneumonitis	11 (35)
Hepatitis	7 (22)
Colitis/enteritis	6 (19)
Endocrinopathy	4 (12)
Myocarditis	2 (6)
Other (bullous pemphigoid, auto-immune hemolytic anemia)	2 (6)
Average duration between cycle one and irAE onset	101d (2,579)
Average length of stay	8d (2,24)
# of pts who required re-admission	7 (22)
Best response to ICI	
Partial response	7 (22)
Stable disease	13 (41)
Progressive disease	9 (28)
Unevaluable	3 (9)
% Alive at the time of this analysis	40%

Conclusion: Severe irAEs requiring inpatient admission, though infrequent, result in considerable morbidity and mortality. Improved understanding of these toxicities and the mechanisms underlying their development is crucial. Novel academic efforts, such as the SIC service, are needed to fully characterize irAEs and ultimately develop novel therapeutic strategies to manage them.

Keywords: irAEs, immunotherapy, toxicity, pneumonitis

P2.04 IMMUNOONCOLOGY
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P2.04-24 NIVOLUMAB IN THE "REAL WORLD": ARE THE RESULTS OF CLINICAL TRIALS REPRODUCIBLE?

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Background: It have passed more than two years since the approval of nivolumab in the second or third lines of treatment of non-small cell lung cancer (NSCLC) in advanced or recurrent stages, so that we know the results in patients in our area.

The main objective of this study is to analyze the results in a "real" population of different hospitals in Spain since we will be able to compare our results with the once published previously. **Method:** We have reviewed 129 patients with NSCLC, advanced or recurrent stages, treated with nivolCutumab either in second and subsequent lines of treatment, after progression to a platinum-based scheme from its expanded use until April 2018, in five hospitals in Spain. The information was collected retrospectively of clinical, analytical, pathological and treatment characteristics of the patients. Statistical analysis was performed using the SPSS software vs 21.0, considering the statistical significance if p <0.05 **Result:** With a median follow-up of 6 months (0-31), the overall survival (OS) was 9 months (5.86-12.14). Patients with ECOG 0-1 presented a median OS of 11 months compared to 3 months of median OS in patients with ECOG 2 (p: 0.001) If the response to previous treatment was complete response, partial response or stabilization of the disease, they will have a median OS of 12 months compared to 6 months if the best response was progression (p: 0.002).There is also a statistically significant difference in terms of overall survival in relation to the existence of toxicity for immunotherapy or not (median of 13 versus 6 months p: 0.004). The overall survival of patients who had progressed beyond 6 months after the start of treatment with prior chemotherapy was significantly greater than patients who had progressed in the first 6 months after the start of chemotherapy (median of 4 months versus median of 13 months, p: 0.001) **Conclusion:** Immunotherapy has come to stay taking part of the usual clinical practice of patients with lung cancer. The results obtained in our population are comparable to those previously published, with an important group of patients that responded to immunotherapy or stabilized even for a long time. However, we highlight that also there is a percentage of patients, who progress early. We see fundamental to find or recognize, not just the ideal biomarker that helps to predict response, but those clinical characteristics that can make us presage a poor result.

Keywords: Immunotherapy, Nivolumab, non small cell lung cancer

P2.04 IMMUNOONCOLOGY
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P2.04-25 RANDOMIZED CLINICAL TRIAL COMPARING IMMUNOTHERAPY PLUS SABR (I-SABR) VERSUS SABR ALONE FOR EARLY STAGE NSCLC

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Background: Section not applicable Stereotactic ablative radiotherapy (SABR), which delivers high biologically effective radiation doses, can kill cancer cells, release tumor-associated antigens, and activate tumor-specific T cells, thereby functioning as a cancer-specific vaccine in situ. The combination of the immune-triggering effects of ionizing radiation with immune check point PD-1inhibitor may leverage the effects of radiotherapy, transforming what was once considered a local therapy to a novel systemic treatment. Further, the combined effects of local tumor control plus systemic control may improve cure rate in early stage NSCLC. **Method:** Section not applicable This is a randomized phase II trial (NCT03110978) designed to study SABR (biological effective dose >100 Gy) with or without concurrent and adjuvant Nivolumab for total of 7 doses in early stage or isolated recurrent NSCLC. Inclusion criteria: stage I disease (tumor size ≤5 cm, N0M0) OR selected cases of stage IIa disease (tumor size >5 cm but ≤7 cm, N0M0), including multiple primary tumors, OR isolated lung-parenchymal recurrent or persistent NSCLC suitable for SABR. Tumor tissue /blood/stool samples will be collected before/during/after treatment and at the time of recurrence. Primary endpoints: Event-free survival (EFS), defined as local recurrence, regional recurrence, distant metastasis, secondary malignancy and death; secondary endpoints: overall survival; toxicity; exploratory analyses of potential predictive markers and immunologic mechanisms of action. Statistical design: It is considered clinically significant with a decrease of the 4-year cumulative event rate from 46% to 23%. Assuming a one-sided type I error rate of 0.05, an accrual rate of 3.5 patients per month, and an additional 20 months of follow-up, a study with 70 patients in each arm will have 85% power to detect an improvement of 23% in 4-year EFS rate. One interim analysis will be done to allow early termination of the trial should evidence at that time reveal that I-SABR is superior to SABR-only or that no difference is found between the two treatment arms. **Result:** Section not applicable Up to April 30, 2018, 36 of planned 140 patients have been enrolled. **Conclusion:** Section not applicable Phase II randomized clinical trial comparing immunotherapy plus Stereotactic Ablative Radiotherapy (I-SABR) versus SABR Alone for stage I, selected stage IIa or isolated lung parenchymal recurrent Non-Small Cell Lung Cancer is ongoing and met with anticipated enrolment rate.

Keywords: Immunotherapy, Stereotactic ablative radiotherapy, lung cancer

P2.04 IMMUNOONCOLOGY
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P2.04-26 INTERIM RESULTS FROM A PHASE I/II TRIAL OF NIVOLUMAB IN COMBINATION WITH CIMAVAX-EGF AS SECOND-LINE THERAPY IN ADVANCED NSCLC

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Background: CIMAvax-EGF (CE), a recombinant anti-human epidermal growth factor (EGF) vaccine, has demonstrated survival benefit as maintenance therapy in advanced NSCLC. We report the results from the dose-escalation phase I portion of the study investigating CE in combination with Nivolumab(N) in patients (pts) with advanced

stage, previously treated immunotherapy-naïve NSCLC. **Method:** This is an open-label phase I dose-escalation study with a 3+3 design. Intramuscular CE is investigated in two dose levels (1.2 and 2.4 mg, given q 2 weeks x 4 doses during the induction phase, then q monthly during the maintenance phase) in combination with 240 mg iv N q 2 weeks. Pts remain on treatment until disease progression, serious toxicity or consent withdrawal. The primary objective is to determine the safety and recommended phase II dose (RP2D) of CE in combination with N. Secondary objectives include tumor response and correlative markers of immune response. Toxicities are graded according to CTCAE v4.03. No intra-pt dose escalation is allowed **Result:** 9 pts have completed DLT assessments (7Female: 2Male). Median age is 58 (range 46-69). All pts have EGFR, KRAS and ALK wildtype NSCLC. Adenocarcinoma is the predominant histologic subtype (7/9). One pt had Gr 3 myocarditis (LVEF 25%-30%) attributed to N alone on Cycle 1 day 8 and taken off study. LVEF improved (60%-65%) but pt eventually had Gr 5 brain hemorrhage due to brain metastasis, unrelated to treatment, on Cycle 1 day 29. No other treatment-related CTC grade 3+ AEs attributed to either N and/or CE. The RP2D dose was established at 2.4 mg for CE. Objective response rate of 44% was seen (4 PRs: 3 adenocarcinoma, 1 squamous; 3 PD-L1 <1%, 1 PD-L1 60%). There is a significant inverse correlation (p<0.001) between the temporal change in anti-EGF Ab titers and the change in serum EGF levels based upon a generalized linear model. 71% of pts (95% CI 36%-92%) achieved an anti-EGF Ab titer of > 1:4000 after 3 vaccine doses by day 43. We will present additional information on safety, efficacy profile and correlative data in the meeting **Conclusion:** Combination of N+CE did not show unexpected toxicities. Preliminary efficacy and immunological data warrant further investigation.

Keywords: CIMAvax, Nivolumab, Vaccine

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P2.04-27 PH II STUDY OF ORAL SELECTIVE AXL INHIBITOR BEMCENTINIB (BGB324) IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH ADVANCED NSCLC

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Background: Bemcentinib (BGB324) is a first-in-class, highly selective oral inhibitor of the AXL tyrosine kinase currently in phase II clinical development across several cancer types. AXL overexpression has been observed in pts failing anti-PD-1 therapy in several cancers whereas AXL inhibition via bemcentinib has shown synergistic effect with checkpoint blockade in pre-clinical models of NSCLC. In pts with advanced, pre-treated NSCLC, bemcentinib monotherapy led to disease stabilisation in 2 out of 8 pts including evidence of tumour reduction. Combination therapy of bemcentinib with EGFR inhibition indicated the potential of AXL blockade to reverse resistance to targeted therapy in advanced EGFR therapy resistant NSCLC. Evidence of immune activation following bemcentinib monotherapy was observed in AML patients. This open label, single-arm, two-stage Phase 2 study was designed to test whether AXL inhibition may increase the efficacy of pembrolizumab in patients with advanced, previously treated adenocarcinoma of the lung. **Method:** Patients with documented Stage IV adenocarcinoma of the lung who had progressed on previous platinum chemotherapy and – if applicable – at least one line of licensed EGFR or ALK targeted therapy, received 200 mg/d bemcentinib po and 200 mg/q3wk pembrolizumab iv. Patients were required to consent to a fresh pre-treatment biopsy. Tumour assessments were done 9-weekly. The primary endpoint was ORR. Tumour biopsies were analysed for PD-L1 and AXL as well as immune cell populations. Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM) in patients pre-dose and at C2D1. **Result:** As of time of writing, the study had fully recruited its first stage. Of 24 patients enrolled, 14 were ongoing. 6 of 10 patients who had reached their first scan showed evidence of tumour shrinkage including 3 pts with partial responses in their target lesions. 2 patients had stable disease. There were no grade 4 treatment-related events. Dose reduction from 200 to 100 mg/d of bemcentinib as a consequence of adverse events was required in 12% of patients. Correlation of AXL and PD-L1 expression with response was evaluated. Soluble AXL plasma levels were increased following one cycle of treatment indicative of target engagement. **Conclusion:** A preliminary analysis of response to combination treatment during the first stage of this study as well as biomarker correlation will be presented at the meeting. Clinical trial information: NCT03184571

Keywords: Axl, pembrolizumab, combination

P2.04 IMMUNOONCOLOGY
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P2.04-28 USE OF IMMUNE CHECKPOINT INHIBITORS (ICIS) IN PATIENTS WITH REFRACTORY NON-SMALL CELL LUNG CANCER (NSCLC) AND POOR PERFORMANCE STATUS (PS)

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Background: Patients with poor PS generally do not tolerate chemotherapy well, and best supportive care is advocated for patients with Eastern Cooperative Oncology Group (ECOG) PS of 3 or greater. However, immune checkpoint inhibitors (ICIs) are generally better tolerated than conventional chemotherapy, making these drugs attractive options for poor PS patients. Scant literature exists on the safety and efficacy of ICIs in patients with poor PS. **Method:** We retrospectively identified patients who received single-agent programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors for refractory NSCLC between January 2015 and December 2017 at our institution. Descriptive tables of patient-, disease-, and treatment-related variables were generated. Overall survival (OS) was stratified by performance status and compared utilizing the Kaplan-Meier method. Multivariable survival analysis was performed using a Cox regression model. **Result:** In total, 111 patients received PD-1/PD-L1 inhibitors for refractory NSCLC. PS was 0 in 6 (5%) patients, 1 in 53 (48%) patients, 2 in 37 (33%) patients and 3 in 10 (9%) patients, and 5 patients did not have a recorded PS. Median OS was significantly longer in the PS 0-1 group than the PS 2-3 group (11.3 months vs 4.1 months, p=0.02). Poorer PS (ECOG 2-3) was significantly associated with increased risk for death when controlling for confounding variables (HR 2.1, p=0.004). Specifically, within the PS 3 group, 2 of 10 patients developed objective responses (1 partial response, 1 complete response). Two patients (20%) had progressive disease. Six patients were non-evaluable for response due to death. The median overall survival was 2.6 months, with the two responding patients both alive over 540 days from initial ICI dose. However, 5 of the 10 patients died within 50 days of initial ICI dose. One of the responding patients developed nivolumab-induced pancreatitis requiring hospitalization, and the other responding patient developed significant, permanent cognitive decline without clear etiology. **Conclusion:** This study confirms PS as a strong predictor of OS in refractory NSCLC patients receiving ICIs. Overall, patients with PS 3 suffered poor outcomes with ICIs. However, 2 patients with PS 3 responded to ICI, and both were still alive over 1.5 years from the initial ICI dose. Still, ICI toxicity was common in this population. More experience with PS 2-3 patients should be reported to further evaluate the safety and efficacy of ICIs in this setting. Biomarker-driven selection with high tumor PD-L1 or tumor mutation burden may help improve appropriate utilization of ICIs in this challenging population.

Keywords: performance status, non-small cell lung cancer, immune checkpoint inhibitor

P2.04 IMMUNOONCOLOGY
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P2.04-29 PRELIMINARY RESULTS WITH TISLELIZUMAB IN CHINESE PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: NSCLC accounts for 80–85% of all lung cancers and has a poor prognosis at later stages. Immune checkpoint inhibitors have shown efficacy in patients (pts) with advanced NSCLC. Tislelizumab is a humanized IgG4 monoclonal antibody with high affinity/specificity for PD-1. Tislelizumab was specifically engineered to minimize $F_cγR$ binding on macrophages that, based on preclinical evidence, is believed to

minimize potentially negative interactions with other immune cells. In a phase 1 study, tislelizumab was generally well tolerated and showed antitumor activity in NSCLC pts; 200 mg IV Q3W was established as the recommended tislelizumab dose. **Method:** In the ongoing indication-expansion phase of this study, Chinese pts with histologically confirmed NSCLC were enrolled into PD-L1-high (PD-L1$^+$; ≥10% tumor cells expressing PD-L1) and PDL1low (PD-L1$^-$) cohorts. Antitumor activity (RECIST v1.1) and safety/tolerability (NCI-CTCAE v4.03) were assessed. **Result:** As of 8 Dec 2017, 42 NSCLC pts (median age 54 yr [range 37–72]) were enrolled; 17 were PD-L1$^+$ and 25 were PD-L1$^-$. Most pts were male (69%), former/current smokers (57%), and had received prior therapy (95%). Adenocarcinoma was the most prevalent histology (57%). Median follow-up was 4.5 mo and 23 pts remain on treatment. Of the 39 response-evaluable pts, 4 (n=2/14, PD-L1$^+$; n=2/25, PD-L1$^-$) achieved confirmed PR and 20 (n=6/14, PD-L1$^+$; n=14/25, PDL1$^-$) achieved SD, including 4 (n=2, PD-L1$^+$; n=2, PDL1$^-$) with unconfirmed PR. Across the study population, ORR was 10% and DCR was 61.5%. ORRs by cohort were 14% (PDL1$^+$) and 8% (PD-L1$^-$), respectively. Common treatment-related AEs were increased AST (24%), increased ALT (19%), hypothyroidism (12%), and rash (12%). Five grade ≥3 treatment-related AEs occurred in 4 pts (increased AST [n=2], hyperglycemia, increased ALT, and increased GGT [n=1 each]). No treatment-related grade 5 events were reported. **Conclusion:** Tislelizumab was generally well tolerated and demonstrated antitumor activity in previously treated pts with advanced NSCLC. A global phase 3 study (NCT03358875) of tislelizumab vs docetaxel as potential second/third-line therapy in NSCLC pts who progressed after a platinum-based regimen is ongoing.

Keywords: NSCLC, PD-1, tislelizumab (BGB-A317)

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P2.04-30 PD-1/PD-L1 INHIBITION MIGHT BE AN OPTION FOR THE TREATMENT OF ADVANCED PRIMARY PULMONARY LYMPHOEPITHELIOMA-LIKE CARCINOMA

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Background: Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare subtype of non-small-cell lung cancer mostly reported in Asian countries, which is frequently associated with Epstein-Barr virus (EBV) infection. There is no consensus on the choice for the treatment of advanced primary pulmonary LELC. The utility of PD-1/PD-L1 inhibitor to this cancer type remains poorly understood. **Method:** From January 2008 to April 2017, a total of 53 patients receiving surgical removal and diagnosed as primary pulmonary LELC in Guangdong Lung Cancer Institute (GLCI) were enrolled in this study. Sections formalin-fixed and paraffin-embedded (FFPE) tumor samples were stained with PD-L1 antibody (clone E1L3N, Cell Signaling Technology) by immunohistochemistry (IHC). PD-L1 expression more than 1% in tumor cells was considered as PD-L1 positive. Moreover, we reviewed the medical records of 13 primary pulmonary LELC patients who received the treatment of PD-1/PD-L1 inhibitors in GLCI. Their clinicopathological characteristics and relevant prognostic data were analyzed. **Result:** Among the 53 patients with operable disease, the median age was 56 (36-78), there were 26 males and 27 females, 15 smokers and 38 nonsmokers. Positive rates of PD-L1 in the early pulmonary LELC were 78.8% (41/52,one specimen can't evaluate) and 73.1% (38/52) and 23.1% (12/52) respectively at the cutoff values of 1% and 5% and 50% positivity in tumor cells. ORR of PD-1/PD-L1 inhibition in the evaluable 12 patients with advanced LELC was 16.7% (2/12), and DCR was 75.0% (9/12). In the 6 patients with positive PD-L1 expression, ORR was 33.3% (2/6), DCR was 100.0% (6/6). The two responder patients got 55% and 64% shrinkage of the tumors respectively. All patients had no *EGFR* mutations. **Conclusion:** This preliminary study showed that pulmonary LELCs have remarkably high incidence of PD-L1 expression. PD-1/PD-L1 inhibitors might be an option for the treatment of advanced primary pulmonary LELC, which needs further investigation.

Keywords: lymphoepithelioma-like carcinoma; LELC ; PD-1/PD-L1 inhibitors

P2.06 MESOTHELIOMA
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P2.06-01 SHORT-TERM OUTCOME OF ENTIRE PLEURAL INTENSITY-MODULATED RADIOTHERAPY IN A NEOADJUVANT SETTING FOR MALIGNANT MESOTHELIOMA

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Background: The purpose of this study is to evaluate the safety and efficacy of the tri-modality treatment with neoadjuvant intensity-modulated radiotherapy (IMRT) for a resectable clinical T1-3N0-1M0 malignant pleural mesothelioma (MPM). **Method:** A total of ten malignant mesothelioma patients who received neoadjuvant radiotherapy between March 2016 and April 2018 were reviewed. Patients received 25Gy in five fractions to entire ipsilateral hemithorax including clinically suspicious lymph nodes. All patients were treated with helical tomotherapy. **Result:** All of the patients were men with a median age of 60 years. Epitheloid subtype was found in nine patients (90%) and type was unknown in one patient (10%). All patients received neoadjuvant chemotherapy with Alimta-cisplatin(AP) regimen. Nine patients (90%) completed 25Gy/5fxs radiotherapy and one (10%) completed 20Gy/4fxs. IMRT was well tolerated with only one acute grade 3 radiation pneumonitis. Surgery was performed one week (1 - 15 days, median 7.5) after completing IMRT. Extrapleural pneumonectomy (EPP) was performed in three patients (30%), and pleurectomy and decortications (PD) in six (60%). There was no grade 3+ surgical complication except one patient died from septic shock after EPP in one-month. Based on operative findings and pathologic stagings, adjuvant chemotherapy was delivered in six patients (60%), and one (10%) was decided to start adjuvant radiotherapy. After a median follow-up of 10.6 months (range 1.7 - 24.2), there is no evidence of local recurrence or distant metastasis. **Conclusion:** Neoadjuvant intensity-modulated radiotherapy (IMRT) can be safely delivered with a favorable radiation complication. An optimal strategy has to be made in resectable MPM patients who would benefit from neoadjuvant radiation and surgery. Further studies need to look at long-term outcomes.

Keywords: neoadjuvant radiotherapy, intensity-modulated radiotherapy, malignant mesothelioma

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P2.06-02 FEASIBILITY OF INTENSITY MODULATED RADIOTHERAPY AFTER PLEURECTOMY/DECORTICATION FOR MALIGNANT PLEURAL MESOTHELIOMA PATIENTS

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Background: Treatment strategies for patients with malignant pleural mesothelioma (MPM) include pneumectomy followed by radiation with considerable efficacy, although post-surgical morbidity and mortality are frequent. Recently, more conservative surgical approaches have been implemented, including Pleurectomy/Decortication (P/D), which spares the lung tissue while removing the malignant pleura and visible tumor. Although this approach significantly reduces surgical morbidity, it poses a challenge for post-surgical radiotherapy, as the risk of developing radiation pneumonitis is high. In this feasibility study we evaluated the loco-regional control and toxicity profile in patients with MPM treated with induction chemotherapy followed by P/C and Intensity Modulated Radiotherapy (IMRT) to the entire thoracic cavity. **Method:** Patients with MPM treated from October 2011 to February 2014 were screened for inclusion. All patients underwent 4 cycles of induction chemotherapy with cisplatin/gemcitabine or cisplatin/pemetrexed without progression followed by P/D. Thereafter, patients received IMRT to the thoracic cavity (50.4-54 Gy in 28-30 fractions), treated with 9-11 non-coplanar fields. **Result:** A total of 20 patients were screened for inclusion, from these, 13 patients were included in the final analysis. The median age was 61.3 ±10.3 years; 69.2% (9/13) were classified as low risk according to the European Organization for Research and Treatment of Cancer prognostic group. From the 13 patients, 12 (92.3%) had a histological diagnosis of epithelioid mesothelioma, while one patient (7.7%) presented with a sarcomatoid histology. Partial response to chemotherapy was observed in 61.5% (8/13) and stable disease in 38.5% (5/13). After P/D, only 23% (3/13) had residual macroscopic disease. The median follow-up was 23.6 months (7.5-44.7). Nine patients had recurrence or progression (6 distant [67%] and 3 loco-regional recurrences [33%]). 2-year Progression Free Survival was 31.3% (95%CI [8.72-57.51]). Only one patient died due to

hepatic metastases. Any grade Pneumonitis was reported in 69.2% (9/13), however only 22.2% (n=2) of patients presented grade ≥3 pneumonitis. The V5 of the contralateral lung was above 70% and the V20 of the total lung was 45% in these patients. No IMRT-related deaths were observed throughout the study. **Conclusion:** Results from this pilot study show that it is feasible to administer IMRT to patients who have undergone P/D while maintaining an adequate toxicity profile. In our study pulmonary toxicity was frequent; however there was only one event of grade 4 pneumonitis, meanwhile the loco-regional control using this treatment modality shows great promise. However, a larger study with a more robust sample size is required to draw strong conclusions.

Keywords: intensity modulated radiotherapy, pleurectomy/decortication, Mesothelioma

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P2.06-03 CAN WE PREDICT PATHOLOGICAL NODAL POSITIVITY IN MALIGNANT PLEURAL MESOTHELIOMA FROM PREOPERATIVE CLINICAL VARIABLES?

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Background: The associated morbidity from radical surgery implies that it should only be offered to those with the best prognosis. The prognosis following radical surgery for mesothelioma is significantly influenced by the presence of pathological nodal metastases. However, the prediction of nodal positivity is inaccurate and complicated. This can be attributed to the unique lymphatic drainage pattern in which many nodal groups (internal mammary, intercostal) cannot be biopsied preoperatively. Previous studies have correlated preclinical variables with poor prognosis (Pass, J Thorac Oncol.2014;9:856-64). **Method:** We have correlated clinical variables known to be associated with overall prognosis in mesothelioma with the pathological findings of systematic nodal dissection at thoracotomy and pleurectomy/decortication. The variables analysed: patient demographics, Haemoglobin and CRP, T and N stage on preoperative CT scan, duration of symptoms of weight loss and chest pain and cell type on preoperative biopsy. Data were summarised as median (range), mean (SD) and subject to Chi-squared test for the categorical data and Mann-Whitney Test for the numeric data and to regression analysis. **Result:** 32 patients(25males:7females)underwent extended pleurectomy decortication with intraoperative systematic nodal dissection. On pathologic diagnosis post-resection, 20(62%) patients were diagnosed with nodal metastasis. On univariate analysis, only age and CRP was statistically significant (p=0.049,respectively 0.05). The remaining variables did not achieve statistical significance. There were statistical trends suggesting that nodal positivity was more likely in the younger males with a lower Haemoglobin and a raised CRP.

Median (range)	Node negative n=12	Node positive n=20	P value
Age (years)	71 (58-76)	66 (33-78)	0.049
Symptom duration (months)	6 (4 -10)	6 (4-10)	0.711
BMI	25.5 (22-40)	26 (19-38)	0.952
Hb (g/l)	133.5 (98-145)	118 (82 -145)	0.077
WBC	7 (4 – 14.8)	7.7 (2.5 -10.6)	0.826
Platelets	318 (170-599)	291 (132 -918)	0.675
CT T stage	3 (1-4)	3 (1-4)	0.436
CT N stage	0.5 (0-2)	0.5 (0-2)	0.194
C-reactive protein	7 (1-123)	23 (1-154)	0.053
Epithelioid:non-epithelioid	1:1	3:1	0.306

CT correctly predicted positive node status in 30% of cases and negative node status in 80% of cases. **Conclusion:** Nodal positivity in patients suitable for EPD cannot be reliably predicted by CT but can be inferred from certain clinical variables. Future work in a larger population is required to identify a definitive pre-operative model. This will allow for better selection of patients for primary surgical intervention or alternatively for induction chemotherapy.

Keywords: Mesothelioma, Lymph nodes, Pleura

P2.06 MESOTHELIOMA
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P2.06-04 THROUGHPUT OF A SPECIALIST MESOTHELIOMA MULTIDISCIPLINARY TEAM MEETING AT A RADICAL TREATMENT CENTRE IN THE UNITED KINGDOM

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Background: Multidisciplinary team (MDT) meetings are of particular value in cases where decision making is complicated by clinical equipoise. Patients should be actively considered for all established treatment and clinical trial options for which they are suitable. **Method:** A specialist regional mesothelioma MDT - involving physicians, radiologists, oncologists, surgeons, and allied health professionals - was established in 2013. Patients were considered for the full range from palliative to radical surgical treatment options, all of which are offered locally at our institution. Electronic records of MDT activity were retrospectively analysed. **Result:** 543 patients - 82% were male, average age 71±9 years - were discussed in our specialist MDT, between July 2013 and March 2017, with referrals from 50 hospitals from around the United Kingdom. 61% of patients were from outside the direct specialist referral (regional) catchment area. Patients were recommended for radical surgery (44%), chemotherapy or radiotherapy (36%), active symptom management (14%), or palliative care (6%). Average survival post MDT discussion was 8±6 months. **Conclusion:** A specialist regional mesothelioma MDT is invaluable in the context of patient throughput; and is valuable in determining treatment strategies. Its impact on survival and quality of life outcomes is still to be determined.

Keywords: Multidisciplinary Team, MDT, Mesothelioma

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P2.06-05 TTFIELDS APPLIED TO THE TORSO AND UPPER ABDOMEN: SAFETY META-ANALYSIS OF 176 PATIENTS FROM FOUR PHASE I-II TRIALS

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Background: Tumor Treating Fields (TTFields), a non-invasive, antimitotic treatment delivered through transducer arrays, is approved for glioblastoma. The phase 3 trial in newly diagnosed glioblastoma showed no significant increase in systemic adverse events (AEs) except for localized dermatitis underneath the arrays. The safety of TTFields was investigated in four phase I-II non-brain malignancies: non-small-cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), pancreatic cancer and ovarian cancer. **Method:** The TTFields phase I-II studies analyzed were: EF-15 (n=41, advanced NSCLC with pemetrexed), PANOVA (n=40, advanced pancreatic adenocarcinoma with gemcitabine +/- nab-paclitaxel), STELLAR (n=64, MPM with platinum/pemetrexed) and INNOVATE (n=31, recurrent ovarian carcinoma with weekly paclitaxel). TTFields were applied for 12-18 hours at 150-200 kHz per tumor histology. Patients received standard-of-care systemic chemotherapy for their disease. Severity and frequency of AEs and association with TTFields were evaluated (CTCAE V 4.0). **Result:** Patient median age was 69 years (range 41-81), 73 (49-81), 68 (43-78) and 60 (45-77) for EF-15, PANOVA, STELLAR and INNOVATE, respectively. Patients were ECOG status 0-1, except for 7 patients in EF-15 with ECOG 2. Observed toxicities were mostly related to underlying disease or standard chemotherapy. Grade 1-2 gastrointestinal (GI) toxicities were: constipation (16%), diarrhea (14%), nausea (27%) and vomiting (13%). Grade 1-2 general disorders such as asthenia were common but less than 20%. Grade 3-4 dyspnea was observed in 6% of NSCLC patients. No clinically significant cardiac AEs were observed and mild arrhythmias were observed in less than 2% of patients. The common TTFields-related AE was dermatitis under the transducer arrays (50% Grade 1-2; 6% Grade 3 dermatitis and 7% Grades 1-2 pruritus). Dermatologic AEs managed using published guidelines were fully resolved. **Conclusion:** Treatment of solid tumors with TTFields (150-200 kHz) to the lungs, pleura, abdomen and upper pelvis did not result in treatment-related pulmonary, cardiac, hematological or gastrointestinal toxicity. Expected dermatological toxicity (50%) beneath the transducer arrays was easily managed.

Keywords: TTFields; torso arrays; Safety meta-analysis

P2.06-06 ROLE OF GITRL-GITR SYSTEM IN PROMOTING PROLIFERATION OF MALIGNANT MESOTHELIOMA

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Background: Using microarray analysis to compare the gene expression profile of untreated murine mesothelioma cell line (RN5), RN5 treated with cisplatin, RN5 treated with radiation, and enriched mesothelioma stem cell (RN5-EOS-Puro2), we found 41 genes potentially linked to cell stemness. Among those 41 genes, Tnfsf18(GITRL) was one of the cell surface markers which is likely related to tumor proliferation. We therefore decided to analyze the role of this ligand and it's receptor (GITRL-GITR system) in proliferation of human mesothelioma cancer cells. **Method:** Three human mesothelioma cell lines (CRL5820, CRL5915, CRL5946) were used in this study. They were treated with cisplatin and Cs-137 irradiator respectively. The rt-PCR and Western Blot were used to evaluate the GITRL and GITR expression level at different time points. To evaluate the effect of GITRL-GITR system in mesothelioma cell lines we design in vitro and in vivo model for it. A neutralizing monoclonal antibody (mAb) was used to break the GITRL-GITR system in vitro and in vivo. In the in vitro model, mesothelioma cells were seeded into 96 well plates and the MTT test was used to compare cell proliferating rate 4 days after seeding. In the in vivo model we injected the CRL5946 cells into the peritoneal cavity and implanted patient-derived xenograft subcutaneously of the NOD/SCID mice. We sacrificed mice 4 weeks later to evaluate tumor spheres formation number and draw tumor growing curve. **Result:** All the three mesothelioma cell lines demonstrated increased expression of Tnfsf18 (GITRL) and Tnfrsf18(GITR) at an mRNA and protein levels after treatment with chemotherapy or radiothreapy. Breaking the GITRL-GITR system with neutralizing mAb decreased cell growth and survival rate in mesothelioma cell lines after chemotherapy or radiotherapy. In vitro cell viability test, the MTT test results showed in cisplatin-treated or radiation-treated cell lines with adding mAb to break GITRL-GITR system, the cell viability decreased. In vivo xenografting model of CRL5946 cell line which is treated in advance by chemotherapy or radiotherapy, the average tumor sphere number (>100um) also decreased after using mAb intraperitoneally. The inhibiting effect of GITR neutralizing monoclonal antibody could be demonstrated in vitro and in our in vivo model. In patient-derived xenografting subcutaneous model, the mAb could also delay cell growth. **Conclusion:** The results of our study demonstrate that the GITRL-GITR system could play an important role in mesothelioma cells growth and survival especially after chemotherapy or radiotherapy.

Keywords: Mesothelioma, GITRL-GITR system

P2.06-07 GENOMIC DELETION OF BAP1 AND CDKN2A ARE BETTER MM DIAGNOSTIC BIOMARKERS.

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Background: Malignant mesothelioma (MM) is deadly cancer caused by asbestos exposure and has limited treatment options. More reliable MM biomarkers and more accurate detection methods are urgent requirements for early identification of this cancer. MM cell cultures are essential *in vitro* models for potential treatment options analysis. In this study, we established primary MM cell lines and characterised them with current biomarkers as well as utilising the latest digital droplet PCR instrument for genomic deletion analysis. We aim to discover better diagnostic biomarkers for detection of MM. **Method:** Pathologically confirmed MM samples from patients were used to establish MM cell lines. MM cells were grown over 20 passages to ensure homogenous MM cell populations. Original MM tissue samples and established MM cells were stained with H&E and verified with a diagnostic biomarker panel (CK-8/18, Calretinin, CK5/6, CD141, WT-1, D2-40, EMA, CEA, Tag-72, BG8, CD15, TTF-1 and BAP1). MM cells were grown in 2D and 3D conformations for biomarker staining and compared to stained tissue biomarkers. Scores and comments were provided by pathologists experienced in MM diagnosis. Laser Capture micro-dissected (LCM) MM samples and established cells were used for DNA isolation. Genomic deletions were analysed by digital droplet PCR for copy number variations of BAP1 and CDKN2A. **Result:** 15 MM cell lines established from original tissue were grown over 20 passages which produced homogeneous cell populations under normal cell culture conditions. Cells grown in 3D with H&E staining exhibited better tumour architecture, cell-to-cell contacts and tumour cell-like morphology when compared to cells grown in standard 2D culture. The percentage of MM biomarker levels showed variation between original tissue and cells established in culture. Genomic deletions of BAP1 and CDKN2A, however, showed consistent levels between the two. **Conclusion:** Conventional immunohistochemistry MM biomarkers did not show sustained correlation between tissues of origin to established cell culture, whereas genomic deletion analysis did. Genomic deletion analysis has the potential to be used as more accurate biomarkers for MM diagnosis.

P2.06-08 ABT-806 DERIVED ANTIBODY DRUG CONJUGATES (ADCS) INHIBIT GROWTH OF MALIGNANT MESOTHELIOMA IN-VIVO

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Background: Malignant mesothelioma (MM) is an aggressive malignancy of the pleura with limited therapeutic options, and is associated with a poor prognosis. EGFR is known to be highly over-expressed in mesothelioma with reported EGFR overexpression between 44 to 97%. We have developed an anti-EGFR antibody (ABT-806), which is tumour specific and robustly inhibits EGFR-expressing tumours. We aimed to establish the validity and feasibility of targeting tumour expressed EGFR in MM using ABT-806 novel ADCs (ABT-414 and ABBV-221). **Method:** We evaluated EGFR and mAb 806 immunohistochemistry in 4 MM cell lines (MSTO-211H, NCI-H2052, NCI-H28, NCI-H2452) and performed *in-vitro* cell proliferation assays to evaluate the antineoplastic potential of mAb806-related ADCs. In-vivo therapeutic studies using the biphasic mesothelioma cell line (MSTO-211H) were conducted with treatment groups involving ABT-414, ABBV-221, ADC control, cisplatin chemotherapy. We also performed quantitative biodistribution and imaging of mAb806 ADC uptake (^{89}Zr mAb806 ADC) to allow correlation of mAb806 ADC concentration in tumours. **Result:** mAb806 to be bound strongly to three of four MM cell lines (MSTO-211H, NCI-H2052 and NCI-H28). Cell proliferation assays (CPA) also demonstrated ABT-414 and ABBV- 221 had significant cell growth inhibition demonstrated in the range between 1 to 10ug/ml for MM cell lines. In MSTO211H xenograft model significant anti-tumour response to both ABT-414 and ABBV-221 ($p<0.01$), was demonstrated. High, specific targeting of ^{89}Zr-ch806 to MM tumour in-vivo was also shown. **Conclusion:** ABT-806 ADCs show potent anti-tumour activity in MM model, and warrant further exploration as a potential therapy for MM.

Keywords: antibody drug conjugate, epidermal growth factor receptor (EGFR), Mesothelioma

P2.06-09 MIST3: A PHASE II STUDY OF ORAL SELECTIVE AXL INHIBITOR BEMCENTINIB (BGB324) IN COMBINATION WITH PEMBROLIZUMAB IN PTS WITH MALIGNANT MESOTHELIOMA

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Background: Mesothelioma is a cancer with significant unmet need, with only one line of therapy licenced in the UK. AXL is a member of the TAM (Tyro3, AXL, Mer) family of receptor tyrosine kinases that regulate multiple cellular processes including survival, proliferation and migration. An analysis of AXL expression in patients with mesothelioma reported an overexpression in 74% of the tumours examined. Several cell types associated with the suppressive tumour immune microenvironment express AXL, including natural killer cells and tumour-associated macrophages. AXL is an important regulator of tumour plasticity

related to epithelial-to-mesenchymal transition, thereby contributing to evasion of antitumour immune response. Hence, AXL signalling contributes uniquely to tumour intrinsic and microenvironmental immune suppression. Bemcentinib (BGB324), a potent, selective orally bioavailable small molecule inhibitor of AXL, has demonstrated effective inhibition in pre-clinical models and is currently being trialled in combination with pembrolizumab in patients with advanced non-small-cell lung cancer, breast cancer and melanoma. Pembrolizumab has high affinity and potent receptor blocking activity for PD-1, therefore inhibiting the interaction with PD-L1. Recent data showed that the combination of bemcentinib with anti-PD-1 blockade profoundly enhanced anti-tumour activity in the syngeneic Lewis Lung (LL/2) lung carcinoma model. **Method:** This is a single arm phase IIA clinical trial of bemcentinib and pembrolizumab in patients with relapsed mesothelioma. MiST3 is one arm of a broader umbrella study- a stratified multi-arm phase IIA clinical trial to enable accelerated evaluation of targeted therapies for relapsed malignant mesothelioma. 25 patients recruited to MiST3 will receive a loading dose of 400mg bemcentinib, followed by daily doses of 200mg, alongside IV infusions of 200mg pembrolizumab on day-one of each 21-day cycle. The primary objective is to establish 12 week disease control rate (DCR), secondary objectives include safety and tolerability, objective response rate and 24 week DCR, as assessed by modified RECIST. Patients will continue therapy until disease progression, unacceptable toxicity or a maximum 2-year duration. A pre-treatment biopsy and serial plasma samples will be mandatory for exploratory research. Exploratory objectives include; correlation of PD-L1 and AXL expression levels with response to treatment, tumour mutation burden to interrogate the genomic correlates of treatment response, immune regulated gene signature in RNA extracted from tumour samples, to correlate the impact of tumour infiltrating lymphocytes with response, and correlations between gut microbiome composition and response to therapy will be sought using 16sRNA sequencing. First patient first visit is anticipated- Q3 2018. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Mesothelioma, Immunotherapy, Axl inhibition

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P2.06-10 COMBINATION CHEMOTHERAPY WITH CISPLATIN, PEMETREXED, AND NIVOLUMAB FOR MALIGNANT PLEURAL MESOTHELIOMA: A TRIAL IN PROGRESS

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Background: Combination chemotherapy with cisplatin and pemetrexed is the standard treatment regimen for malignant pleural mesothelioma (MPM); however, the median overall survival (OS) is just about 12 months. Additional treatment options are urgently needed. The aim of this study is to assess the efficacy and safety of combination chemotherapy with cisplatin, pemetrexed, and nivolumab for unresectable MPM. **Method:** This is a single-arm, prospective, non-randomized, non-comparative, open label, multicenter, phase II trial. This study will assess the efficacy and safety of the first-line combination therapy of cisplatin, pemetrexed, and nivolumab for advanced or metastatic MPM. Key inclusion criteria includes 1) age older than 20 years, 2) pathologically-confirmed MPM, 3) measurable lesion designated by modified RECIST criteria, 4) tumor sample available to test for Programmed Death-Ligand 1 (PD-L1) expression, 5) Eastern Cooperative Oncology Group Performance Status is 0 or 1. Combination chemotherapy with cisplatin (75 mg/m^2), pemetrexed (500 mg/m^2), and nivolumab (360 mg/body) is administered every 3 weeks for a total of 4 to 6 cycles. Then, maintenance therapy with nivolumab will be administered until disease progression, unacceptable toxicities, or the patient's condition meets the withdrawal criteria. The primary endpoint is the centrally-reviewed overall response rate. The secondary endpoints include the disease control rate, overall survival, progression-free survival. Safety and adverse events will also be evaluated. **Result:** This phase II trial commenced in January 2018. A total of 18 patients will be enrolled from four Japanese institutions within 1 year. **Conclusion:** This is the first prospective trial to evaluate the effect of an anti-PD-1 antibody combined with cisplatin and pemetrexed for unresectable MPM. This trial has been registered in the UMIN Clinical Trials Registry as UMIN000030892.

Keywords: programmed death-1, immune checkpoint inhibitor, asbestos

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P2.06-11 A PHASE I/II STUDY OF INTRAPLEURAL AD-SGE-REIC ADMINISTRATION IN PATIENTS WITH REFRACTORY MALIGNANT PLEURAL MESOTHELIOMA

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Background: Reduced expression in immortalized cell (REIC)/Dickkopf-3 (Dkk-3) is a tumor-suppressor gene and REIC/Dkk-3 expression was markedly downregulated in various human cancer cells. REIC/Dkk-3 protein is also known as a key player, namely an antagonist of the Wnt signaling pathway. Ad-SGE-REIC is an adenoviral vector carrying REIC/Dkk-3 that mediates cancer cell death induction and anti-cancer immunity augmentation. **Method:** We conducted a phase I/II, 3+3 design, dose escalation study in malignant pleural mesothelioma (MPM) patients (pts) with measurable lesions. Pts with refractory to or unsuitable for standard chemotherapy received 2 intrapleural administrations of Ad-SGE-REIC on days1 and 4. Three escalating doses of level (DL) 1: 3.0×10^{11}, DL2: 1.0×10^{12} and DL3: 3.0×10^{12} viral particles were employed. This dosage and regimen were set by considering the reason of manufacturing and neutralizing anti-body for adenovirus. The safety and dose-limiting toxicities (DLTs) of Ad-SGE-REIC were evaluated for 32 days. Continuous safety and efficacy were assessed for 172 days using modified RECIST (mRECIST). The concentrations of REIC/Dkk-3 in pleural fluid also were measured as indirect indication of targeted gene expressions. **Result:** From 07/2015 to 09/2017, a total of 13 pts have been treated at DL1 (n=4 included one fatal case within 32 days), DL2 (n=3) and DL3 (n=6). Male: 100%; median age 70; PS 0: 23%, 1: 69%, 2: 8%; epithelial/biphasic histology: 69%/15%; Stage III-IV: 77%; previous chemotherapy use with platinum-pemetrexed: 92%. Treatment-related AEs (TRAEs) were all Grade 1-2 and no DLTs occurred. The most frequent TRAEs were fever and CRP increase based on adenovirus infection. Tumor responses assessed by independent central review showed that there was no objective response and DCR was 62% (8/13 pts). Median PFS was 3.4 months at all groups and 5.7 months at DL3. A remarkable increase of REIC/Dkk-3 concentration in pleural fluid was determined (6/13 pts, prominently high in DL3). **Conclusion:** The intrapleural administration of Ad-SGE-REIC up to 2 cycles was safe and well tolerated in MPM pts and promising results of efficient REIC/Dkk-3 expression and durable disease control were obtained. We are planning phase II study using repeated intrapleural or intratumoral administration.

Keywords: Wnt antagonist, gene therapy, Mesothelioma

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P2.06-12 IMPROVING QUALITY OF CARE FOR PLEURAL MESOTHELIOMA: 2018 NATIONAL MESOTHELIOMA AUDIT RESULTS FOR ENGLAND AND WALES

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Background: The National Lung Cancer Audit (NLCA) has previously produced reports detailing standards of care for mesothelioma in 2013 (covering diagnoses in 2008-2012) and in 2015 (covering 2014), funded by Mesothelioma UK. We have completed a further analysis using the most recent data available. **Method:** Data on patients in England and Wales with a diagnosis of mesothelioma in the years 2014-2016 were extracted from the National Cancer Registration and Analysis Service (England), and the Cancer Network Information System Cymru (Wales). The data were linked to other datasets, including Hospital Episode Statistics (HES), the National Radiotherapy Dataset (RTDS), the Systemic Anti-Cancer Dataset (SACT), pathology reports and death certificate data. **Result:** 6,932 cases of malignant pleural mesothelioma were analysed. 84% of cases were male. Performance Status (PS) was recorded in 69% (falling) and tumour stage in 54% (rising). 88% of patients had a pathological confirmation of the diagnosis, and in 64% there was a pathological subtype recorded. 51% of patients received active anti-cancer treatment, and 59% of PS 0-1 patients received chemotherapy (up

from 41% and 54% in previous reports). 4% of patients received radical debulking surgery. One-year survival of 38% was lower than previous reports but should be interpreted with caution. Three-year survival was only 7%. Variation in the quality of the pathological diagnosis and in rates of treatment and survival are seen across regions (Table 1).

Cancer Network	No. of Cases	Pathological Subtyping[1]	Anti-cancer treatment[2]	Chemotherapy[3]	Surgery[4]	Radiotherapy[5]	One-year survival[6]
London Cancer Alliance (N44)	436	70.3	56.0	78.3	5.0	20.9	41.4
Cheshire and Merseyside (N50)	259	69.2	45.9	50.8	1.9	26.6	38.2
Greater Manchester, Lancs and S. Cumbria (N51)	616	37.1	55.2	70.7	1.3	20.6	36.9
Northern England (N52)	528	74.9	50.4	69.4	0.8	20.3	37.3
Yorkshire and The Humber (N53)	772	49.6	46.4	54.7	3.0	18.3	37.6
East of England (N54)	827	73.3	49.7	56.3	7.5	18.0	40.2
East Midlands (N55)	466	71.9	51.7	53.3	14.4	13.7	38.4
West Midlands (N56)	466	52.8	51.1	52.3	6.0	28.5	30.8
South West (N57)	586	73.8	48.0	51.1	1.4	26.1	39.8
South East Coast (N58)	661	61.6	54.3	62.7	5.4	22.7	35.7
Thames Valley (N59)	238	52.7	56.7	58.6	7.1	30.7	41.9
Wessex (N60)	462	73.5	50.2	48.6	1.7	28.8	37.8
London Cancer (N61)	325	66.8	58.2	59.3	3.1	24.6	40.3
North Wales (NWW)	78	60.0	42.3	54.1	3.8	16.7	39.0
South Wales (SWCN)	212	77.7	53.8	60.5	0.0	23.6	39.4

[1] Proportion of patients where mesothelioma histological subtype is recorded [2] Proportion of patients receiving one of surgery, radiotherapy or chemotherapy [3] Proportion of patient with PS 0-1 who received chemotherapy as treatment of their mesothelioma [4] Proportion of patients undergoing radical surgery as treatment of their mesothelioma [5] Proportion of patients receiving radiotherapy as treatment of their mesothelioma [6] Proportion of patients with mesothelioma who survive at least 1 year following diagnosis

Table 1: Main performance measures by Cancer Network (pleural mesothelioma)

Conclusion: Despite a rise in the number of eligible patients receiving chemotherapy, there remains poor long-term survival for patients with mesothelioma. As well as introduction of novel therapies, improvements in care and outcome could be achieved by reducing variation.

Keywords: Pleural mesothelioma, variation, outcome

P2.06 MESOTHELIOMA
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P2.06-13 POOR NUTRITIONAL STATUS IS A POOR PROGNOSTIC FACTOR IN MALIGNANT PLEURAL MESOTHELIOMA

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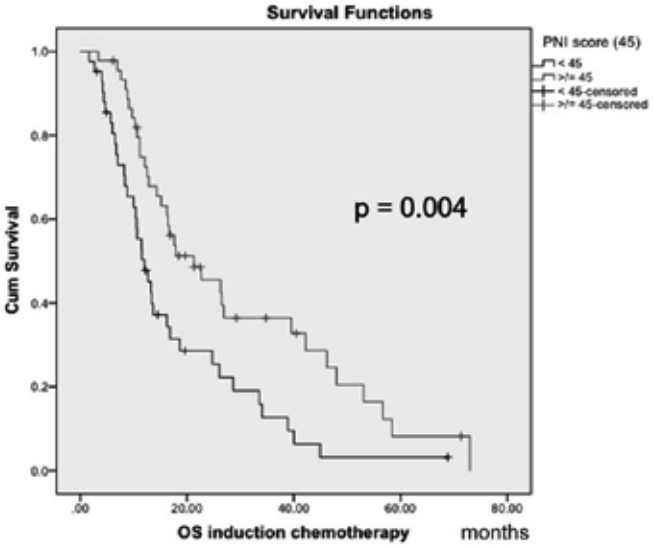
Background: To investigate the clinical meanings of nutritional status in malignant pleural mesothelioma (MPM). **Method:** We retrospectively reviewed 87 MPM patients intended to be treated within a multimodality treatment (MMT) concept between September 1999 and April 2017. We used the prognostic nutritional index (PNI) to evaluate the nutritional status; serum albumin (g/l) + 5 × lymphocyte (G/L) in peripheral blood. Primary endpoint of this study was to investigate the correlation between PNI and overall survival (OS), and secondary endpoint was to investigate the association between PNI and completion rate of MMT. **Result:** Of 87 enrolled patients, 61 (70.1%) patients were completed MMT. Median pretreatment PNI was 45.1 (range: 24.5–58.8). We divided this cohort into Low-PNI group (PNI < 45, n=42) and High PNI group (PNI >= 45, n=45). The completion rate of MMT was significantly higher in High PNI group than Low (82.2% vs 57.1%, p=0.018). On survival analyses, Low PNI group had significantly (p=0.004) shorter median OS than High PNI group (12.0 vs 21.3 months, p=0.004). In multivariate analysis using Cox regression model, which showed Low PNI had increased the risk of death compared with High-PNI (HR: 2.64; 95%CI, 1.32-5.28; p=0.006), as well as elevated C-reactive protein (HR: 20.8; 95%CI, 1.17-3.70; p=0.012)



Kaplan-Meier survival curves evaluate overall survival according to the prognostic nutritional index (PNI) value.

Conclusion: Pretreatment PNI is a novel prognostic factor in MPM patients intended to be treated within MMT concept. Low PNI was significantly associated with low completion rate of MMT.

Keywords: Mesothelioma, nutritional status, multimodal treatment

P2.06-14 DOES SIZE MATTER? A POPULATION-BASED ANALYSIS OF MALIGNANT PLEURAL MESOTHELIOMA

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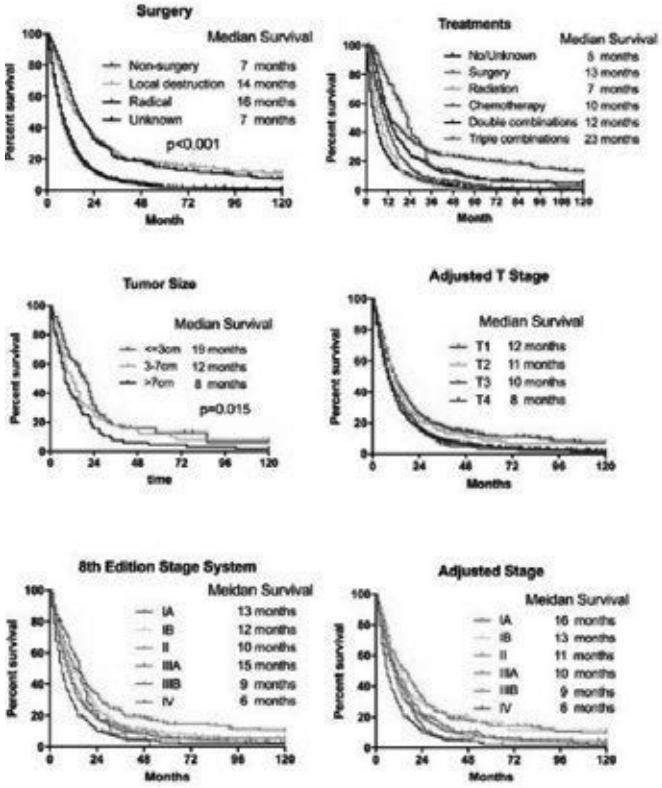
Background: The malignant pleural mesothelioma (MPM) is a rare and aggressive malignancies. A validated staging system is crucial for disease evaluation, treatment selection and follow-up strategy. The 8th edition staging system for MPM has been recently proposed. However, it has not been widely accepted due to the absence of validation of large cohort. Besides, the size of tumor is not taken into consideration. We intend to elucidate the prognostic value of the size of MPM and evaluate the current staging system via the data of SEER database. **Method:** All cases of primary MPM were identified and extracted from the SEER database during the period of 1973-2013. Kaplan-Meier method was used to analyzed overall survival and cancer-specific survival. The prognostic factors were identified by Cox regression. LOWESS smoothing regression curve was also utilized. The cut-off points of size in different strata were identified based on the graphical characteristics. The tumor stage was established incorporating tumor extension and size. The adjusted clinical staging system was proposed and compared with the previous MPM staging system by likelihood ratio test. **Result:** A total of 2138 patients were included. The 1,3 and 5-year survival rates of MPM were 39.4%, 11.8% and 3.8%. Tumor extension, lymph node involvement and metastasis, tumor size, histology and differentiatial grade were significant prognostic factors. Radical surgery and local destruction might have the similar effect in early stage patients. Triple combination treatments showed a superiority to others. The cut-off points of tumor size were ≤3cm and >7cm. The adjusted staging system was proved to be more accurate.



Conclusion: Tumor size matters in the prognosis of MPM especially in early stages. The adjusted TNM staging system incorporating tumor size has better accuracy than the 8th edition. However, some stages had not been fully verified. More cases of early stages are warranted for essential revision.

Keywords: stage, SEER, malignant pleural mesothelioma

P2.06-15 MALIGNANT PLEURAL MESOTHELIOMA IN YOUNG ADULT PEOPLE IN UGANDA

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Background: O**bjectives:** malignant pleural mesothelioma (MPM) is characterized by long latency period between exposure to asbestos and development of the disease so we hypothesize that MPM in the young has different characteristics **Method:** This is a retrospective study including all eligible patients with malignant pleural mesothelioma presenting to Uganda Cancer Institute, Makerere University during the period from 2014 to 2017. Patients were divided into two groups: Group 1: patients aged ≤ 45 years. Group 2: Patients aged > 45 years. Both groups were assessed regarding different clinic-pathological features .Primary Objectives: comparison of different epidemiological features of both groups. Secondary Objectives: Assessment of clinical response (CR), progression free survival (PFS) and overall survival (OS) in both groups **Result:** 102 Patients were included with median follow up of 14.4 months. Group (1) included 35 patients with mean age 40± 3.65 years (31 to 45 years).Group (2) included 67 patients with mean age of 58.6± 8.5 years (46 to 87 years). 68% of group (1) came from endemic areas which is significantly higher than group (2): (35.8%), p = 0.02. History of Asbestos exposure was highly significantly different between the 2 groups, 77.1% in group (1) versus 38.8% in group (2), p < 0.001. Other factors showed no significant differences between the two groups. Overall clinical response (CR+PR) was 20% in group (1) versus 17.9 % in group (2). P=0.7. There was a trend towards longer median PFS in young patients, (19.8 ± 8.4 versus 6.9 ± 1.4 months). p = 0.09. The median OS of young patients is significantly longer (20.6± 6.3 months) than older patients (11.4 ± 3.6).p = 0.05. **Conclusion:** Mesothelioma in the young adult is more sensitive to asbestos exposure, has better OS and likely a different disease entity which needs further studies to understand its underlying biological features.

P2.06-16 YB-1: AN IMPORTANT DRIVER OF MESOTHELIOMA DRUG RESISTANCE AND A POTENTIAL NOVEL THERAPEUTIC TARGET

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Background: Malignant pleural mesothelioma (MPM) is an aggressive malignancy and current therapy is essentially palliative. Novel therapy targets are urgently needed. YB-1 is a multifunctional oncoprotein associated with poor patient outcome and is related to increased chemoresistance in tumours including NSCLC. It is widely accepted that YB-1 plays a role in the cell growth of many cancers, and we recently confirmed this in MPM cells. Here, we begin to evaluate YB-1 as a therapeutic target in this disease. **Method:** YB-1 expression was determined by Western blot in MPM cell lines and their drug resistant sublines. Growth and colony formation assays were conducted after transfection with YB-1- or control-siRNA. These were also carried out in combination with cisplatin, gemcitabine or vinorelbine treatment. Apoptosis was assessed by PI and annexin V staining in YB1 knockdown MPM cells. Migration of MPM cells was measured using videomicroscopy and manual cell tracking. Luciferase-expressing MPM cells transfected with YB-1- or control-siRNA were injected into female SCID mice (n=10, intra-peritoneal injection). Tumour growth was monitored via luminescence by injecting luciferin (intra-peritoneal injection) and measuring bioluminescence on an In Vitro Imaging System (IVIS) once a week for 4 weeks. Tumour weight determined after humane euthanasia of animals at the termination of the experiment. **Result:** YB-1-siRNA significantly inhibited the growth of MPM cell lines *in vitro* and was overexpressed in MPM cells compared to the immortalised mesothelial cell line MeT-5A. Growth of MeT-5A and primary mesothelial cell lines was not affected significantly by YB-1 knockdown. Mice injected with YB-1 knockdown cells displayed significantly lower tumour burden, evidenced by bioluminescence in live mice using IVIS and lower tumour weight after harvest. TALI assays showed an increase in apoptotic cells after YB-1 siRNA transfection *in vitro*, and cells transfected with siRNA showed sensitisation to cisplatin and vinorelbine. YB-1 was expressed at higher levels, and higher migratory capacity was observed in drug resistant MPM cell lines compared to parental cell lines. **Conclusion:** These results highlight the importance of YB-1 in MPM biology both *in vitro* and *in vivo*. YB-1 knockdown inhibits growth via apoptosis, sensitises MPM cells to

commonly prescribed drugs and contributes to a change in behaviour of drug resistant MPM cells. This project serves as a basis for the further investigation of YB-1 as a novel therapeutic target.

Keywords: Y-box binding protein-1, Mesothelioma, drug resistance

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P2.06-17 REAL-WORLD ACCURACY OF MALIGNANT PLEURAL MESOTHELIOMA (MPM) PREOPERATIVE MAGNETIC RESONANCE IMAGING (MRI) FOR STAGING THE DIAPHRAGM.

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Background: Magnetic resonance imaging (MRI) of the chest is commonly employed for preoperative staging of patients with malignant pleural mesothelioma. Here we evaluate the accuracy of preoperative MRI for detection of diaphragmatic invasion in patients undergoing pleurectomy in a real-world setting. **Method:** All adult patients who had a MRI of the chest performed as part of routine preoperative staging with subsequent pleurectomy for malignant pleural mesothelioma during a 20-month interval were identified. Patients without available MRI imaging reports were excluded. MRI reports for each patient were reviewed by a thoracic radiologist for evidence of diaphragmatic invasion and correlated with intraoperative findings. The MRI images for those patients with discrepant readings between MRI exam and intraoperative findings of diaphragm invasion were directly reviewed by the radiologist to assess for technical aspects that may have contributed to limitations in imaging interpretation. **Result:** A total of 16 adult patients with MPM, 14 male and 2 female, had preoperative MRI examinations performed with reports that were available for review, noting that a subset of examinations were obtained at outside community imaging sites resulting in variability of the imaging techniques and scanner types. Five patients had suspected or definitive diaphragmatic invasion on MRI, all of which were confirmed at pleurectomy. However, 9 of the patients that were initially assessed by MRI as not having diaphragmatic invasion, were later found at surgery to have some degree of diaphragmatic invasion necessitating diaphragmatic repair or diaphragmatic graft placement. When MRI exams were analyzed from patients that had missed diaphragmatic invasion on MRI interpretation, technical parameters such as differences in study image acquisition and technical artifacts due to cardiac, aortic pulsation and respiration motion may have contributed to the lack of identification of diaphragmatic invasion. **Conclusion:** MRI for preoperative planning in patients with MPM may miss diaphragmatic invasion. Further study is needed to determine if technical factors may contribute to limitations in detection of diaphragmatic invasion in MPM with a goal to optimize and harmonize MRI imaging protocols for preoperative staging.

Keywords: Mesothelioma, magnetic resonance imaging, Staging

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P2.06-18 COMPARISON OF EXTUBATION TIME OF PLEULECTOMY/ DECORTICATION WITH LOBECTOMY UNDER GENERAL ANESTHESIA USING DESFLURANE

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Background: Pleurectomy/decortication (P/D) is an operation to dissect the entire visceral and parietal pleura. Chief complications are hemorrhage and prolonged air leak. To avoid mechanical ventilation postoperatively, good recovery of spontaneous respiration and emergence are importent. We evaluated emergence status in patients who were underwent P/D with desflurane (DES) anesthesia in the clinical settings. **Method:** Records of consecutive patients at our hospital who were underwent P/D from May 2013 to January 2018 and lung lobectomy via thoracotomy from June 2016 to August 2017 were collected. Patients anesthetized with DES were investigated. Lobectomy with chest wall resection were excluded. P/D group (n=19) and control group (n=20) were analyzed. General anesthesia was maintained with DES (3-5%), remifentanil, and rocronium combined with epidural anesthesia. Administration of DES was abruptly discontinued jist after postoperative X-ray examination. A patient was extubated after sugamadex was injected. Extubation time (T1) was defined as duration from the end of operation to extubation. Continuous variables were expressed as median and interququartile range (IQR). Fisher's exact test and Mann-Whitney U-tests were used for statistical analysis. **Result:** There were no significant difference in demographic data (age, gender, BMI, PaO2, Hb, ALB) between the two groups, except for %VC and FEV1%. All patients were extubated after surgery. There was no significant difference in T1 between the two groups. Despite significantly larger amount of blood loss, longer operation and anesthesia time in the P/D group, time independent recovery of DES was achieved as same as the control group.

	P/D group n=19	Control group n=20	P value
%VC (%)	73 (64-89)	98 (84-107)	<0.001
FEV1% (%)	82 (76-85)	75 (64-81)	<0.05
Blood loss (mL/kg)	29 (22-44)	3 (1-7)	<0.001
Operation time (mim)	527 (458-555)	293 (257-326)	<0.001
Anesthesia time (min)	589 (531-626)	360 (313-397)	<0.001
T1 (min)	18 (16-25)	23 (16-29)	0.628

Conclusion: This retrospective clinical study showes good emergence and recovery following prolonged desflurane anesthesia. Desflurane is a useful agent for patients underwent P/D.

Keywords: Inhalation anesthetics, Mesothelioma, Thoracic Surgery

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P2.06-19 TARGETING POLYAMINES AS POTENTIAL ADJUVANT THERAPY IN MALIGNANT PLEURAL MESOTHELIOMA XENOGRAFT MODELS

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Background: Inhaling asbestos fibers is one of the commonest of malignant pleural mesothelioma (MPM). Although the import and use of asbestos have been restricted, the incidence of MPM is still rising due to a long lag time in malignant transformation. In 2004, the US Food and Drug Administration approved a combination of pemetrexed with cisplatin for treatment of unresectable MPM. At the same time, development of novel adjuvant therapeutic options for resected early-stage disease is also urgently needed. Ornithine decarboxylase (ODC) is highly expressed in 211H and H226 MPM xenografts and clinical tumor samples. Upregulation of ODC increases polyamine production and enhances tumor growth. a-difluoromethylornithine (DFMO) is a specific ODC inhibitor. Recent preclinical studies have demonstrated the adjuvant effect of DFMO in colon cancers using xenograft model. However, adjuvant effect of DFMO in MPM has not yet been studied. This study aims to disclose the adjuvant effect of DFMO in MPM xenograft models. The findings from this study will provide scientific foundation for future design of clinical trials of DFMO for adjuvant therapy in early disease for advanced MPM. **Method:** Nude mice were fed with DFMO in drinking water 7 days before subcutaneous inoculation of 200,000 tumor cells (211H (biphasic) or H226 (epithelioid)). Mice with tumor size >600mm3 were considered reaching humane endpoint. Spermidine levels, protein expression, cytokines concentrations, NFkB translocation and apoptosis were investigated by Dot plot, Western blot, ELISA, immunofluorescence staining and TUNEL assay respectively. **Result:** DFMO suppressed tumor growth in both xenografts. DFMO increased median survival from 49.5 days in control arm to 65 days in treatment arm in mice with 211H xenografts (p = 0.08), while from 44 days to 120 days in those with H226 xenografts (p = 0.0002). In H226 xenograft model, 43% of treated mice have not yet reached humane endpoint, mimicking long-term survival. Upon DFMO treatment, decrease in spermidine level, increase in nitrotyrosine content, nuclear translocation of NFkB, elevation of serum IL-6 and activation of apoptosis were observed in both xenografts. In addition, increase in nitrocysteine level, decrease in serum keratinocyte chemoattractant (KC), increase in serum TNF alpha, elevation of DNA lesion and inhibition of Akt/mTOR pathway were induced by DFMO in H226 xenografts, which may explain higher potency of DFMO in this xenograft. **Conclusion:** DFMO may have a potential role as adjuvant therapy in MPM especially epithelioid mesothelioma. Acknowledgment: This research was supported by Hong Kong Pneumoconiosis Compensation Fund Board, HKSAR.

Keywords: Difluoromethylornithine, Mesothelioma, Xenograft models

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P2.06-20 BACTERIA AS NOVEL ANTI-MESOTHELIOMA AGENTS.

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Background: Mesothelioma is a universally fatal malignancy with rising global incidence. Research to date has failed to make significant progress towards the control of mesothelioma, let alone its cure. An entirely different approach is needed. The anti-cancer properties of bacteria have been utilized as novel treatments for some cancers, including resistant bladder cancer in which *Mycobacterium bovis* BCG forms standard treatment. The use of bacteria presents an attractive approach in pleural mesothelioma, as there is strong evidence to suggest that an infection in the pleural space may increase survival in these patients. Our study aimed to capitalize on this phenomenon and determine whether bacteria or their products can be used as anti-mesothelioma agents. **Method:** We tested the efficacy of live (10^5-10^7 CFU/mL) and attenuated (heat-killed) *Streptococcus pneumoniae* (n=5) and *Staphylococcus aureus* (n=5) clinical bacterial isolates obtained from patients with invasive bacterial infection and common laboratory reference strains (n=4) against primary (n=3) and established (n=6) mesothelioma cell lines collected from patients with malignant pleural effusions. Benign mesothelial cells served as controls. Alternatively, conditioned medium (CM) (from *S. aureus*), or mutated bacteria (D39ΔPly or WCH43ΔGlpO), were added to mesothelioma cells. Cell viability was assessed using live/dead staining and analysed using flow cytometry. We also measured key cytokines involved in the pathobiology of mesothelioma and bacterial infection including; IL-1β, IL-6, VEGF and IL-8 using ELISA's. **Result:** Two of the live *Staphylococcus aureus* and *Streptococcus pneumoniae* isolates consistently killed all mesothelioma cell lines (median(IQR)%: 90.4(51.4-97.6)% and 99.6(99.4-99.8)% respectively). The same *S. pneumoniae* isolates also potently killed benign mesothelial cells (99.7(99.4-99.8)%). However, the two *S. aureus* isolates demonstrated significantly less efficacy against benign mesothelial cells (13.7(5.0-23.0)%), supporting the potential for targeted therapy. Attenuated clinical isolates and bacterial CM were not efficacious against mesothelioma cells. We observed increased cytokine levels in response to the most potent clinical isolates in all mesothelioma cell lines. In contrast, cytokine responses were greatly reduced in benign mesothelial cells. Pneumolysin and GlpO (α-glycerophosphate oxidase) did not mediate the cytotoxic effects of *S. pneumoniae* on mesothelioma cells as evidenced by comparison of mesothelioma cell killing to wild-type controls. **Conclusion:** We showed, for the first time, that clinical bacterial isolates can potently kill patient-derived mesothelioma cells with some specificity. Combined with our published data, which demonstrated the efficacy of a bacterial toxin against mesothelioma tumours *in vivo*, our data suggests that bacterial therapy is a promising novel approach for the treatment of mesothelioma and warrants further investigation.

Keywords: Novel Therapy, Bacterial Therapy, Mesothelioma

P2.06 MESOTHELIOMA
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P2.06-21 LOW INTRATUMORAL PLATINUM CONCENTRATION IS ASSOCIATED WITH UNFAVORABLE CLINICAL OUTCOME IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is a rare but devastating malignancy characterized by poor prognosis. Systemic anti-MPM therapy is based on platinum compounds. Unfortunately, however, chemoresistance is a major obstacle in the treatment of MPM. Although inadequate intracellular drug uptake is one of the most frequent causes of platinum resistance, the impact of tumor tissue and circulating platinum concentrations on clinical outcome in MPM patients remains unclear. **Method:** Spatial distribution and average tumor concentration of platinum was assessed by laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) in tumor samples of MPM patients (n=26) receiving platinum-based induction chemotherapy followed by surgical resection. Circulating platinum concentration was also analyzed by ICP-MS in serum samples (n=29) taken prior to surgery. Tumor and serum drug levels were correlated with various clinicopathological parameters. **Result:** Patients with low average tissue platinum concentrations had significantly shorter overall survival. Interestingly, the spatial distribution of platinum was very heterogenous in the tissue samples. The drug accumulated in collagen-rich, post-necrotic scar tissue compartments, while its level was relatively low in the viable tumor areas. Circulating cisplatin levels negatively correlated with the time between the last chemotherapy cycle and blood sampling. **Conclusion:** By using an innovative technique for lateral trace element distribution analysis, we demonstrate here for the first time that low tissue platinum uptake is associated with significantly worse clinical outcome in MPM and, furthermore, that relatively higher platinum levels are confined to areas of intratumoral scar tissue. Our results suggest that insufficient drug uptake might be an important factor of cisplatin resistance in the clinics. Further studies are needed to clarify the significance of heterogeneous intratumoral platinum distribution.

Keywords: mesothelioma, intratumoral platinum distribution, resistance

P2.06 MESOTHELIOMA
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P2.06-22 PROPOSAL OF A NEW LOCAL RECURRENCE SCORE FOR PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA

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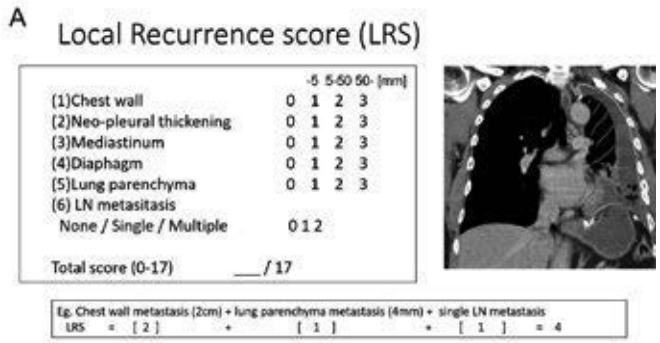
Background: Malignant pleural mesothelioma (MPM) is associated with high rates of local recurrence (LR) up to 75%. Second line treatment should be applied tailored to relapse pattern. The aim of the present study was to establish a new score for LR pattern with prognostic and treatment impact. **Method:** From 2001 until 2017, 165 consecutive MPM patients with LR after macroscopic complete resection either by extrapleural pneumonectomy (EPP) or (extended) pleurectomy/decortication ((e)P/D) were enrolled in this retrospective study. Due to missing data 37 patients were excluded from analysis. Further analysis was done with remaining 128 patients (EPP: n=61 and eP/D: n=67). We divided the thoracic cavity into the following sections: chest wall (CW), mediastinum (Med), diaphragm (Di), lung parenchyma (LP), neo-pleural thickening (N-PT) and lymph node (LN) (Figure 1A). We assessed the prognostic impact of local recurrence score (LRS=size ((Measurement of perpendicular diameter)) of recurrence sites multiplied by the number of LR sites) using cox regression model. **Result:** The frequency of the location was as follows; CW 47.7%, Di 24.2%, Med 38.3%, N-PT 61.7%, LP 25.0% and LN 55.5% (Figure 1B). The median LRS was 4 (range: 1-12). Low LRS (<= 4) was significantly correlated with longer survival after LR (low score 16.4 vs high score 9.8 months, p=0.03). Of 6 locations, first recurrence at CW (negative 16 vs positive 9.8 months, p=0.044) and LN (negative 17.2 vs positive 9.2 months, p=0.015) had significant negative prognostic impact on OS. In subgroup analysis, LRS was significantly higher after eP/D compared to EPP (median LRS: 6 vs 4, p<0.001), but survival after LR was significantly longer after eP/D compared to EPP (14.6 vs 9.6 months, p=0.004).



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Conclusion: LRS might be a useful prognosticator in MPM patients with LR after MMT and might be helpful for further use as second line treatment allocation tool.

Keywords: multimodal treatment, malignant pleural mesothelioma, local recurrence

P2.06 MESOTHELIOMA
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P2.06-23 ASSOCIATION OF TWO BRM PROMOTER POLYMORPHISMS AND TOBACCO EXPOSURE WITH MALIGNANT PLEURAL MESOTHELIOMA (MPM) RISK AND SURVIVAL

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Background: Brahma (BRM) is a critical ATPase subunit of the SWI/SNF chromatin remodeling complex. Homozygous 6-7bp insertion variants at two polymorphic promotor sites (BRM-741/BRM-1321) cause epigenetic suppression of BRM expression and they have been reported as susceptibility and/or prognostic markers in many malignancies, including non-small cell lung cancer. As epigenetic silencing of BRM can be reversed pharmacologically, targeting BRM polymorphisms has significant therapeutic potential. We evaluated BRM-741/BRM-1321 polymorphisms' association with risk and prognosis of malignant pleural mesothelioma (MPM). While the effect of tobacco in MPM remains controversial, its interaction with genetic polymorphisms in MPM is largely unknown. We evaluated associations between BRM polymorphisms-tobacco exposure and MPM. **Method:** MPM and age-distribution matched asbestos-exposed controls were recruited as part of an asbestos-exposure surveillance program. Participants were genotyped for BRM polymorphisms. Multivariable logistic regression assessed risk of MPM in case-control analyses. Association of BRM variants with overall survival (OS) was assessed by multivariable Cox regression. Secondary subset analyses were performed, stratified by smoking status. **Result:** Of 265 MPM cases, 146 (55%) were ever-smokers; 51 (19%) were female; median age was 66 (range:21-84) years. Median OS was 18 months; median follow-up time was 15 months. Compared to 795 controls, there were no significant associations of BRM with risk (P>0.10, all comparisons). In contrast, compared to the wild-type genotype, the homozygous variant of BRM-741 and BRM-1321 were associated with lower OS, with adjusted hazard ratio (aHR)=2.56 [95%CI:1.7-3.8] and 2.07 [95%CI:1.4-3.1], respectively. Compared to patients carrying the double wild-type, patients homozygous at both loci had lower OS (aHR=2.70 [95%CI:1.7-4.4]). There was a significant differential effect of BRM polymorphisms on risk of MPM, by smoking status (interaction P<0.001): among ever-smokers, BRM homozygous variants in BRM-741, BRM-1321, or both conferred lower risks (adjusted odds ratios, aORs were between 0.18-0.28; each P<0.001), while for never-smokers, there was significantly greater risk conferred by carrying the homozygous variants (aORs between 2.7-4.4). Likewise, a similar differential effect by smoking status was seen in prognosis (interaction P<0.001): there was no association between BRM polymorphisms and OS in ever smokers (P>0.1, all comparisons), but in never-smokers, the aHR of carrying homozygous variants of BRM-741, BRM-1321 or both were 7.7 [95%CI:3.8-16], 4.0 [95%CI:2.1-7.7], and 8.6 [95%CI:3.7-20], respectively. **Conclusion:** Never-smokers who develop malignant pleural mesothelioma have an increased chance of carrying BRM homozygous variants in their germline DNA, which results in substantially worse prognosis. In contrast, in smokers, there may be a protective effect, with no difference in overall survival.

Keywords: BRM, Epigenetic, Mesothelioma

P2.06 MESOTHELIOMA
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P2.06-24 THE IMPACT OF DEMOGRAPHIC AND SOCIOECONOMIC FACTORS ON SURVIVAL OF PATIENTS WITH MESOTHELIOMA IN THE USA

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Background: Malignant Pleural mesothelioma (MPL) is a rare cancer with about 3000 new cases diagnosed each year in the USA. It has poor prognosis with 5 year survival rate of 10%. We performed a national study to assess the impact of demographic and socioeconomic factors on survival of patients with MPL. **Method:** Patients with MPL diagnosed between 2004-2014 were identified from the National Cancer Database (NCDB). Demographic and socioeconomic factors were collected. The impact on survival was evaluated with Cox regression model after adjusting for the variables. **Result:** Total of 24826 patients with MPL were included. Median age at diagnosis was 73. Majority of patients were men (75 %), white (93%), insured (97%), lived in a metro area (84%) and treated at an academic facility (64%). Most patients lived in either eastern or central geographic location (45% and 39% respectively). Median overall survival (OS) was 9.8 months. Women had significantly better OS (12.4 months) vs men (9.3 months). (Table 1) OS was better with younger age (16.6 months for patients < 60; 12.4 months for 60-69; 9.9 months for 70-79 and 5.6 months for ≥ 80). Other factors associated with better OS included early stage, lower comorbidity, higher income and treatment at an academic facility. Neither insurance status nor education level had any impact on OS. Race did not impact survival except for Native Americans and Alaskans (represented only 0.2 % of patients) who had better OS compared to Whites.

Table 1: Multivariate analysis of socio-demographic factors and survival of MPL patients

Parameter	Hazard ratio	95% Hazard ratio confidence limits	P- value
Sex			
Male	1	Reference	
Female	0.778	0.747-0.811	<.0001
Age			
<60	1	Reference	
60-69	1.222	1.151-1.299	<.0001
70-79	1.435	1.354-1.521	<.0001
≥80	2.138	2.012-2.272	<.0001
Race			
White	1	Reference	
Black	1.030	0.948-1.118	0.4891
Asian/PI	1.104	0.941-1.295	0.2243
Hispanic	0.819	0.636-1.053	0.1198
NA/AN	0.642	0.443-0.930	0.0192
Median local annual income			
<$38,000	1	Reference	
$38,000-$47,999	0.969	0.913-1.029	0.3024
$48,000-$62,999	0.899	0.846-0.956	0.0007
$63,000+	0.854	0.799-0.914	<.0001
Local education level			
<7%, Not high-school graduate	1	Reference	
13-20.9%, Not high-school graduate	0.984	0.930-1.042	0.2945
7-12.9%, Not high-school graduate	1.001	0.956-1.048	0.0014
≥21%, Not high-school graduate	0.972	0.906-1.044	0.6028
Insurance			
Uninsured	1	Reference	
Insured	0.915	0.802-1.044	0.1884
Charlson-Deyo comorbidity score			
0	1		
1	1.106	1.063-1.151	<.0001
2	1.232	1.151-1.318	<.0001
≥3	1.530	1.364-1.717	<.0001
TNM stage			
Stage 1	1	Reference	
Stage 2	1.097	1.035-1.163	0.0018
Stage 3	1.181	1.121-1.243	<.0001
Stage 4	1.542	1.474-1.613	<.0001
Treatment facility			
Non-Academic	1	Reference	
Academic	0.827	0.798-0.857	<.0001

Conclusion: In this largest analysis exploring socio-demographic factors affecting MPL outcomes, we note some disparities. While some of these

factors are non-modifiable, others including access to healthcare, income and treating facility type are modifiable. These must be addressed to minimize disparities in outcomes and realize maximal benefit for patients with this incurable malignancy.

Keywords: Demographic and socioeconomic factors, NCDB, Mesothelioma

P2.06 MESOTHELIOMA
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P2.06-25 COMBINED IMMUNE CHECKPOINT BLOCKADE IN MALIGNANT PLEURAL MESOTHELIOMA: IN VIVO VALIDATION OF IN VITRO RESULTS

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Background: Till today, human malignant pleural mesothelioma (MPM) remains an aggressive cancer with a poor prognosis due to the limited impact on overall survival of the current treatments. Data from us and others about the presence of the immune checkpoint-related molecules PD-1, PD-L1, TIM-3 and LAG-3 in MPM lay the basis to evaluate their suitability as immunotherapeutic targets. Two clinical trials that investigated PD-1 and PD-L1 inhibition in mesothelioma (KEYNOTE-28, JAVELIN trial) have shown promising results with room for improvement. It is of great interest to investigate the effect of combined treatments and compare them to stand-alone treatment to select the best therapeutic strategy for MPM. **Method:** Human cell lines representative for the epithelioid (NCI-H2818 and NCI-H2795) and sarcomatoid (NCI-H2731) subtypes of MPM were placed in allogeneic co-cultures with healthy donor peripheral blood mononuclear cells. The co-cultures were treated with the following immune checkpoint blocking antibodies: anti PD-1 (Nivolumab®, BMS) or anti PD-L1 (Durvalumab®, AstraZeneca) in combination with anti TIM-3 or anti LAG-3. Supernatant was collected and enzyme-linked immunosorbent assays and multiplex electrochemo-luminescence were used to look at the secretion of 7 cytokines, being IFNg, IL-2/5/6/10, IL-1b and TNF-a, as well as the enzyme granzyme B. Statistical analysis was done to investigate the differences between the treatment conditions. **Result:** Treatment with immune checkpoint blockers as monotherapy or in combination resulted in a significant increase in the secretion of granzyme B and the cytokines IFNg, IL-2, IL-5 and IL-10. Although the increased secretion was not always statistically significant for all 3 MPM cell lines of the two subtypes, the same trends were observed among them. Interestingly, highest concentrations of granzyme B and these 4 cytokines were noticed for monotherapy treatment with anti PD-1, anti PD-L1 or either of these antibodies with anti TIM-3. In vivo investigation of PD-1 or PD-L1 blockade in combination with TIM-3 or LAG-3 blockade is currently ongoing to validate our in vitro results. **Conclusion:** Our data show that treatment with anti PD-1, anti PD-L1 or their respective combination with anti TIM-3 resulted in the highest secretion of cytokines and granzyme B, suggesting that these treatments stimulate the antitumor response the most. In vivo experiments are currently ongoing for validation.

Keywords: Mesothelioma, Immune checkpoints, combination therapy

P2.06 MESOTHELIOMA
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P2.06-26 RIBONUCLEOTIDE REDUCTASE SUBUNIT M1 BUT NOT M2 IS ASSOCIATED TO BETTER PFS IN PATIENTS WITH ADVANCED STAGE MESOTHELIOMA

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Background: Ribonucleotide reductase M1 (RRM1) is the catalytic subunit of ribunucleotide reductase, the enzyme responsible for *de novo* synthesis of most of the deoxyribonucleotides. Low-level expression of RRM1 has been associated to better prognosis in patients with solid tumors. A previous study identified that RRM1 is a predictor for freedom from recurrence in patients with malignant pleural mesothelioma (MPM) undergoing induction chemotherapy following extrapleural pneumonectomy. Ribonucleotide reductase subunit M2 (RRM2) is associated with apoptosis, cell proliferation, invasion and migration. Some studies have suggested that expression of RRM2 could play a role in tumorigenesis of several cancers; however, its role in MPM is unknown. **Method:** The expression of RRM1 and RRM2 was assessed by immunohistochemistry using commercial antibodies. Quantitative analysis was performed using computerized image software, namely digital pathology. All of the samples were scanned and the median value of each marker was used as the cutoff value, >median value corresponds to high expression level and <median value to low expression level. The expression levels were determined in samples from 91 patients with advanced MPM, who had received gemcitabine-based chemotherapy. We correlated these data with clinical parameters and disease outcome (Progression Free Survival [PFS]). **Result:** Our study population presented a median age of 60 years (53 -71 yrs), most were male 64.8 %, with asbestos exposure in 57.2% of cases and epithelioid histology in 85.7%. Almost half of the patients received gemcitabine as first-line treatment (n=43; 47.3%). Overall PFS was 14.1 months (95% CI 9.8–18.4 months,) while PFS in patients receiving gemcitabine treatment was 6.8 months (95% CI 5.4–8.2 months). Several factors were associated to an improved PFS, including female vs. male sex (7.2 vs 6.6 months, p=0.062) and epithelial vs. sarcomatoid histology (7.2 vs 3.8 months, p=0.035) after gemcitabine treatment in univariate analysis. In the multivariate analysis, sex (HR 3.06, p=0.085) and no wood-smoke exposure (HR 2.55, p=0.092) were independently associated to gemcitabine treatment. Patients with high expression levels of RRM1 showed better PFS compared to patients with low expression levels (7.6 vs 5.5 months, p=0.049) in univariate analysis; with a HR of 0.204 (0.050–0.831) p=0.026 in multivariate analysis. Conversely, the M2 subunit (RRM2) did not show any significant associations (7.6 vs 6.6 months, p=0.363). **Conclusion:** Our results suggest that high protein expression levels of RRM1 could potentially serve as a biomarker of response to gemcitabine treatment in patients with advanced stage MPM.

Keywords: RRM2, response biomarker, RRM1

P2.06 MESOTHELIOMA
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P2.06-27 EXTRAPLEURAL PNEUMONECTOMY, RADIATION THERAPY, AND CHEMOTHERAPY FOR EPITHELIOID MALIGNANT PLEURAL MESOTHELIOMA

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Background: The treatment strategy for malignant pleural mesothelioma (MPM) has not been established yet. Our improving results of trimodality therapy with extrapleural pneumonectomy (EPP), radiation therapy, and chemotherapy for epithelioid MPM are reported. **Method:** Twenty four consecutive EPP for epithelioid MPM which were performed from February 2011 to August 2017 in our hospital were reviewed. We have instituted a trimodality therapy protocol consisting of EPP, adjuvant 45-50.4 Gy hemithoracic radiation therapy, and adjuvant CDDP plus PEM chemotherapy. 20 patients have been treated with this protocol. However, 4 patients were given induction CDDP plus PEM chemotherapy, and referred to us. They were scheduled to undergo EPP and adjuvant hemithoracic radiation therapy. Overall survival was calculated from the start of treatment using Kaplan-Meier method. This was one institutional retrospective study. **Result:** Median age at EPP was 60 (39 - 69) years old. Female was 8, and male was 16. Right side was 14, and left side was 10. Median EPP time was 7 hours 3 minutes (5 h 52 m – 8 h 56 m). No blood transfusion during EPP was 10 cases (42%). 30 day mortality was zero. Atrial fibrillation was the most common morbidity, and developed in 12 patients (50%). IMIG pathological stage was stage IV in 2, stage III in 13, stage II in 5, and stage Ib in 4. Adjuvant 45-50.4 Gy radiation therapy was completed for 21 patients (88%). 4 patients (17%) could not undergo chemotherapy. 18 patients (75%) underwent trimodality therapy. Postoperative median follow-up period was 4 years. Five year survival, two year survival, and median survival were 41%, 66%, and 40 months.

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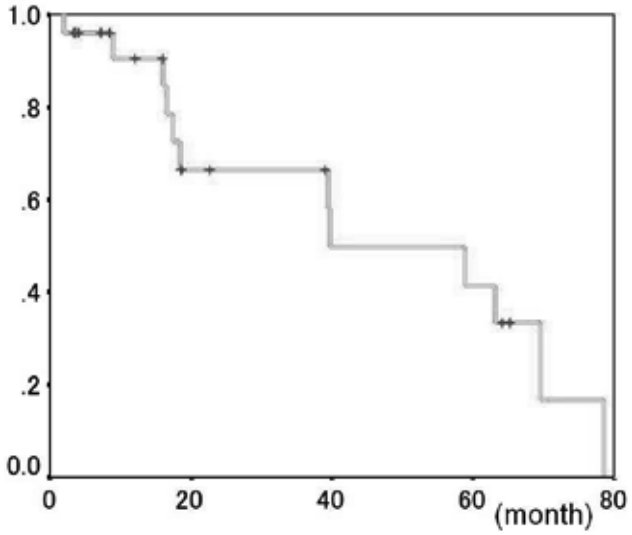

Conclusion: This trimodality treatment strategy with EPP, hemithoracic radiation, and chemotherapy for epithelioid MPM is feasible. Although many advanced cases were treated, the prognosis has been greatly improved.

Keywords: malignant pleural mesothelioma, extrapleural pneumonectomy, trimodality therapy

P2.06 MESOTHELIOMA
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P2.06-28 ASSESSMENT OF CHEST WALL MOTION USING STRUCTURED LIGHT PLETHYSMOGRAPHY (SLP) IN MESOTHELIOMA AND BENIGN PLEURAL DISEASE

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Background: Diagnosis of mesothelioma can be a prolonged and distressing process for patients. Non-invasive assessment of ribcage and abdominal movements is possible with structured light plethysmography (SLP) which is quick and easy to perform; we sought to assess whether changes in respiratory movements could be used to differentiate benign pleural disease from mesothelioma. **Method:** Patients attending the preoperative assessment clinic prior to diagnostic pleural biopsy were recruited prospectively. SLP was performed prior to surgery and the recordings processed by a blinded technician. Binary logistic regression was used performed based upon histology results and the model was assessed with area under the curve (AUC) analysis. Survival analysis (Kaplan Meier plot and Log Rank test) was performed to assess whether survival was different depending on SLP results. **Result:** Seventy-five patients were recruited, meeting the required sample size (40 benign, 35 malignant). Factors entered into the model were the contribution of the affected hemithorax to ribcage tidal volumes, synchrony between abdominal and ribcage movements and variability of inspiratory to expiratory flow. The model was not significant (X^2 4.234, p=0.237, Nagelkerke R^2 0.073) and correctly classified 57.3% of cases. AUC was 0.581 (p=0.230, 95% confidence interval 0.450 to 0.712), this is not sufficient to be a clinically useful test. The contribution of the affected hemithorax to ribcage motion showed a trend for association with survival in patients who had biopsy proven mesothelioma (mean survival 334 days for <45% contribution, 95% confidence interval 218-450, vs 993 days for >45% contribution, 95% confidence interval 633-1353, p=0.065). **Conclusion:** Performing SLP prior to biopsy does not aid in the differentiation of benign versus malignant pleural disease. Further research into the usefulness of assessing chest wall motion in prognostication and staging of mesothelioma is required.

Keywords: Mesothelioma, diagnosis, Prognosis

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P2.06-29 EXPRESSION OF ESTROGEN RECEPTOR BETA (ERB) AND ITS PROGNOSTIC VALUE IN THE PLEURAL MESOTHELIOMA.

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Background: Overexpression of estrogen receptors in malignant pleural mesothelioma has shown to be a good prognostic marker of survival and the use of selective estrogen receptor beta agonists (ERb) increases the susceptibility to antitumor treatment. **Method:** Longitudinal,retrospectiveand unicentric study that analyzes the response of malignant pleural mesothelioma with an expression of ERb to chemotherapy in the first line. The study had 22 patients pathologically diagnosed with malignant pleural mesothelioma between April 2014 to September 2015 at the National Institute of Respiratory Diseases, who underwent immunohistochemistry for ERb (mouse monoclonal antibody PPG5/10), used a qualitative system determined by direct observation of the pathologist with a scale 1+ for weak staining and 3+ for very intense staining, as well as the percentage of expression, was considered as high when it was increased to 50% of the cells. The primary endpoint was overall survival and ERb expression variable; secondary outcomes were progression-free survival and response rate to chemotherapy based on RECIST 1.1. **Result:** The sample is formed by 13 men (59.1%) and 9 women (40.9%), with a clinical stage of IV in 54.5%, III in 36.4%, II and IA both with 4.5%. Were smokers 54.5% with an average of 5.9 packs/year. In 95.5% there was an epithelioid pattern and 3.5% was biphasic. The 77.2% of the patients expressed a high percentage ERband 22.8% a low or null percentage. The response to the treatment by RECIST 1.1 was 54.5% for partial response (12 patients), stable disease in 22.7% (5 patients) and progression 13.6% (3 patients), no patient had a complete response. Of the patients who had a partial response, 75% (9 patients) had a high percentage of ERb expression in the tumor cells and 25% had a low or null percentage. The progression-free survival of patients with high ERbexpression had a median of 12.2 months compared to 9.3 months with low or null expression (p = 0.67, 95% CI 4.5 - 12-9), overall survival was 19.5 months in those with high expression of the receptor and 10.3 months for patients with low or null expression (this had a greater tendency to be higher in the ERb high expression for 9.2 months) (p = 0.054, 95% CI 9.79-10.01) **Conclusion:** ERb high expression in patients with an advanced clinical stage of malignant pleural mesothelioma was associated with a better response to chemotherapy treatment (without being statistically significant), with a better progression-free survival and possibly overall survival trend.

P2.06 MESOTHELIOMA
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P2.06-30 ASSOCIATION OF HISTOPATHOLOGICAL PATTERNS OF MESOTHELIOMA AND RESPONSE TO TREATMENT WITH CHEMOTHERAPY

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Background: Mesothelioma is a neoplasm with a high mortality, there are different prognostic factors that influence survival, within these, the histological type has been associated directly. **Method:** Descriptive, observational, retrospective and unicentric study, that analyzes the response of the different histopathological patterns of malignant pleural mesothelioma to chemotherapy. The study had 28 patients pathologically diagnosed with malignant pleural mesothelioma between April 2014 to August 2015 at the National Institute of Respiratory Diseases. The primary objectives were overall survival and mesothelioma histopathological patterns variable, and secondary objectives was progression free survival and response rate to chemotherapy based on RECIST 1.1. **Result:** The sample was formed by 18 men (64%) and 10 women (36%), 57% had asbestos exposure and 43% another exhibition (textile, fiber glass, cement, fertilizer, petroleum, solvents and coal). The 46% were smokers with an average of 6.6 packs/year. The method of biopsy as a diagnostic was thoracoscopy, which was used in 57% of the patients. The 94.4% had epithelioid pattern and 3.6% biphasic; in the epithelioid pattern, the solid subtype was the most predominant with 51.8%, followed by tubulopapillary with 14.9%, acinar with 14.8%,

papillary and micropapillary both with 7.4% and pleomorphic with 3.7%. In overall survival and progression-free survival were higher the subtypes: micropapillary with 27 months, solid with 23 and 20 months, tubulopapillary with 20 and 18 months and acinar with 15 and 17 months respectively, the poorer prognosis was pleomorphic subtype with 4 months, similar to the biphasic pattern with 6 months. The median progression free survival for all patients was 17 months, the men were higher to the women with 17 and 12 months respectively. We found a relationship between overall survival and the nuclear calretinin, with a better prognosis for that patients who are not expressers (27.3 months) comparative to that patients with any level of expression (17 months). Within the therapeutic schemes used in the first line, by permetrexed plus cisplatin was superior to others in the disease-free survival; in the compound of platinum, the combined with cisplatin proved to be superior, not influencing the therapeutic scheme in the overall survival. **Conclusion:** The histopathological pattern is a prognostic factor in progression free survival and overall survival. Nuclear calretinin is a prognosis factor. The best therapeutic scheme of front line was permetrexed plus cisplatin in progression free survival, cisplatin schemes offer a better PFS compare to carboplatin schemes, not influencing in the overall survival.

P2.06 MESOTHELIOMA
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P2.06-31 INHIBITION OF HEAT SHOCK PROTEIN 70 FUNCTION SUPPRESSES PROLIFERATION IN MESOTHELIOMA CELLS

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Background: Although Therapies for mesothelioma have been developed, their efficacy remains limited. Newer therapies based on improved molecular understanding of mesothelioma are needed. We have previously found that proliferation of mesothelioma cell lines is suppressed by transfecting small interfering RNA (siRNA) of dishevelled-3 (Dvl-3), an intermediator of Wnt signaling. Furthermore, when analysis of various mesothelioma cell lines using two-dimensional gel electrophoresis assay was conducted, heat shock protein 70 (HSP70) expression was commonly suppressed after transfection of Dvl-3 siRNA. To clarify the effect of inhibiting HSP70 function in mesothelioma cell lines, a small molecular compound VER-155008, adenosine-derived inhibitor of HSP70, was treated to cells, and its effects were evaluated. VER-155008 is adopted in various researches including Alzheimer's disease, infectious diseases and so on, and other reports showed that it inhibits the function of HSP70 without altering the expression of HSP70. **Method:** Mesothelioma MSTO-211H (211H), NCI-H2452 (H2452) and NCI-H28 (H28) cell lines were cultured with VER-155008 for the following analyses. The expression of HSP70 was confirmed using Western blotting. Cell viability was estimated using Cell Counting Kit-8 at 24, 48 and 72 h after adding 0.5–40 μM VER-155008 while mesothelioma cell lines were cultured on 96-well plates at 500-1000 cells/well. Colony formation and cell cycle analysis was conducted, after mesothelioma cell lines were cultured with 1–20 μM VER-155008 on 35-mm dishes. Furthermore, to estimate the synergistic effect with other anticancer drugs on cell growth, mesothelioma cell lines were cultured with VER-155008 and 0.5-5 μM cisplatin or gefitinib **Result:** HSP70 protein was expressed in mesothelioma cells: 211H, H2452 and H28. Its expression was not altered by VER-155008 in these cells. VER-155008 dose-dependently suppressed mesothelioma cell growth. The colony formation was significantly suppressed with VER-155008 at 20 μM. The proportion of cell counts in G1 phase significantly increased in 211H and H28 cells. Cisplatin or gefitinib did not show synergistic growth suppression after 48 h of treatment with VER-155008. **Conclusion:** These results suggest that VER-155008 have ability to suppress mesothelioma proliferation with G1 arrest through inhibition of HSP70 function. Furthermore, we will elucidate HSP70 function and its relationship with other mechanisms for proliferation and surviving including signal transduction and autophagy in mesothelioma.

Keywords: Mesothelioma, heat shock protein 70, VER-155008

P2.06 MESOTHELIOMA
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P2.06-32 YB-1 - A KEY FACTOR IN MESOTHELIOMA AGGRESSIVE GROWTH AND BEHAVIOUR

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Background: Malignant pleural mesothelioma (MPM) is a devastating disease characterized by aggressive growth and local invasion, poor outcome and limited therapeutic options. YB-1 is a multifunctional oncoprotein, which is often up-regulated in cancer and associated with aggressiveness and poor patient outcome. Also, YB-1 is actively secreted by cells upon various stresses. Besides numerous other functions, YB-1 has been described to stimulate cancer cell migration and invasion via regulation of EMT-related factors such as Snail and Twist. **Method:** Cells were treated with LPS (20 ng/ml) or grown under hypoxic conditions (1% O_2, N_2 balanced) for 24 hours. YB-1 levels in supernatants were quantified via western blot. Changes in EMT markers were measured by qPCR. Cell migration and cell cycle was assessed by live cell videomicroscopy followed by manual single cell tracking and analysis using ImageJ and DiPer software, respectively. YB-1 overexpression was achieved by stable transfection with an expression plasmid and confirmed via qPCR and western blot. **Result:** YB-1 is secreted by MPM cells as well as the immortalised mesothelial cell line Met-5A after exposure to LPS or under hypoxic conditions. When MPM cells as well as primary mesothelial cells derived from pericardial fluid were exposed to soluble YB-1, we observed an upregulation of EMT markers such as SNAIL and TWIST as well as significantly increased migratory capacity. Similar effects were observed in cell lines which overexpress YB-1. YB-1 overexpressing cells migrated at significantly higher speed and covered a larger area. Also, when grown at low density, EMT-like changes in cell morphology as well as scattering was observed. Additionally, while cell divisions occurred at higher frequencies, the duration of the M phase was significantly prolonged. **Conclusion:** Our data highlight a crucial role of both intracellular and soluble YB-1 in the regulation of migration and invasion, which are key characteristics of MPM. Additionally, YB-1 also interferes with the cell cycle of MPM cells. These findings contribute to a better understanding of the biology of MPM and highlight YB-1's potential as a therapeutic target.

Keywords: Mesothelioma, YB-1, cell migration

P2.06 MESOTHELIOMA
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P2.06-33 HETEROGENEITY IN CARE PATHWAYS FOR PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA PRESENTING AT A QUATERNARY THORACIC ONCOLOGY CENTER IN QUEBEC

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Background: Malignant pleural mesothelioma (MPM) is a rare disease for which diagnostic and therapeutic trajectories are ill-defined. We hypothesize that MPM patients experience delays during their diagnostic and therapeutic trajectory with significant heterogeneity in care pathways. Thus, we evaluated management practices at the MUHC over the past 10 years to address the need for a centralized program and dedicated care team. **Method:** We conducted a retrospective chart review of MPM cases diagnosed at our center from 2006 to 2016. Clinical, pathologic, and treatment variables were collected. We assessed time from first abnormal imaging to definitive diagnosis, time from definitive diagnosis to first treatment and time from definitive diagnosis to palliative care consult. Overall survival was analyzed by Kaplan Meir method. **Result:** We identified 145 patients over a 10-year period and report outcomes on 92 cases with complete data. Demographic data are presented in Table 1. Overall survival was 1.4% at 5-years for all patients, with a median survival of 1 year following a definitive diagnosis. Forty-five percent of patients underwent an investigational PET/CT scan, 89% of patients had M0 status prior to treatment, of whom 20% developed extra-thoracic metastases. Sixty-three percent of patients received some form of treatment. Eight treatment combinations were identified, irrespective of intent, lymph node involvement, and metastatic status. With regards

to delays in care pathway, median time from first abnormal imaging to definitive diagnosis was 34 days (IQR 20.5 to 55), definitive diagnosis to first therapeutic intervention was65 days (IQR 35.8 to 163.8), and definitive diagnosis to palliative consult was 289 days (IQR 3 to 1651).

Table 1. Demographics and treatment characteristics of patients diagnosed with MPM at the McGill University Health Center over a 10-year period.

Characteristics	Overall
Sample size	92
Age	Number (%)
Median (IQR)	72 (62-79.5)
Female Gender, n (%)	19 (20.7)
Previous or current smoker, n (%)	36 (39.1)
Asbestos Exposure	
No	20 (21.7)
Yes	36 (39.1)
Unknown	36 (39.1)
Type of MPM	
Biphasic	9 (9.8)
Desmoplastic	3 (3.3)
Epitheliod	67 (72.8)
Sarcomatoid	3 (3.3)
Not otherwise specified	10 (10.9)
Treatment	
No	28 (30.4)
Yes	58 (63.0)
Unknown	6 (6.5)
Treatment Course	
Chemotherapy only	8 (13.8)
Chemo & Radiotherapy	5 (8.6)
Radiotherapy only	15 (25.9)
Surgery only	10 (17.2)
Trimodality therapy	7 (12.1)
Surgery and Chemo	7 (12.1)
Surgery and Radiotherapy	4 (6.9)
Concurrent therapy	2 (3.4)
Intent at first treatment	
Curative	31 (53.4)
Palliative	24 (41.4)
Unknown	3 (5.2)

Conclusion: Overall outcomes for MPM patients presenting at our center are equivalent to historical controls. However, significant heterogeneity and delays exist during the patient trajectory. A centralized approach to diagnosis and treatment may lead to a more efficient and beneficial trajectory for these patients.

Keywords: Patient trajectory, quality improvement, retrospective

P2.06 MESOTHELIOMA
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P2.06-34 INHIBITION OF THE HGF/C-MET PATHWAY FOR MALIGNANT MESOTHELIOMA WITH AN INTRA-THORACIC INJECTION OF THE NK4 EXPRESSING ADENOVIRAL VECTORS

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Background: The HGF/c-Met pathway is up-regulated in human mesothelioma. In a preclinical study, the HGF/c-Met suppression with NK4, homologous to HGF, produced anti-tumor effects to mesothelioma cells. Mesothelioma grows in a thoracic cavity and the distant metastasis to extra-thoracic organs is infrequent which is suitable for local treatment including gene therapy. **Method:** We conducted a phase 1 clinical trial of gene therapy using the NK4 gene-expressing adenoviruses (Ad-NK4) to control the intra-thoracic local tumor growth. We injected Ad-NK4 into the intra-thoracic cavity once with a dose escalation manner from 10^{10} to 10^{12} virus particles per patient and to examine safety and efficacy for a month after the administration. **Result:** A total of 11 patients compatible with the inclusion criteria entered into the study (Low dose 3, Mediumu dose 3, High dose 5). Most frequent occurred adverse event was Grade 1 transient fever after injection. Severe adverse effects (Grade3 or 4) or treatment-related death were not found, and 3 long survivor were currently followed up. Tumor shrinkages were not observed and response to therapy were SD at best. Antibody to adenovirus was observed in most cases that lasting longer than 30-days. An investigation on a gene transduction level is now on-going. **Conclusion:** Direct injection of Ad-NK4 vectors into the pleural cavity, up to the dose of 10^{12} v,p is safe. Combination ANK4 gene therapy with chemotherapy or immunotherapy may be feasible.

Keywords: gene therapy, malignant pleural mesothelioma, NK4

P2.06 MESOTHELIOMA
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P2.06-35 PLEURECTOMY DECORTICATION VERSUS EXTRAPLEURAL PNEUMONECTOMY IN MALIGNANT PLEURAL MESOTHELIOMA: SPARCS DATA

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Background: Malignant pleural mesothelioma (MPM) is a rare but grave cancer with poor survival. To date, the debate on the surgery of choice in patients with operable MPM is still ongoing. We evaluated surgery-related mortality and post-operative complications among patients treated with Extrapleural Pneumonectomy (EPP) vs Pleurectomy Decortication (P/D) in the New York Statewide Planning and Research Cooperative System (SPARCS) database. **Method:** SPARCS is an all payer claim database for the State of New York. Data of inpatient stays (1995-2012) were used to extract 3826 unique patients with a diagnosis of MPM (ICD-9-CM: 163 identifying 233 patients treated with EPP (ICD-9-CM codes: 325, 3259) and 267 patients treated with P/D (ICD-9-CM codes: 345, 3451). We used propensity score methods using a logistic regression model matching patients on the following variables: age, race, the presence or absence of comorbidities, type of insurance and type of admission (using 1:1 matching with absolute difference in scores of 0.08). **Result:** There was no difference in the proportion of males between EPP (76.2%) and P/D (80.9%). EPP patients were younger (mean age 60.8 vs 68.6 years), significantly more likely to be white (94.0% vs 85.2%), privately insured (56.6% vs 29.9%) and admitted for an elective procedure (97.9% vs 66.8%) than P/D patients. There were significantly more comorbidities in the EPP group (95.3% vs 85.9%). The in-hospital mortality in the matched patients groups comparing EPP and P/D was higher but not significant [OR_{adj}: 2.82 (95% CI: 0.70-11.38)]. The odds of having postoperative complications was 1.22 (95% CI: 0.68-2.20) when comparing EPP and P/D. Supraventricular arrhythmia as postoperative complication was significantly more frequent after EPP compared to P/D (OR_{adj}: 2.73; 95% CI: 1.14-6.50). **Conclusion:** The analysis showed a tendency towards higher odds of in-hospital mortality for EPP versus P/D however not statistically significant. While the odds of postoperative complications were not significantly different between EPP and P/D patients, the odds of supraventricular arrhythmia as postoperative complication were 2.7 times higher after EPP versus P/D. P/D, a less invasive surgical approach, may provide a better option when technically feasible for MPM patients.

Keywords: Mesothelioma, Surgery, complications

P2.06-36 EORTC 1205: RANDOMIZED PHASE II STUDY OF PLEURECTOMY/DECORTICATION PRECEDED OR FOLLOWED BY CHEMOTHERAPY IN EARLY STAGE MPM

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Background: Case series show a prolonged survival in resectable malignant pleural mesothelioma (MPM) with a combined modality approach of surgery and chemotherapy. Extrapleural pneumonectomy is the most commonly used surgical procedure in MPM, but is associated with a significant morbidity; the MARS trial (Treasure, *Lancet Oncol 2011*) suggests no outcome benefit and a possible harm to the patient. Retrospective studies suggest a better outcome with lung sparing resection (extended pleurectomy/decortication, e-P/D), but the procedure lacks uniformity and standardization. The optimal sequence of surgery and chemotherapy, the latter given either adjuvant or neo-adjuvant has not yet been determined. **Method:** EORTC 1205 is a phase II, randomized (1:1) multi-centre trial comparing both approaches. Primary end-point is the successful completion of the multimodality treatment within 20 weeks. Secondary end-points are PFS, OS, treatment-failure-free survival (TFFS), toxicity/safety, operative mortality/morbidity and surgical quality and uniformity indicators. Patients with pathologically proven malignant pleural mesothelioma of all histological subtypes, early stage (cT1-3 N0-2 M0 according to TNM 7), WHO-PS 0-1 and fit for chemotherapy and surgery are eligible. No previous treatment, including prophylactic track irradiation, is allowed, except for diagnostic thoracoscopy with talc pleurodesis, which must be performed before randomization. Patients are randomized between arm A - immediate surgery (extended pleurectomy/decortication), followed by 3 cycles of cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 on day 1 q3w, or arm B - deferred surgery, preceded by 3 cycles of chemotherapy. **Result:** Currently 4 of 6 planned sites have opened and 10 patients have been randomized in 2 centres.

	Arm A (n=5)	Arm B (n=5)
Male/female	4/1	4/1
Median age	59.4 years [54.6-76.9]	67.1 years [58.8-69.1]
Median PS	1 [0-1]	0 [0-1]
Stage I/II/III	3/2/0	3/0/2

Conclusion: EORTC 1205 addresses the issue of optimally sequencing chemotherapy and e-P/D and will rigorously record the quality of the latter in a multicentre setting. Accrual is ongoing according to expectation. Updated interim results will be presented at the WCLC meeting.

Keywords: Mesothelioma, Surgery, chemotherapy

P2.06-37 FOUR IMMUNOHISTOCHEMICAL ASSAYS TO MEASURE THE PD-L1 EXPRESSION IN MALIGNANT PLEURAL MESOTHELIOMA

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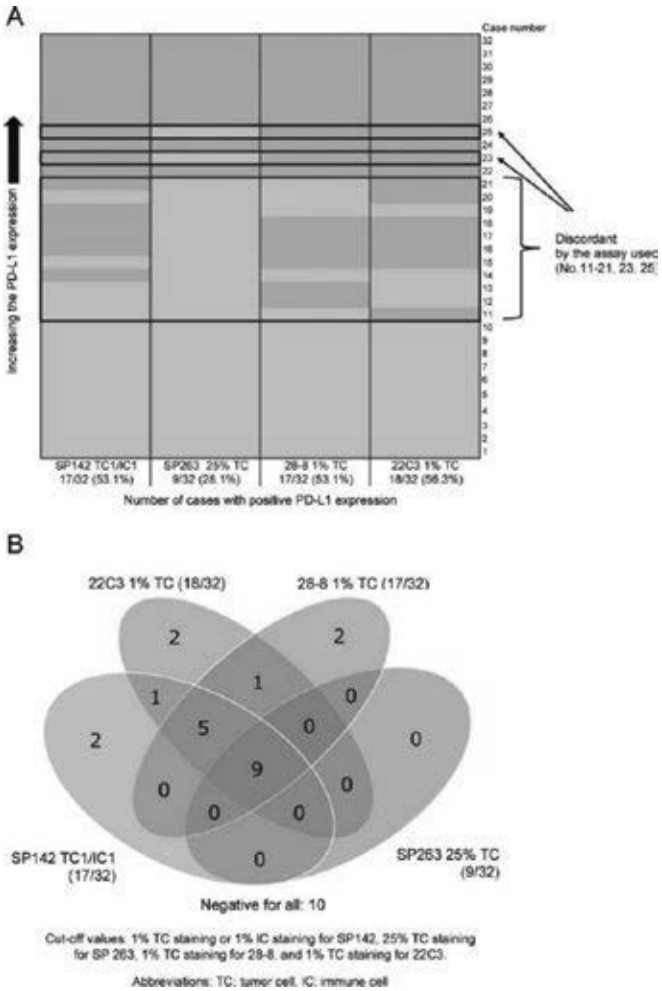
Background: Malignant pleural mesothelioma (MPM) is a rare disease with no effective standardized systemic therapy. Immune checkpoint inhibitors (ICIs) targeting the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) pathway are expected to be a novel therapy for MPM patients. However, the PD-L1 expression, which is a predictor of the response to ICIs, is unclear in MPM. **Method:** We studied the PD-L1 expression using four immunohistochemical, companion diagnostic assays (SP142, SP263, 28-8 and 22C3) in 32 MPM patients. The PD-L1 expression in tumor cells (TCs) and immune cells (ICs) was evaluated to clarify the rate of PD-L1 expression and the concordance among the four assays in MPM. The cut-off values were set at 1% TC or 1% IC for SP142, 25% TC for SP263, 1% TC for 28-8, and 1% TC for 22C. **Result:** The positivity rate of PD-L1 expression was 53.1% for SP142, 28.1% for SP263, 53.1% for 28-8, and 56.3% for 22C3. Nine cases were positive and 10 were negative for all assays. Discordance among the four assays was found in 13 cases. The concordance rates between SP142 and 22C3 and between 28-8 and 22C3 were the highest (84.4%). The concordance rates between SP263 and the other three assays were low (71.9% to 75.0%).



Conclusion: The PD-L1 expression in MPM was almost equivalent for three of the assays. Given the cut-off values set in our study, these findings suggested that these assays, except for SP263, can be used for accurate PD-L1 immunostaining in MPM.

Keywords: malignant pleural mesothelioma, Immunohistochemistry (IHC), programmed death 1 (PD-1)

P2.06-38 MESOTHELIOMA STEM CELLS MAY BE THE CRITICAL FACTOR OF TREATMENT FAILURE

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Background: Cancer cell repopulation during treatments of chemotherapy or radiotherapy is a major factor resulting in treatment failure. It has been indicated that cancer stem cells (CSC) may play critical roles during this process. The goal of our study is to characterise mesothelioma stem cells (MSC) and evaluate the prognostic values in those patients with malignant pleural mesothelioma (MPM). The eventual aim would be to design specific target therapy against MSC and develop novel approaches in clinical practice. **Method:** We have screened a group of genes that are most likely MSC-specific. Further characterization of the selected genes will be of critical importance in tumorigenesis, progression and prognosis. Murine mesothelioma AB12 and RN5 cells treated with either chemotherapy or γ-ray irradiation in culture, were used to compare

gene expression profiles. The selected genes were confirmed by real-time PCR, flow cytometry and immunostaining. In vivo models, peritoneal lavage was collected at different time points after RN5 cell injection, to perform magnetic ranking cytometry with antibody-nanoparticle conjugates, and microarray assay. The expression of Tnfsf18 and Ngfr (CD271) genes associated with prognosis was evaluated in tumor tissues from MPM patients treated with SMART vs pre-SMART protocols, as SMART protocol has already shown significant clinical benefit. Image analysis was performed using Apero Imagescope program. **Result:** The proportion of MSC significantly increased after RN5 parental cells were treated with either chemotherapy, or γ-ray irradiation, or in combination, while MSC showed more resistance to the above treatments, suggesting that chemoradiation resulted in MSC enrichment. Upregulation of genes Tnfsf18, Serpinb9b, Ly6a (Sca-1), Ngf, and Nppb were confirmed. CD271, the receptor of NGF, was shown to be upregulated after chemoradiation, especially after γ-ray radiation with a dose of 10Gy. Mesothelial precursors captured with magnetic nanoparticles conjugated to anti-Msln and trapped in the microfluidic device in the presence of a magnetic field showed an increase over time from 2-8weeks. Image analysis of human section slides indicated that total positive area of CD271 staining was significantly lower in those who were treated with SMART protocol than those with pre-SMART protocol ($p<0.0025$). Similar results were obtained in the high, medium and low positive areas from the SMART group, and p values are 0.0013, 0.0017 and 0.0035, respectively, when compared with the pre-SMART group. **Conclusion:** MSC-specific genes like CD271 and Tnfsf18 might be used as potential prognostic indicators and therapeutic targets.

Keywords: Murine mesothelioma, Gene Expression, Mesothelioma stem cell (MSC)

P2.06 MESOTHELIOMA
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P2.06-39 NEXT GENERATION SEQUENCING REVEALS GENETIC LANDSCAPE OF MALIGNANT MESOTHELIOMA

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Background: Malignant mesothelioma (MM) is a rare form of cancer affecting the mesothelium lining. The 5-year survival rate of advanced patients is less than 1% due to the lack of effective medical therapies. To investigate the possibility of targeted therapy for MM patients, a deeper understanding of the genetic basis is required. **Method:** We reviewed 26 samples taken from 22 MM patients who underwent genetic testing at our institute from 2016 to the present. Somatic mutation profiles were analyzed using hybridization capture based next-generation sequencing (NGS), which enables the simultaneous detection of single-nucleotide variants, insertions/deletions, rearrangements, and copy-number alterations of at least 59 genes (range 59 – 1021 genes). **Result:** The 26 samples included 8 tumor tissue samples, 17 blood samples and 1 ascetic fluid sample. The most frequently mutated genes were *TP53* (11/21), followed by *NF2* (6), *RB1* (4), *NF1* (3), *FLT1* (3), *BAP1* (2), *EGFR* (2), *FAT2* (2), *FGFR4* (2), *KIT* (2), *MAP3K1* (2), *MLL4* (2), *STK11* (2), *APC*, *ATR*, *BRAF*, *BRCA2*, *CDKN2A*, *ERBB3*, *FBXW7*, *MET*, *KRAS*, *PIK3CA* and so on. Among these mutations, 5 of *NF2* mutations and 2 of *NF1* mutations were loss-of-function mutations, which suggests the possible sensitivity of mTOR inhibitors administration. Besides, patients with the active or inactive mutations of *KRAS*, *BRAF*, *CDKN2A*, *ERBB3*, *MET* and *PIK3CA* gene might be sensitive to corresponding targeted drugs. *MET* exon 14 skipping mutation, commonly identified in non-small-cell cancer (NSCLC) patients, had never been reported in MM patients before. c-Met inhibitors such as crizotinib and cabozantinib may be of efficacy for this patient. Apart from predicting therapeutic effectiveness of MEK inhibitors, the detection of *KRAS* activating mutation may also provide prognostic information. **Conclusion:** NGS can identify genetic mutations comprehensively and provide predictive and prognostic implications for MM patients. It is a cost-effective tool to describe the genetic landscape of MM, which will facilitate the development of novel therapeutics for the treatment of MM patients.

Keywords: Genetic landscape, Mesothelioma, NGS

P2.06 MESOTHELIOMA
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.06-40 VISTA IS HIGHLY EXPRESSED IN MALIGNANT PLEURAL MESOTHELIOMA (MPM) AND INDEPENDENT OF PD-L1 EXPRESSION

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Background: PD-1 blockade is effective in only a minority of MPM patients and predictors of response in MPM are unclear. Recent TCGA analysis of MPM revealed VISTA (V-domain Ig-containing suppressor of T cell activation), another inhibitory T cell checkpoint protein, to be frequently expressed in MPMs. In search of other immunotherapeutic targets in MPM, we evaluated the expression of VISTA, its relationship with expression of PD-L1, and the association with response to PD-1 blockade in MPM. **Method:** We retrospectively interrogated the MPM database at Memorial Sloan Kettering to identify patients who received immune checkpoint inhibitors (ICIs). Archival tissue, where available, was obtained and we performed immunohistochemistry (IHC) using antibodies to PD-L1 (clone E1L3N) and VISTA (clone D1L2G), both from Cell Signaling Technology. Imaging studies were reviewed with a thoracic radiologist according to the modified RECIST criteria. **Result:** 37 patients were identified as having received at least one dose of ICI, of whom 26 patients had tissue for VISTA/PD-L1 testing. VISTA was positive ($\geq$1%) in 25 (96%) and $\geq$50% in 22 (84%). PD-L1 was positive in 11 (42%) and $\geq$50% in two (8%). No evident correlation between VISTA and PD-L1 expression was seen. Correlation with response will be reported. **Conclusion:** In contrast to PD-L1, VISTA is highly expressed in most patients with MPM. Its expression appears independent of PD-L1 expression. Molecules targeting VISTA and its ligand should be prioritized for clinical development in MPM.

Keywords: VISTA, Mesothelioma, Immunotherapy

P2.06 MESOTHELIOMA
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.06-41 DIFFERENTIATING SARCOMATOID MESOTHELIOMA FROM PLEOMORPHIC CARCINOMA AND CHEST WALL SARCOMA USING GATA-3/MUC4/BAP1 IHC

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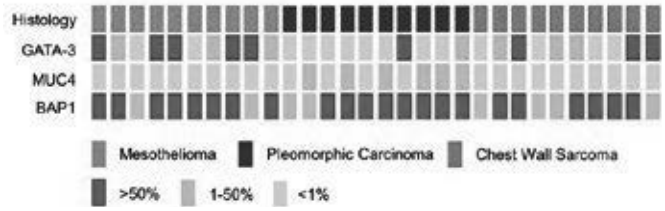
Background: Current immunohistochemistry (IHC) biomarkers, or so-called "mesothelial markers", lack sensitivity and specificity in differentiating sarcomatoid mesothelioma from pleomorphic carcinoma of the lung, and poorly differentiated chest wall sarcoma. Hence it frequently poses a diagnostic challenge for pulmonary pathologists. In this pilot study we evaluated the diagnostic performance of two recently proposed IHC biomarkers, GATA-3 and MUC4, in conjunction with BAP1. **Method:** Sarcomatoid mesothelioma or sarcomatoid- predominant biphasic mesothelioma (10 cases), pleomorphic carcinoma of the lung (10 cases) and poorly differentiated primary or metastatic chest wall or pleural sarcoma (10 cases) were retrieved from our diagnostic archive. Resections or large biopsies were selected over small biopsies whenever possible. All the cases were diagnosed between 2009 and 2017 by a specialist pulmonary pathologist and discussed at the local multi-disciplinary team meeting in relation to final diagnosis. Whole slide GATA-3 (L50-823, pre-diluted), MUC4 (8G7, 1:50) and BAP1 (C-4, 1:50) immunohistochemistry was performed using Ventana Benchmark ULTRA system. Lymphocytes (GATA-3/BAP1) and bronchiolar epithelium (MUC4) were used as internal positive controls. Loss of GATA-3/BAP1 and MUC4 staining was defined as complete loss of nuclear or membrane & cytoplasmic signals, respectively. Any staining intensity above the external negative controls was accepted as positive. Extent of positive staining was grouped as <1%, 1-50% and >50%. **Result:** GATA-3 was positive in 8/10 sarcomatoid mesothelioma, 6/10 chest wall/pleural sarcoma and 2/10 pleomorphic carcinoma of the lung. MUC4 positivity was observed exclusively in pleomorphic carcinoma of the lung (6/10), but only focally. BAP1 loss was infrequently observed in all three types of tumours.



Conclusion: The combination of GATA-3 and MUC4 immunohistochemistry show promise as markers that would help in distinguishing these three tumours. The role of BAP1 is uncertain. These pilot results warrant an extended study that consists of a larger cohort to evaluate the utility of these biomarkers.

Keywords: Sarcomatoid mesothelioma, Pleomorphic carcinoma, Chest wall sarcoma

P2.06 MESOTHELIOMA
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.06-42 AXL, C-MET AND VEGFR2 TYROSINE KINASE RECEPTORS AS THERAPEUTIC TARGETS IN MALIGNANT PLEURAL MESOTHELIOMA.

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Background: Malignant pleural mesothelioma (MPM) is a highly aggressive and rare tumour arising from the pleura, primarily associated with asbestos exposure. Therapeutic options are limited to surgical resection, chemotherapy and thoracic radiation, unfortunately no target therapies are currently recommended for MPM. Previous studies suggested that the activation of multiple receptor tyrosine kinases (RTKs) play a central role in MPM pathogenesis and progression. In this context, AXL, c-MET and VEGFR2 overexpression could represent new possible therapeutic targets in MPM. **Method:** A Tissue MicroArray of MPM was built, including 40 epithelioid 7 sarcomatoid and 11 mixed. AXL, c-MET and VEGFR2 expression was assessed by Immunohistochemistry using specific antibodies. Fluorescence in Situ Hybridization analysis were performed in order to define AXL and c-MET genes stauts, using LSI AXL 19q13.2/CEN19q probes and LSI MET 7q31.2/CEN7 probes, respectively. Studies in vitro were performed in a wide panel of human MPM cell lines according to different histological type of original tumor, including epithelioid type (NCI-H290, NCI-H2052, NCI-H2452), sarcomatoid type (NCI-H205, NCI-H2373, NCI-H28), and biphasic type (Y-MESO-8A, Y-MESO-14, MSTO-211H). **Result:** AXL expression was observed in 16.6% of cases, while altered gene status in 14.5% of cases, including cases harboring gene amplification and polisomy of chromosome 19. However, no association was observed between AXL immunhistochemical expression and gene amplification. MET protein expression was observed in 20.8% of cases, while gene amplification was identified only in 2.0% of cases. VEGFR2 overexpression was identified in 31.25% of cases. 10.4% of cases showed co-expression of AXL and MET proteins, related significantly with epithelioid histotype ($p < 0.05$) and 6.25% of cases AXL, c-MET and VEGFR2 co-expression. Studies in vitro showed that multitargets inhibitor blocked cancer cell proliferation, metastasis and angiogenesis in four human mesothelioma cell lines: NCI-H2452, NCI-H2052, NCI-H28 and MSTO. A dose dependent inhibition of cell viability was examined after 72h treatment of human mesothelioma cell lines with increasing doses of multitargets inhibitor, observing a decrease in cell proliferation with IC50 value between 0.5 and 1 μM. Similar effects were detected for apoptosis assay and anchorage-independent colony forming abilities, in particular migration ability of H2052 and MSTO cell lines decreased to about 60% with 0.5 and 1 μM of multitargets inhibitor. **Conclusion:** AXL/c-MET/VEGFR2 co-expression represents a frequent event in MPM, especially in epithelioid phenotype, suggesting a possible cooperation of these RTKs in the pathogenesis of this neoplasia. Multitargets AXL/c-MET/VEGFR2 inhibitors could be a promising therapeutic weapon in mesothelioma.

Keywords: Multitargets inhibitors, Mesothelioma, tyrosine kinase receptors

P2.09 PATHOLOGY
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P2.09-01 TUMOR-ASSOCIATED IMMUNE CELL INFILTRATION PATTERNS IN EARLY STAGE SQUAMOUS LUNG CARCINOMA

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Background: With the recent clinical success of immunotherapy in non-small cell lung carcinoma, the character of the inflammatory infiltrate associated with these tumors is now the subject of increasing interest. Molecular studies have suggested that tumors can be stratified by the character of their inflammatory infiltrate. We now describe the detailed histological appearances of a multi-institutional series of early stage squamous carcinomas and correlate them with mutation burden, PDL1 expression patterns and clinical outcome. **Method:** Histologic sections of from 250 tumors were evaluated by two pathologists independently for squamous subtype (WHO classification), percentage and character of intratumoral inflammatory cells, percentage and character of para-tumoral infiltrate and presence or absence of scalloping at tumor cell/stromal interface by inflammatory cells along the edges of tumor cell nests, a feature possibly related to existing immune reaction. The ratios of infiltrating inflammatory cells to tumor cells were estimated in 10% increments by microscopic inspection. Quantity and character of infiltrates was assessed by Kaplan-Meir testing for effect on survival and by Pearson bivariate testing for relationships among variables. **Result:** The character and extent of inflammatory infiltrates were highly heterogeneous. The infiltrates could be divided into intratumoral and paratumoral patterns according to their location in relation to microscopic tumor cell nests. Intratumoral infiltrates could be further subdivided into two patterns: one consisted exclusively lymphocytes, usually few in number; a second polymorphous pattern contained many inflammatory cell types including polymorphonuclear leukocytes (PMNs). In paratumoral tissue, three patterns could be discerned: lymphocytic, plasmacytic and polymorphous. Inflammatory cell infiltrate quantity or character did not correlate with survival for either intratumoral or paratumoral infiltrates and there was no evident relationship to mutational burden or to PDL1 expression by IHC. Scalloping at the tumor cell stromal interface was also not prognostically significant. **Conclusion:** The inflammatory infiltrates in early stage squamous lung carcinoma are highly heterogenous and are not associated with outcome. However, the complexity of tumor infiltrating inflammatory cells is worthy of further evaluation in future immunotherapeutic trials.

Keywords: Tumor-associated immune cell, infiltration patterns, early stage squamous lung carcinoma

P2.09 PATHOLOGY
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P2.09-02 COMPREHENSIVE ASSESSMENT OF PD-L1 IMMUNOHISTOCHEMISTRY ON PAIRED TISSUE AND CYTOLOGY SPECIMENS IN NON-SMALL CELL LUNG CANCER

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Background: Molecules targeting Programmed Death Receptor 1 (PD-1) and its ligand (PD-L1) are now part of the therapeutic arsenal for patients presenting with advanced stage non-small cell lung carcinoma (NSCLC). PD-L1 staining assessed by immunohistochemistry (IHC) is currently used as a predictive biomarker to select patients likely to respond to PD-1/PD-L1 inhibitors. Despite recent data, it is still not clear if cytology specimens provide reliable and valid PD-L1 results, when compared to tissue specimens. In this project, we aimed to compare PD-L1 IHC results on tissue (biopsy and surgery) and cytology specimens from the same patient. We also wanted to assess the performance of two IHC kits as well as the intra and interobserver agreement in evaluating cytology specimens. **Method:** A retrospective cohort comprising 46 patients

with a diagnosis of NSCLC was selected. Each patient had a surgical specimen with a corresponding cytology sample (cell block), including 20 pleural effusions, and/or a biopsy, for a total of 182 specimens. IHC was performed using 28-8 and SP263 PD-L1 kits. PD-L1 staining was measured as the percentage of tumor cells with membranous staining (tumor proportion score, TPS) as rated blindly by four evaluators. Sixty slides were then blindly reevaluated for documenting intraobserver agreement. PD-L1 TPS was grouped as <1%, 1-49% and >50%. Fleiss and Cohen's kappas were used to evaluate TPS concordance between tissue and cytology specimens and to assess the inter and intraobserver agreement. **Result:** Respectively for 28-8 and SP263 kits, 37.5 and 25.0% of the 32 patients with a cytology sample had a PD-L1 TPS of >50% with a good agreement between the kits (k=0.73, CI95% 0.50-0.97). The agreement between the cytology and surgical specimen was good (28-8: k=0.76, CI95% 0.46-1.0, SP263: k=0.75, CI95% 0.42-1.0) and was slightly lower between the 26 patients with a biopsy and a cytology specimen (28-8: k=0.71, CI95% 0.31-1.0, SP263: k=0.67, CI95% 0.19-1.0). For the evaluation of PD-L1 TPS in cytology specimens, the interobserver agreement was good (28-8: k=0.71, CI95% 0.60-0.82, SP263: k=0.63, CI95% 0.52-0.74) and the intraobserver agreement was excellent (k=0.93, CI95% 0.85-1.0). **Conclusion:** We showed that PD-L1 TPS evaluated in cytology samples have a good concordance with biopsy and surgical specimens. We also demonstrated that the evaluation in cytology specimen is feasible as the inter and intraobserver agreement was good to excellent. Overall, our results support the use of PD-L1 IHC on cytology specimens, however, this will need to be correlated with the clinical response to immunotherapy.

Keywords: cytology, Immunotherapy, PD-L1 immunohistochemistry

P2.09 PATHOLOGY
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P2.09-03 RAPID-IMMUNOCYTOCHEMISTRY FOR EVALUATION OF SURGICAL MARGIN IN SUBLOBAR PULMONARY RESECTION

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Background: Histological evaluation of surgical margin for pulmonary malignant tumor in sublobar resection is difficult in automatic suture instrument (stapler) used in thoracoscopic surgery. In order to solve this problem, we devised a novel surgical margin assessment method that combined with rapid-immunocytochemistry (R-ICC) of stapler lavage solution and examined its usefulness. We developed a device that enables rapid-IHC (R-IHC) analyses within 20 minutes. By applying this device to R-ICC, we can perform intraoperative R-ICC within 30 minutes. By using this method, it is a possibility that the surgical margin can be accurately evaluated more than papanicolaou staining alone. **Method:** From September 2016 to December 2017, we examined 21 lesions of pulmonary malignant tumor in 21 patients who underwent sublobar resection at Akita University Hospital. There were 12 male and 9 female patients whose ages ranged from 45 to 83 years old. Six patients underwent segmentectomy and 15 of ones underwent wedge resection. Histological diagnosis of staple stump and cytological diagnosis of staple lavage fluid (papanicolaou staining) and R-ICC were performed. The cases were classified by pathological results, and each cases were followed up. We performed R-ICC using each antibodies against for cytokelatin (CK) 20, CK 7 and Thyroid transcription factor-1 (TTF-1) in adenocarcinoma, p-40 in squamous cell carcinoma, respectively. **Result:** The histological diagnoses were 4 lung adenocarcinomas, 5 squamous cell carcinomas, 7 colorectal adenocarcinomas, 1 renal cell carcinoma, 1 hepatocellular carcinoma, 1 duodenal cancer, 1 endometrial cancer and 1 bile duct cancer. No histological diagnosis of staple stump observed malignant findings in all cases. On the other hand, in conventional cytological diagnoses there were 2 cases of class V, 1case of class IV and 1 case of class III. R-ICC were positive in all 4 cases of class III or higher. Among 4 cases, we performed additional resection in two cases of class V, but not in the other two cases because difficulty in further resection. In the case of class IV without additional resection, local recurrence was observed in 4 months after surgery. **Conclusion:** Among 21 cases, local recurrence was observed in one patient with positive cytological diagnosis and positive R-ICC diagnosis. There is a possibility that staple lavage fluid cytology can more accurately evaluate the stump than the tissue crushed by the staple. If there are very few cancer cells in the lavage fluid, R-ICC may be useful for cancer cell detection.

Keywords: surgical margin, sublobar pulmonary resection, rapid-immunocytochemistry

P2.09 PATHOLOGY
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P2.09-04 PD-L1 EXPRESSION IN PRIMARY LUNG ADENOCARCINOMA AND ITS RELATION WITH EGFR / KRAS MUTATION AND CLINICOPATHOLOGICAL FEATURES

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Background: Programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) pathway-targeted immunotherapy is becoming standard practice in the management of lung cancer. Theexpression of PD-L1protein is expected to apply to evaluatethe prognosis or to predict the response to PD-1-blocking antibodies. The immunohistochemistry(IHC) assay forPD-L1, 22C3 pharmDx, has revealed that about30% of all non-small cell lung cancer (NSCLCs) express the PD-L1 with a high level. The association between PD-L1 positivity and the clinicopathological features in lung adenocarcinoma (ADC) remains unclear, however. **Method:** We retrospectively evaluated the PD-L1 expression in the surgically resected tumor tissues by IHC with the 22C3 assay, from 233 primary lung ADC patients. The PD-L1 tumor proportion score (TPS) was calculated as the percentage of at least 100 viable tumor cells with complete or partial membrane staining. TPS was reported in three categories (no expression, <1%; low expression, 1-49%; and high expression, ≥50%). **Result:** Of the 233 cases analyzed, the median age was 60 (range, 34-82 years), 149 (63.9%) patients were female, 167 (71.7%) patients were never-smokers, and 55 (23.6%) patients had stage III (50) and IV (5) disease. Among them, 139 (59.7%) patients had activating *EGFR* mutations, and 23 (9.9%) patients were *KRAS* mutant. Proportions in each PD-L1 TPS category were: <1%, 63.9%(149/233); 1-49%, 23.6%(55/233); ≥50%, 12.5%(29/233). Wilcoxon rank sum test(Mann-Whitney U test) revealed that PD-L1 positivity had negative correlation with patient age (p = 0.027), and positive correlation with male (p = 0.001), smoker (p = 0.007), advanced stage (p < 0.001). *EGFR*-mutated tumors (n= 139) demonstrated lower rates of PD-L1 expression [TPS <1% (72.7%); 1-49% (22.3%); ≥50% (5.0%); P<0.001];meanwhile,*KRAS*-mutated tumors (n= 23) showed higher rates of PD-L1 expression [TPS <1% (43.5%); 1-49% (30.4%); ≥50% (26.1%); P<0.001]. **Conclusion:** This investigation shows that in primary lung adenocarcinoma the PD-L1 expression was significantly associated with younger age, male, smokers, high stagedisease, *EGFR* wild-type and *KRAS* mutant. Therefore, it is rational to choose a different checkpoint inhibitor according to the driver gene mutation status and to combine targeted therapies and anti-PD-L1 agents.

Keywords: PD-L1, Adenocarcinoma, lung

P2.09 PATHOLOGY
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P2.09-05 EVALUATION OF PD-L1-STAINED TUMOR CELLS VIA THE 22C3 AND SP-142 ANTIBODIES IN COHORT OF PATIENTS TREATED ON KEYNOTE-001

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Background: Four PD-L1 antibodies have been utilized in NSCLC clinical trials, with an analytical comparison demonstrating a high level of concordance between the percentage of PD-L1–stained tumor cells with three of these antibodies (22C3, 22C3, 28-8, and SP263), but not a fourth, SP-142 (Hirsch et al, JTO 2017). This finding led us to evaluate the relationship between the percentage of PD-L1–stained tumor cells with 22C3 and SP-142, as well as the association between the PD-L1 levels identified by each antibody and clinical outcomes in 28 NSCLC patients treated on KEYNOTE-001. **Method:** We performed a retrospective analysis of 28 NSCLC patients treated with pembrolizumab on the KEYNOTE-001 trial at UCLA (23pts) or MSKCC (5pts) with data cut-off 12/2017. Patients had PD-L1–stained tumor cell levels assessed by both the 22C3 antibody (Dako), via central evaluation as previously described (Garon et al, NEJM 2015) and the SP-142 antibody (Spring Bioscience) at UCLA in accordance with established methods (Zaretsky et al, NEJM 2016). Survival curves for PFS and OS were estimated using the Kaplan-Meier method and formally compared between groups using the log-rank test. The association between PD-L1–stained tumor cell levels identified by the two antibodies was assessed using the Pearson correlation coefficient. **Result:** In 61% (17/28) of patients, PD-L1 levels

were grouped similarly (either <1%, 1-49%, or ≥50%) by both antibodies. Specifically, compared to 22C3 staining, SP-142 led to the same grouping for 63% (5/8) pts with ≥50% staining, 85% (11/13) pts with 1-49% staining, and 14% (1/7) pts w <1% staining. Evaluating the relationship between PD-L1 grouping and clinical outcomes via the SP-142 antibody revealed improved PFS and OS in pts with higher PD-L1 expression levels, while the 22C3 antibody predicted for improved PFS in these patients, but not improved OS [SP142 (PFS,OS): (p=0.0039, p=0.0425)][22C3 (PFS,OS): p=0.0121, p=0.1222). The PD-L1 results from the SP-142 and 22C3 antibodies were strongly associated (r =0.58, p=0.001). **Conclusion:** The PD-L1–stained tumor cell levels in the majority of patients evaluated were similarly grouped into one of three categories (<1%, 1-49%, or ≥50%) by both 22C3 and SP142. This analysis is limited by small patient number, but suggests that the number of PD-L1–stained tumor cells identified by each antibody is similar and a higher PD-L1 level identified by either antibody predicts for improved clinical outcomes with pembrolizumab.

Keywords: PD-L1, pembrolizumab, KEYNOTE-001

P2.09 PATHOLOGY
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P2.09-06 EXPRESSION OF PD-L1 ON ROUTINE NON-SMALL CELL LUNG CARCINOMA SECTIONS: COMPARATIVE ASSESSMENT OF SP263 (VENTANA) AND 22C3 (DAKO PHARMDX)

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Background: The SP263 (Ventana Benchmark) antibody as a predictive immunohistochemical marker for pembrolizumab therapy provides an avenue for local testing. Pathologists without access to the Dako Autostainer Link 48 platform (certified for the Dako 22C3 antibody) have been restricted to referrals at external departments, resulting in an increased turnaround time. Here we report the results of our local verification of SP263. **Method:** Specimens previously assessed for 22C3 PD-L1 expression at either Royal Liverpool Hospital or Queen Elizabeth Hospital Birmingham were selected from the archives of Wythenshawe Hospital. Cases with less than 100 viable residual tumour cells were excluded. The same tumour block was selected for staining with the Roche SP263 clone and specimens were assessed for tumour proportion score (TPS), immune cell proportion and staining intensity. Assays were reported as disagreeing if a differing TPS changed the therapeutic cut-off ranges. **Result:** Expression levels of 22C3 and SP263 were compared across 100 cases (43 resections, 26 biopsies, 26 lymph node aspirates, 5 node excisions); 59 adenocarcinomas, 33 squamous carcinomas, 8 not otherwise specified (70 primary, 30 metastatic). The TPS ranges (<1%, 1 - 49%, > 50%) were in agreement for 78 samples. Of the 22 cases with differing ranges, 15 reflected a TPS of <10% and 7 had greater differences e.g. 10% versus 60%. Reasons for discrepancies included faint membranous staining on a few of the 22C3 sections (not apparent on SP263), scoring of carcinoma in situ, possible scoring of cells at a deeper block level, and variation in interpretation by the scoring pathologists. The overall Pearson correlation coefficient (r) was 0.9025, $p < 0.00001$.

Table 1 Comparison of PD-L1 Ventana SP263 and Dako 22C3 tumour proportion scores

SAMPLE	DIAGNOSIS	SP263	>/= 1%	>/= 50%	Liverpool 22C3	Birmingham 22C3	Discrepancy
Pleural biopsy	Adenocarcinoma	1	No	No	1	N/A	No
Pleural biopsy	Adenocarcinoma	10	No	No	60	N/A	Yes
EBUS node	Metastatic adenocarcinoma	0	No	No	0	N/A	No
EBUS node	Metastatic adenocarcinoma	0	No	No	1	N/A	Yes
Resection	Adenocarcinoma	40	Yes	No	10	N/A	No
EBUS node	Metastatic squamous carcinoma	2	No	No	10	N/A	No
Resection	Adenocarcinoma	5	Yes	No	<1	N/A	Yes
EBUS node	Metastatic adenocarcinoma	0	No	No	0	N/A	No
Bronchial biopsy	Squamous carcinoma	10	Yes	No	70	N/A	Yes
Bronchial biopsy	Squamous carcinoma	0	No	No	0	N/A	No
EBUS node	Metastatic squamous carcinoma	<1	No	No	<1	N/A	No
EBUS node	Metastatic adenocarcinoma	<1	No	No	0	N/A	No
Bronchial biopsy	Squamous carcinoma	40	Yes	No	40	N/A	No
Resection	Squamous carcinoma	5	Yes	No	10	N/A	No
Lung biopsy	Adenocarcinoma	0	No	No	0	N/A	No
Lymph node biopsy	Metastatic adenocarcinoma	100	Yes	Yes	100	N/A	No
Resection	Adenocarcinoma	<1	No	No	N/A	<1	No
Lung biopsy	Adenocarcinoma	0	No	No	N/A	0	No
Resection	Adenocarcinoma	0	No	No	0	N/A	No
Resection	Adenocarcinoma	10	Yes	No	N/A	5 to 10	No
Resection	Adenocarcinoma	20	Yes	Yes	N/A	20-30	No
Resection	Squamous carcinoma	2 to 4	Yes	No	N/A	3 to 5	No
Bronchial biopsy	Squamous carcinoma	<1	No	No	N/A	<1	No
Bronchial biopsy	Squamous carcinoma	2 to 4	Yes	No	1	N/A	No
Lymph node biopsy	Metastatic adenocarcinoma	100	Yes	Yes	100	N/A	No
Bronchial biopsy	NOS	<1	No	No	N/A	<1	No
Bronchial biopsy	Adenocarcinoma	0	No	No	1	N/A	Yes
Resection	Adenocarcinoma	2 to 4	Yes	No	10	N/A	No
Lymph node biopsy	Metastatic squamous carcinoma	80	Yes	Yes	70	N/A	No
EBUS node	Metastatic adenocarcinoma	80	Yes	Yes	80	N/A	No
Bronchial biopsy	Squamous carcinoma	0	No	No	N/A	<1	No
EBUS node	Metastatic adenocarcinoma	90	Yes	Yes	80	N/A	No
Pleural biopsy	Adenocarcinoma	0	No	No	10	N/A	Yes
Bronchial biopsy	Squamous carcinoma	0	No	No	0	N/A	No
Bronchial biopsy	Squamous carcinoma	5	Yes	No	N/A	0	Yes
EBUS node	Metastatic squamous carcinoma	50	Yes	Yes	50	N/A	No
Bronchial biopsy	Squamous carcinoma	2 to 4	Yes	No	10	N/A	No

SAMPLE	DIAGNOSIS	SP263	>/= 1%	>/= 50%	Liverpool 22C3	Birmingham 22C3	Discrepancy
EBUS node	Metastatic adenocarcinoma	70	Yes	Yes	N/A	70	No
EBUS node	Metastatic adenocarcinoma	100	Yes	Yes	100	N/A	No
Bronchial biopsy	Squamous carcinoma	1	Yes	No	20	N/A	No
Resection	Adenocarcinoma	5	Yes	No	0	N/A	Yes
Resection	Adenocarcinoma	0	No	No	0	N/A	No
EBUS node	Adenocarcinoma	<1	No	No	0	N/A	No
Resection	Adenocarcinoma	5	Yes	No	10	N/A	No
EBUS node	Sarcomatoid carcinoma	0	No	No	0	N/A	No
Resection	Adenocarcinoma	0	No	No	N/A	<1	No
Lymph node biopsy	Metastatic squamous carcinoma	0	No	No	N/A	<1	No
Resection	Adenocarcinoma	60	Yes	Yes	N/A	60-70	No
Bronchial biopsy	Squamous carcinoma	0	No	No	0	N/A	No
Pleural biopsy	Adenocarcinoma	2 to 4	Yes	No	10	N/A	No
Lung biopsy	Squamous carcinoma	0	No	No	5	N/A	Yes
EBUS node	Metastatic adenocarcinoma	5	Yes	No	30	N/A	No
Resection	Pleomorphic carcinoma	70	Yes	Yes	80	N/A	No
Resection	Squamous carcinoma	0	No	No	1	N/A	Yes
Bronchial biopsy	Squamous carcinoma	10	Yes	No	20	N/A	No
Resection	Adenocarcinoma	50	Yes	Yes	N/A	10 to 20	Yes
Resection	Adenocarcinoma	0	No	No	N/A	<1	No
Resection	Pleomorphic carcinoma	1	Yes	No	20	N/A	No
Resection	Adenocarcinoma	0	No	No	0	N/A	No
Resection	Adenocarcinoma	10	Yes	No	N/A	2 to 3	No
EBUS node	Metastatic adenocarcinoma	100	Yes	Yes	100	N/A	No
Resection	Adenocarcinoma	5	Yes	No	N/A	<1	Yes
EBUS node	Metastatic adenocarcinoma	100	Yes	Yes	100	N/A	No
EBUS node	Metastatic squamous carcinoma	50	Yes	Yes	N/A	80	No
Resection	Adenocarcinoma	90	Yes	Yes	95	N/A	No
Resection	Adenocarcinoma	<1	No	No	N/A	<1	No
Resection	Adenocarcinoma	0	No	No	1	0	Yes
Resection	Adenocarcinoma	<1	No	No	5	N/A	Yes
Resection	Adenocarcinoma	20	Yes	No	20	N/A	No
Bronchial biopsy	NOS	50	Yes	Yes	60	N/A	No
Resection	Adenocarcinoma	2 to 4	Yes	No	N/A	5 to 10	No
Resection	Adenocarcinoma	0	No	No	10	N/A	Yes
Soft tissue	NOS	1	Yes	No	20	N/A	No
Bronchial biopsy	Sarcomatoid carcinoma	<1	No	No	N/A	<1	No
EBUS node	Metastatic adenocarcinoma	70	Yes	Yes	N/A	60 to 70	No
Pleural biopsy	Adenocarcinoma	80	Yes	Yes	N/A	70	No
Resection	Squamous carcinoma	<1	No	No	1	0	Yes
Resection	Adenocarcinoma	50	Yes	Yes	N/A	5 to 10	Yes
Resection	Adenocarcinoma	10	Yes	No	50	N/A	Yes
Resection	Adenocarcinoma	0	No	No	0	N/A	No
Resection	Squamous carcinoma	1	Yes	No	N/A	<1	Yes
Resection	Squamous carcinoma	100	Yes	Yes	100	N/A	No
Resection	Squamous carcinoma	5	Yes	No		10	No
Resection	Squamous carcinoma	70	Yes	Yes	N/A	70 to 80	No
Resection	Squamous carcinoma	90	Yes	Yes	N/A	10 to 20	Yes
EBUS node	Squamous carcinoma	<1	No	No	N/A	<1	No
EBUS node	Adenocarcinoma	0	No	No	N/A	0	No
EBUS node	Metastatic adenocarcinoma	70	Yes	Yes	N/A	80	No
EBUS node	Metastatic squamous carcinoma	50	Yes	No	N/A	70	No
Resection	Adenocarcinoma	<1	No	No	N/A	<1	No
EBUS node	Metastatic adenocarcinoma	40	Yes	No	30	N/A	No
Resection	Squamous carcinoma	90	Yes	Yes	N/A	100	No
Resection	Adenocarcinoma	40	Yes	No	40	N/A	No
EBUS node	Metastatic adenocarcinoma	80	Yes	Yes	N/A	70 to 80	No
EBUS node	Metastatic squamous carcinoma	1	Yes	No	N/A	<1	Yes
Bronchial biopsy	Squamous carcinoma	1	Yes	No	1	N/A	No
EBUS node	Metastatic adenocarcinoma	5	Yes	No	60	N/A	Yes
Primary EBUS	Pleomorphic carcinoma	100	Yes	Yes	90	N/A	No
Resection	Adenocarcinoma	90	Yes	Yes	90	N/A	No
Lymph node biopsy	Adenocarcinoma	<1	No	No	<1	N/A	No

Conclusion: Tumour expression profiles of PD-L1 are similar for the 22C3 and SP263 antibodies, with a rate of variation similar to previous reports. Cases that are discrepant may reflect differences in pathologist interpretation rather than the assay.

Keywords: PD-L1, SP263, 22C3

P2.09-07 DOES METASTATIC SITE MATTER FOR PD-L1 TESTING IN STAGE IV NSCLC?

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Background: Stage IV non-small cell lung cancer (NSCLC) often presents with metastasis to multiple distant sites. Currently PD-L1 expression by immunohistochemistry (IHC) testing with Tumor Proportion Score (TPS) ≥ 50% and ≥1% is required for first- and second-line Pembrolizumab treatment respectively. However, it is not well known if PD-L1 expression differs in NSCLC specimens sampled from different distant metastatic sites. In this study, we evaluate PD-L1 expression in distant metastatic sites. **Method:** A total of 400 NSCLC specimens from distant metastatic sites are included in this study. The metastatic sites include brain, bone, non-regional lymph nodes, serous membranes (pleura, pericardium and peritoneum) and organs outside the chest (liver, adrenal gland, skin, soft tissue). The samples are either cytology cell blocks, small biopsies or surgical resections. IHC was performed using Dako PD-L1 IHC 22C3 pharmDx. A total of 100 viable tumor cells is required for adequacy. TPS≥ 50% and 1-49% are defined as high and low PD-L1 expression respectively. **Result:** Overall, the rate of TPS ≥50% ranges from 36-47% in different metastatic organ sites (Table 1). The prevalence of PD-L1 high and low expression is similar for all distant metastatic sites (*P*=0.91). Brain metastases have a slightly lower rate of high PD-L1 expression but the difference is not statistically significant. **Table 1. PD-L1 expression in different metastatic sites**

Metastatic sites	Tumor Proportion Score (TPS)			Total
	≥50% n (%)	1-49% n (%)	0% n (%)	n (%)
Brain	13(36%)	9 (25%)	14(39%)	36 (100%)
Bone	21(44%)	11(23%)	16(33%)	48 (100%)
Nonregional lymph nodes	6(40%)	3(20%)	6 (40%)	15 (100%)
Serous membranes	91(40%)	62(27%)	74(33%)	227 (100%)
Organ outside chest	35(47%)	20(27%)	19(26%)	74 (100%)
Total	166(42%)	105(26%)	129(32%)	400 (100%)

P=0.91 **Conclusion:** Our results suggest that the specimens for PD-L1 IHC testing can be sampled from any accessible distant metastatic site.

Keywords: PD-L1 testing, metastatic sites, stage IV NSCLC

P2.09-08 CLINICAL OUTCOMES OF HISTOLOGY VERSUS CYTOLOGY PD-L1 22C3 ANTIBODY TESTING IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Immune checkpoint inhibitors (CPIs) are now an accepted standard of care along the treatment algorithm for advanced non-small cell lung cancer (NSCLC). PD-L1 expression using 22C3 immunohistochemistry (IHC) help determine the line of therapy in which CPI are used. Previous studies demonstrated that PD-L1 expression is comparable on cytology versus solid biopsy/histology specimens. We assess the clinical outcomes between patients with PD-L1 expression ≥50% (high positive) tested using cytology versus histology specimens. **Method:** This retrospective cohort study includes specimens processed between January 2015 to June 2017 on samples dating back to March 2014. Patients were included in the study if they were seen by a medical oncologist for consideration of systemic treatment for advanced NSCLC. Clinical characteristics were extracted from electronic medical records. Overall survival (OS) was defined as time from diagnosis of advanced NSCLC to death and compared by method of PD-L1 analysis (cytology versus histology), adjusting for age, ECOG, weight loss, and receipt of palliative intent radiotherapy, targeted therapy, and CPI. **Result:** 148 (30.8%) of 481 samples tested ≥50% for PD-L1 expression. Amongst those, 32 and 37 patients fulfilled eligibility criteria with cytology and histology samples respectively. Baseline characteristics of the two groups are comparable in age, gender, ECOG, histological subtype, and receipt of CPIs. The cytology group had a significantly higher number of patients with baseline pleural effusion (10 vs 4 patients, p=0.035) and receipt of any systemic therapy (28 vs 22 patients, p=0.009). The histology group received more palliative intent radiation (24 vs 13, p=0.044). There was no difference in OS between the cytology and histology groups. Median OS in the cytology group was 11.9 versus 8.0 months in the histology group; adjusted HR 0.98 (95% CI 0.43-2.26). Amongst patients who received systemic therapy, survival was longer if patients were exposed to CPI during their course of treatment regardless of cytology or histology groups; adjusted HR 0.45 (95% CI 0.22 – 0.90). **Conclusion:** In advanced NSCLC, CPI treatment guided by specimens analyzed by cytology versus histology were equivalent in survival. Regardless of sample source, patients exposed to CPI in any line of therapy had significantly longer survival than patients without exposure to CPI amongst patients testing high positive for PD-L1. Ongoing analyses are comparing clinical outcomes in patients with other expressions of PD-L1.

Keywords: outcomes, PD-L1 testing, cytology

P2.09-09 PRECISION AND REPEATABILITY OF VENTANA DLL3 (SP347) ASSAY IMMUNOHISTOCHEMISTRY ASSAY IN FINE NEEDLE ASPIRATIONS OF SMALL CELL LUNG CANCER

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Background: Fine needle aspirations (FNA) are a common type of sample that is obtained for diagnostic purposes in small cell lung cancer (SCLC) patients due to its relatively less invasive nature. Several delta-like protein 3 (DLL3) therapies that target DLL3 in SCLC are under development. We recently developed an immunohistochemistry assay utilizing a rabbit monoclonal antibody that can be used to identify patients that may potentially respond to DLL3 targeted therapies. Due to the high prevalence of FNA samples in SCLC, the robustness of the VENTANA DLL3 (SP347) Assay (DLL3 (SP347)) in FNAs is examined. **Method:** Formalin-fixed, paraffin-embedded (FFPE) FNA samples of SCLC were used in a series of studies addressing precision of performance of DLL3 (SP347). FNA SCLC samples were stained with the VENTANA DLL3 (SP347) Assay and assessed by a pathologist for percent tumor cell staining (%TC), at any stain intensity at ≤4X magnification. The samples were placed into quartile bins (0-24, 25-49, 50-74 and 75-100 %TC) and evaluated for intra-day repeatability and inter-day precision. For each case, the modal staining result based on %TC bin was determined and the result from each test sample was compared to its respective case-level modal staining result and deemed concordant or discordant. Results were aggregated across cases and the overall percent agreement (OPA) was calculated for each study. **Result:** Both studies (Table 1) showed >90% OPA for DLL3 concordance to the %TC bins.

Table 1: Precision and Repeatability of FNA SCLC Samples

Study	# of Cases	# DLL3 Observations	OPA
Intra-day	21	63	100%
Inter-day	21	124	98.4

Conclusion: The presented data shows that VENTANA DLL3 (SP347) Assay can precisely evaluate DLL3 expression in FNA SCLC samples.

Keywords: DLL3, SCLC, Immunohistochemistry

P2.09-10 QRT-PCR AS AN EFFICIENT AND RELIABLE DIAGNOSTIC SCREENING APPROACH FOR THE DETECTION OF EML4-ALK FUSION GENE IN NSCLC SAMPLES: A PILOT STUDY

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Background: ALK gene rearrangement occurs in 3-5% of NSCLC patients and provides an oncogenic driver in these tumors and generally responds to Crizotinib therapy. Identification of this EML4-ALK fusion gene requires a very sensitive and specific method. Both FISH and IHC are widely used in clinical laboratories for the detection of ALK rearrangements in NSCLC tumor samples. RT-PCR-based assays have not yet been as widely used as FISH and IHC for the detection of ALK rearrangements in NSCLC. Our Our aim is to review performance of RT-PCR assay in comparison with FISH and IHC for the detection of EML4-ALK in NSCLC **Method:** A total of 100 cases of EGFR wild type were selected and were performed by FISH, IHC and RT-PCR simultaneously. **Result:** Out of 105 tumor FFPE samples of NSLC, 76 % of tumor samples were biopsies and cytology and 24% were resections of archival lung and brain metastasis. The RT-PCR test (diagnostic cut-off Δ Ct of ≤ 8) was shown to be highly sensitive (100%) when compared to FISH and IHC. The overall specificity of the RT-PCR test for the detection of ALK in cases without full-length ALK expression was 94% in comparison to FISH. No significant association was observed between *EML4-ALK* fusion gene and clinical stage. **Conclusion:** In contrast to FISH (Vysis ALK Break Apart probe) testing, as per the WHO guidelines, today IHC (Ventana ALK (D5F3 FDA approved) method is well accepted for the detection of EML4-ALK. However, in our study using FISH and IHC or FISH alone in comparison to RT-PCR have demonstrated that RT-PCR has a high sensitivity and specificity. This test has also shown the rapid TAT and has advantage of doing with ease as compared to FISH and IHC and can be done on biopsy as well as on cytology samples with lower tumor content. Our result indicates that identification of the specific variant by RT-PCR based ALK assay can potentially be used as a reliable standalone diagnostic screening approach and cost effective test and, which may apparently become important in the future for predicting patient response to ALK inhibitors. NGS fusion panels as the sole platform for detecting ALK and other NSCLC biomarkers in a single test are attractive.

Keywords: FISH, IHC, qRT-PCR comparison

P2.09-11 TMB ESTIMATED WITH TARGETED NGS IN EARLY STAGE SQUAMOUS CELL CARCINOMA: CORRELATION WITH PD-L1 EXPRESSION AND LYMPHOCYTE DENSITY

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Background: It has been proposed that a combination of assays may refine the prediction of response to checkpoint inhibitors, with tumour mutation burden (TMB) being lately the strongest biomarker associated with efficacy. Although some targeted next generation sequencing (NGS) assays provide a good estimate of whole exome sequencing TMB, they are only available throughout referral laboratories. We sought to investigate the possibility of profiling TMB *in-house* with a commercially available targeted NGS assay, and to correlate the results with survival, the status of *TP53*, PD-L1 overexpression and tumor-infiltrating lymphocytes (TILs). **Method:** The study included samples from 40 patients diagnosed with early-stage lung squamous cell carcinoma. PD-L1 immunohistochemistry (IHC) was performed with two clones (SP263 and SP142, Ventana Medical Systems). CD8+ TILs were scored with a digital algorithm. The status of *TP53* (exons 4–10) was investigated with direct sequencing. Ion Torrent™ Oncomine™ Tumor Mutation Load Assay (ThermoFisher Scientific), a targeted NGS assay which covers 1.7Mb across 409 cancer driver genes, was used to assess TMB. NGS was performed on genomic DNA from FFPE tumor samples using the Ion S5™ system. The results were analyzed with the Ion Reporter™ software. According to the manufacturer's instructions, TMB was calculated based on the number of non-synonymous somatic mutations, after removing polymorphisms and known or predicted driver mutations from all the variants. We investigated the correlation between TMB and PD-L1 expression, lymphocyte density, *TP53* status and survival. **Result:** TMB data was available for all 40 patients. The mean and median number of mutations was 13 and 11, respectively. CD8+/mm^2 TILs within the peritumoral stromal compartment ranged from 312 to 4793 and within the intraepithelial compartment ranged from 17 to 2002. Sixty percent and 32% of cases were positive in tumor cells with SP263 or SP142, respectively (1% cut-off). Immune cells PD-L1 expression (1% cut-off) was observed in 92% of samples with both clones. No correlation was found between PD-L1 expression or lymphocyte density and TMB. Tumors with *TP53* mutations showed non-significant higher numbers of mutations than those wild-type (p=0.075). Accordingly, there was a similar trend for overall survival using the median number of mutations as a cut-off (p=0.137, HR, 5.29). **Conclusion:** It is feasible to use targeted NGS to estimate TMB. In our pilot study, there was no obvious correlation with other immunooncology predictive biomarkers. Funding: AES 2017/Feder. ISCIII: PI17/01001

Keywords: TMB, NGS, Lung squamous carcinoma

P2.09-12 EGFR MUTATION STATUS IN SQUAMOUS CELL CARCINOMA OR NON-SMALL CELL CARCINOMA FAVOR SQUAMOUS CELL CARCINOMA DIAGNOSED FROM SMALL LUNG BIOPSIES

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Background: Epidermal growth factor receptor (EGFR) mutation testing is strongly recommended in non-small cell lung cancer (NSCLC) patients with adenocarcinoma subtypes, or patients with mixed-type tumors containing adenocarcinomatous components. However, in clinical practice, patients showing squamous cell carcinoma (SqCC) morphology on small biopsies cannot be ruled out to have an adenocarcinomatous component elsewhere in the lesion due to sampling bias. Therefore, *EGFR* mutation testing may have been neglected in such circumstances, which would affect the clinical management of patients. In this study, we sought to examine the frequency of *EGFR* mutations in lung cancer patients with SqCC or Non-Small Cell Carcinoma (NSCC) favor SqCC diagnosed from small biopsies. The correlation between *EGFR* mutation status and clinicopathological characteristics was also evaluated. **Method:** One hundred and forty-eight patients diagnosed as SqCC or NSCC favor SqCC from small lung biopsies were enrolled. All of these cases were histologically confirmed by evaluating cellular morphology using hematoxylin-eosin (HE) staining and TTF1, p40 or CK5/6 expression using immunohistochemistry. *EGFR* mutations were examined using real-time PCR based assay. **Result:** Among 148 small biopsy cases, 135 (91.2%) were diagnosed as SqCC while 13 (8.8%) were NSCC favor SqCC. Approximately 8.8% (13/148) of all cases were found to have *EGFR* mutations, including 7 (53.8%) L858R mutation, 4 (30.8%) exon 19 deletion, and 2 (15.4%) cases with coexistent L858R and T790M mutations. *EGFR* mutation-positive cases accounted for 5.2% (7/135) in SqCC, 46.2% (6/13) in NSCC favor SqCC, and 83.3% (10/12) of all these cases were never smokers. The multivariate analysis showed that *EGFR* mutations were more prevalent in non-smokers than those in smokers (83.3% versus 16.7%, p = 0.03) and in patients diagnosed as NSCC favor SqCC than in those diagnosed as SqCC (46.2% versus 5.2%, p = 0.002). In addition, 4 out of 13 *EGFR* mutation-positive patients with SqCC or NSCC favor SqCC morphology were eventually diagnosed as adenosquamous carcinoma after further undergoing surgical resection. **Conclusion:** To the best of our knowledge, this is the first study directly addressing the importance of *EGFR* mutation testing in lung cancer patients with SqCC or NSCC favor SqCC diagnosed from small biopsies. Our findings suggest that *EGFR* mutation testing should not be excluded in such populations, especially in never-smokers, or patients with NSCC favor SqCC subtypes.

P2.09-13 CORRELATION OF ROS1 (SP384) IMMUNOHISTOCHEMISTRY WITH ROS1 REARRANGEMENT DETERMINED BY FLUORESCENCE IN SITU HYBRIDIZATION

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Background: With the approval of crizotinib as treatment for ROS1 positive patients, identification of ROS1 status has become standard of care for non-small cell lung cancer (NSCLC). Immunohistochemistry (IHC) can be used to detect aberrant ROS1 expression; however, current commercially available IHC assays do not have optimized recommended protocols, or data correlating ROS1 protein expression to fluorescence *in situ* hybridization (FISH). Hence, the ROS1 (SP384) Rabbit Monoclonal Primary Antibody (ROS1 SP384) was developed, and here we present correlation data to *ROS1* FISH status across multiple scoring algorithms using our optimized IHC staining protocol. **Method:** 120 formalin-fixed, paraffin-embedded (FFPE) NSLC cases with known FISH status were procured. 4µm sections were cut and stained with H&E, Rabbit Monoclonal Negative Control Ig, and ROS1 SP384. The slides were evaluated for percent positivity of tumor cells in each intensity level (evaluated separately for staining within the nuclear, cytoplasmic, and membranous compartments). The intensity level of staining was evaluated on an integer scale of 0-3: 0 = no, 1 = weak, 2 = moderate and 3 = strong staining intensity. The data was analyzed several scoring algorithms to assess its correlation with FISH status. **Result:** ROS1 SP384 showed high correlation with FISH status, with multiple scoring algorithms (Table 1) examined. Of note, a positive percent agreement of 97.8% and negative percent agreement of 89.2% was achieved when comparing ROS1 SP384 IHC staining ≥2+ at a cutoff of > 30% staining in the cytoplasm of tumor cells with FISH status. Table 1. VENTANA ROS1 (SP384) Rabbit Monoclonal Primary Antibody IHC vs FISH analytical comparison data

	FISH Status			Agreement		
	Positive	Negative	Total	Measure [a]	% (n/N)	95% CI [b]
≥2+ staining in cytoplasm in any of tumor cells	45	18	63	PPA	97.8 (45/46)	(88.7, 99.6)†
≥2+ staining in cytoplasm not in any of tumor cells	1	56	57	NPA	75.7 (56/74)	(64.8, 84.0)†
Total	46	74	120	OPA	84.2 (101/120)	(76.6, 89.6)†
≥2+ staining in cytoplasm in > 25% of total tumor cells	45	11	56	PPA	97.8 (45/46)	(88.7, 99.6)†
≥2+ staining in cytoplasm in ≤ 25% of total tumor cells	1	63	64	NPA	85.1 (63/74)	(75.3, 91.5)†
Total	46	74	120	OPA	90.0 (108/120)	(83.3, 94.2)†
≥2+ staining in cytoplasm in > 30% of total tumor cells	45	8	53	PPA	97.8 (45/46)	(88.7, 99.6)†
≥2+ staining in cytoplasm in ≤ 30% of total tumor cells	1	66	67	NPA	89.2 (66/74)	(80.1, 94.4)†
Total	46	74	120	OPA	92.5 (111/120)	(86.4, 96.0)†
≥2+ staining in cytoplasm in > 50% of total tumor cells	42	5	47	PPA	91.3 (42/46)	(79.7, 96.6)†
≥2+ staining in cytoplasm in ≤ 50% of total tumor cells	4	69	73	NPA	93.2 (69/74)	(85.1, 97.1)†
Total	46	74	120	OPA	92.5 (111/120)	(86.4, 96.0)†

[a] PPA = positive percent agreement; NPA = negative percent agreement; OPA = overall percent agreement.
[b] Two-sided 95% confidence interval: †the Wilson Score method.

Conclusion: Herein, we present evidence thatROS1 (SP384) Rabbit Monoclonal Primary Antibody may provide an effective means of stratifying cases by aberrant ROS1 protein expression prior to confirmation with orthogonal methods.

Keywords: ros1, Immunohistochemistry, crizotinib

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-14 THE DETECTION OF EGFR GENE MUTATION FROM WASHING SOLUTION OF DEVICES USED FOR THE BRONCHOSCOPIC EXAMINATION

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Background: The detection of epidermal growth factor receptor (EGFR) gene mutation is necessary for selection of lung cancer treatment. Recently, biopsy specimens are used in many genomic and immunohistochemical examination methods to select the treatment policy, so it is important not to waste valuable cancer cell samples. For detection of EGFR gene mutation we examine the washing solution of devices used for the bronchoscopic examination in order to solve the issue. In this report, we investigate the detection ratio of EGFR mutation using this cytological sample. **Method:** A total of 336 washing solution samples from lung cancer patients were examined for EGFR gene mutation testing in the period between November 2010 and October 2017. 328 cases of 336 excepting 8, which were carried out as re-biopsy, were surveyed in this examination. After the regular biopsy or scraping method, all devices were washed with 10ml saline liquid. Half volume of washing solution was used for regular cell examination to detect cancer cells. Only if a sufficient amount of non-small cancer cells were observed from it, the other volume was submitted for EGFR mutation examination. Final diagnosis was decided by histological specimen. Presence or absence of EGFR mutation and their types were observed from 328 samples retrospectively. **Result:** Histological diagnosis of all 328 biopsy specimens are as follows; 200 Adenocarcinoma (AD), 100 Squamous cell carcinoma (SQ), 13 non-small cell lung carcinoma(NSCLC), 3 adenosquamous cell carcinoma(ADSQ), 7 high grade neuroendocrine carcinoma (HGNEC), and 5 others. The detection number of EGFR mutation from AD, SQ, ADSQ and NSCLC are 65, 4, 2, and 3 respectively. There is no EGFR mutation from remaining histology cases. In all of 74 EGFR mutation positive cases, Exon 19 deletion was detected in 33 cases (45%) and Exon 21 L858R was detected in 33 cases (45%). **Conclusion:** The detection rate of EGFR gene mutation from washing solution of devices is 33% (65/200) in AD and 4% (4/100) in SQ. These results are approximate to previous reports. Consequently, it is acceptable to use this method to investigate EGFR gene mutation of non-small lung cancer patients. Furthermore, it is an advantage that we can carry out an EGFR mutation test using this method with a cytology sample earlier than a method with a histology sample.

Keywords: EGFR gene mutation, cytological sample, bronchoscopic examination

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-15 A NEXT GENERATION SEQUENCING (NGS) RNA-SCAN MULTIPLEX PANEL (QIASEQ) TO IDENTIFY GENE-REARRANGED NON-SMALL CELL LUNG CANCER

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Background: Oncogenic fusion gene rearrangements are detected in up to 10% of advanced NSCLC with important therapeutic (eg. ALK, ROS1) or translational impact (eg. RET, NTRK1). The 'QIAseq' fusion panel is a 31-gene NGS multiplex assay that synchronously detects multiple oncogene fusion transcripts from formalin-fixed paraffin-embedded (FFPE) tissue derived RNA (Figure 1).

Targeted genes		
ALK, BAG4, CCDC6, CD74, CUX1, DCBLD1, EML4, EZR, FGFR1, FGFR3, GOPC, HIP1, KIF5B, KLC1, LRIG3, MPRIP, NRG1, NTRK1, RET, ROS1, RP1-179P9.3, RP11-45M22.3, RP11-73M18.2, SDC4, SLC34A2, STRN, TACC3, TFG, TPM3, TPR, TRIM33		
Total number of targeted genes	31	
Primers in targeted genes	131	
Primers outside of gene regions	2	to detect gDNA contamination
Primers in reference genes	4	COPA, MRPS14, CIAO1, UBE3C

Method: QIAseq analysis was undertaken in 33 samples (31 NSCLC samples, 2 commercial controls). 12/31 NSCLC samples were positive controls with a known fusion genotype identified by Quantide X NGS or FISH +/- RT-PCR. The remaining 19/31 fusion negative NSCLC controls included 6 samples with *EGFR/KRAS/NRAS* mutations. Analysis required a minimum 2x 5µM thick FFPE scrolls with >30% neoplastic cell content. Manual RNA extraction was undertaken in all samples except n=6 (ExScale automation extraction). NGS fusion breakpoints, crossing and spanning reads were calculated in QIAseq fusion-detected samples. An additional validation cohort of 40 NSCLC samples, including 20 with unknown fusion status will optimise QIAseq thresholds for fusion detection. **Result:** 48 QIAseq sequencing experiments was undertaken in 33 samples with ≥2 sequencing runs in 12 samples. QIAseq analysis detected a corresponding NGS fusion breakpoint in 14/14 (100%) positive controls including EML4-ALK (n=8), CLTC-ALK (n=1), CD74-ROS1 (n=3), CCDC6-RET (n=1) and 5-fusion control (n=1). QIAseq analysis was negative in 17/19 (89.4%) negative controls samples including all *KRAS* (n=4), *NRAS* (n=1) and *EGFR* (n=1) mutation samples. QIAseq detected novel fusion gene CD74 Exon 6-CAMK2A Exon 2 in n=1 sample subsequently confirmed on Sanger sequencing. Two separate runs detected TPM3 Exon 8-S100A7A Exon 2 fusion in n=1 sample not identified with Sanger sequencing. Both fusions have uncertain clinical significance. Validation cohort results will be presented. **Conclusion:** QIAseq detects NSCLC oncogenic fusions with high sensitivity and specificity. Future applications include optimising use of small biopsy specimens for synchronous gene rearrangement screening and identification of novel gene fusion targets.

Keywords: next generation sequencing, fusion, diagnosis

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-16 HETEROGENEITY ANALYSES OF MSLCS——ESPECIALLY IN THE EGFR MUTATION-POSITIVE ONES

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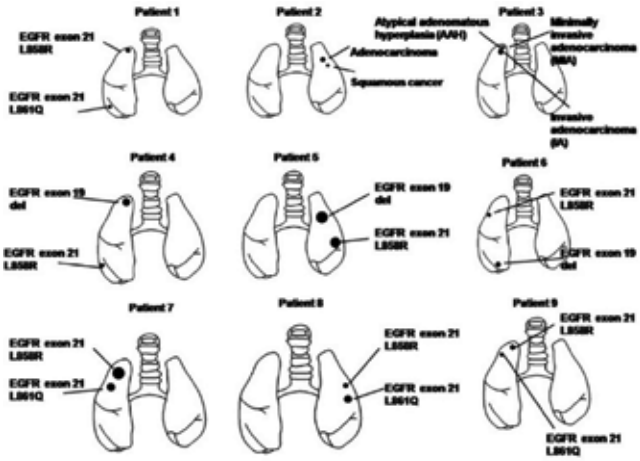
Background: Multiple synchronous lung cancers (MSLCs) are diagnosed as multiple tumor nodules in the same or different lung lobes. MSLCs present a clinical dilemma whether they are primary tumors or metastases. Recent studies showed that MSLCs shared an identical germline genetic background and environmental exposure in the same individual patient, however, different tumor nodules showed highly different heterogeneity, even in all the EGFR mutation-positive focuses. Therefore, we performed this study to further analyze MSLCs as to estimate the pathology and molecule heterogeneity among these nodules. **Method:** Tumor samples were obtained from nine patients diagnosed with MSLCs. Immunohistochemistry were performed by professional pathologists. Whole-exome sequencing (WES) was conducted by IlluminaNovaseq with sequencing depth of 200X. NeoTyping was used to describe the dispersion of sequencing data among MSLCs of the same patient. **Result:** We found different tumor nodules showed obviously pathological and molecular heterogeneities in the same individual (**Figure 1**). More different dispersion was observed among the nodules with more different pathologies in the same patient. The dispersion of 20%, 50% and 100% were observed in MSLCs with the same driver genes (such as EGFR exon21 L858R and L861Q) of lung adenocarcinoma, different evolutional stages (AAH, MIA and IA) and completely different pathologies (adenocarcinoma and squamous cancer), respectively. All the sequencing data showed MSLCs had different gene information, even in all the EGFR mutation-positive nodules, maybe similar, but not the same, which supported that each nodule in one patient was independent with others.



Conclusion: MSLCs could be independent with each other due to their pathological and molecular heterogeneities, even for EGFR mutation-positive nodules which hold the same driver gene, but different mutation site in just one patient. WES should be an effective way to recognize this heterogeneous characteristic, which would be helpful for the whole precise management of one MSLC patient.

Keywords: NSCLC, EGFR, Heterogeneity

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-17 A CALL TO ACTION: RAPID COLLECTION OF POST-MORTEM LUNG CANCER TISSUE IN THE COMMUNITY TO ENABLE LUNG CANCER RESEARCH

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Background: Posthumous rapid tissue donation (RTD) provides an opportunity to understand treatment-resistant lung cancers with preservation of valuable tumor and non-tumor specimens from primary and metastatic sites. **Method:** Consent to participate in the lung RTD program was obtained during patient care. When death occurred, tumor and paired non-tumor, cytology, and blood specimens were preserved as formalin-fixed and frozen specimens. Tissue sections were evaluated with hematoxylin and eosin (H&E) staining and programmed death ligand-1 (PD-L1) immunohistochemistry. Massively parallel sequencing was performed on 11 specimens. **Result:** To date, 21 patients consented to participate in the RTD program. Post-mortem specimens (N=180) were preserved from 9 patients and the other patients remain alive. Evaluation of H&E slides confirmed well-preserved tissue. PD-L1 immunohistochemistry revealed heterogeneous expression between tumor sites. Next generation sequencing provided high quality data on all 11 tested samples. **Conclusion:** Rapid donation of post-mortem tissue from lung cancer patients is feasible and provides high quality specimens for research. Post-mortem tissue collection of primary and metastatic tumors facilitates studies of tumor mutation evolution, mechanisms of drug resistance, and biomarker expression.

Keywords: rapid autopsy, post-mortem, tissue donation

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-18 A CLINICOPATHOLOGIC ANALYSIS OF PULMONARY SCLEROSING PNEUMOCYTOMA IN KOREA : A MUTICENTER STUDY

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Background: Sclerosing pneumocytoma is a rare benign pulmonary neoplasm, which in Asia, most commonly occurs in middle-aged women. Because of the rarity of this disease, no data is available on its nationwide incidence or clinical characteristics. This nationwide survey was conducted by the Korean Cardiopulmonary Pathology Study Group to document the incidence and clinical characteristics of sclerosing pneumocytoma in a Korean population. **Method:** A total of 220 cases of sclerosing pneumocytoma diagnosed at 15 tertiary medical centers in Korea during the period 1994 to 2012 were collected and retrospectively studied. Clinical parameters evaluated were sex, age at diagnosis, tumor size, tumor location, surgical procedure type, status of lymph node metastasis, and distant metastasis. **Result:** The female to male ratio was 7.15:1, and the tumor occurrence rate in middle or lower lobes was significantly higher than that in upper lobes ($P < 0.001$). The peak incidence rate appeared to occur in the sixth decade of life. Tumor was located in right lung in 121 cases and in left lung in 96 cases (43.6%). The mean tumor size in female patients (2.63 cm) was significantly larger than in male patients (2.19 cm) ($P = 0.037$). In 2 cases (0.9%) metastatic tumors were found in regional lymph nodes, and one case (0.5%) showed metastatic lymph nodes and distant metastasis in a lumbar vertebra. **Conclusion:** Age distributions, mean tumor sizes, and tumor locations were similar to those previously reported for sclerosing pneumocytoma, and the female-to-male ratio in our Korean cohort was similar to those previously reported in Asia, but higher than those reported in the West.

Keywords: sclerosing pneumocytoma, Korea, Lung neoplasms

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-19 UTILISING HETEROGENEITY: USING A DIGITAL DATABASE OF LUNG CANCERS AND IMMUNE PROFILE TO COMPLEMENT SUBJECTIVE ASSESSMENT

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Background: Traditional pathological assessment of tissue sections involves subjective analysis of complex and heterogeneous features, typified by the challenge of 'measuring' PD-L1 expression in non-small cell lung cancer (NSCLC) as a guide to its treatment with immune checkpoint inhibitors. Such heterogeneity is generally perceived as a problem but might, in fact, reflect not only biologically important epitope variation, but also important features of the tumour microenvironment and, by extension, be a tool for predicting behaviour. In-depth analysis of a single slide of a tumour by digital pathology, image analysis and machine learning makes more accurate and meaningful analysis a possibility. **Method:** Expression of PD-L1 was assessed by immunochemistry in 250 sections from 137 resected NSCLCs using the Ventana SP263 antibody and a validated protocol and its distribution compared with morphology as revealed by corresponding H&E-stained sections. Slides were scanned to create a digital image using Aperio Scanscope with division of images into 1mm^2 squares using QuPath opensource software, each of which was assigned x and y co-ordinates. Squares were assessed subjectively by two pathologists for morphological features and PD-L1 expression and also subject to automatic image analysis including cell counting and membrane detection. Co-ordinates and values were stored in Microsoft Excel and a digital database was generated for every slide. In-depth analysis of digital data points was achieved using "R" software custom algorithms that included simulating biopsy sampling and applying spatial analysis packages. **Result:** The resulting database, comprising approximately 30,000 data points from the 137 tumours, is being used to simulate needle-core biopsies, assess heterogeneity of PD-L1 expression and relate this to the tumour micro-environment including immune cell populations, immune signature and tumour mutational burden. **Conclusion:** The vast amount of information in every NSCLC cannot be extracted by conventional histopathological analysis. By utilising new technologies and considering alternative paradigms for data acquisition, powerful new approaches may be developed that give information pertaining to not just diagnostic and prognostic features of a tumour, but behavioural traits including likely responses and resistances to novel drugs such as immune checkpoint inhibitors. The methodology described here is an attempt to extract these data in a more objective way and complement the still crucial subjective analysis that is traditionally the prerogative of the histopathologist.

Keywords: Digital Pathology, PD-L1, image analysis

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-20 MINOR COMPONENTS OF SOLID PATTERN IS A SIGNIFICANT POOR PROGNOSTIC FACTOR IN PATHOLOGICAL STAGE I LUNG ADENOCARCINOMA

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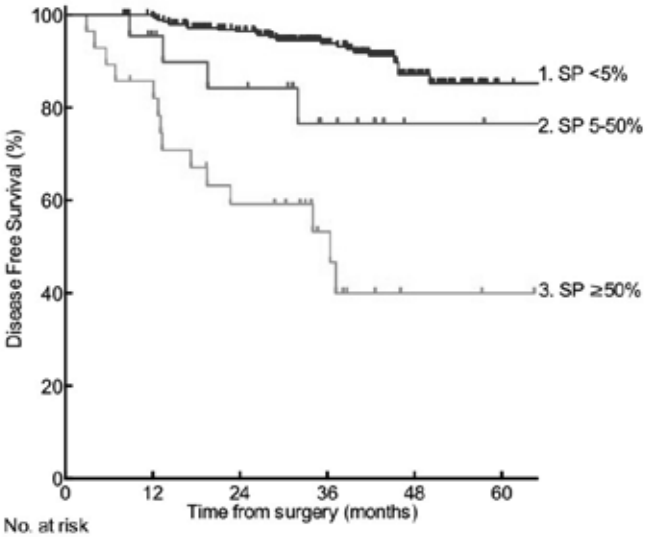
Background: Lung adenocarcinoma with solid pattern (SP) predominant subtype was reported to be associated with poor prognosis. However, whether minor components of SP predict poor prognosis remains unknown. The present study aimed to clarify the influence of different proportion of SP on the prognosis of pathological stage I lung adenocarcinoma. **Method:** Tumors of 341 patients who underwent radical resections were classified according to the IASLC/ATS/ERS classification. Patient contained less than 5% SP in the tumor was determined SP negative and SP positive patients were reclassified to SP minor (5-50%) and SP major (≥50%) groups. Survival analyses were used to determine the association between each group with patient survival. **Result:** 50 (15%) patients were SP positive and compared to SP negative group they showed a significantly lower five-year disease-free survival (DFS) rate (85.2 vs. 55.4%, p<0.001) and overall survival (OS) rate (97.3 vs. 66.7%, p<0.001). Multivariate analysis for DFS showed that SP positive, lepidic pattern negative, KRAS mutation and pathological stage IB were independent poor prognostic factors. In addition, higher proportions (<5%, 5–50% and ≥50%) of SP components were associated with a poorer prognosis (85.2, 76.6, and 40.0% of 5y-DFS, respectively; p<0.001).



No. at risk

1.	292	286	252	152	54	15
2.	22	19	14	11	4	2
3.	28	22	15	12	6	2

Conclusion: Solid pattern is a significant poor prognostic factor and an indicator of early recurrence after radical resection for early stage lung adenocarcinoma. Patients with tumors harboring a higher ratio of SP components have worse survival.

Keywords: lung adenocarcinoma, Prognosis, Solid pattern

P2.09-21 WOMEN WITH SYNCHRONOUS OR METACHRONOUS LUNG AND OVARIAN CANCERS: A MULTI-INSTITUTIONAL REPORT

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Background: In women, lung cancer (LC) and ovarian cancer (OC) are, respectively, the second and eighth malignancies for incidence in developed Countries. Despite increasing incidence and mortality of LC, association with OC is rare and no literature data are available on this topic yet. Our aim was to describe a series of patients with synchronous or metachronous LC and OC and to identify common clinical and pathological patterns. **Method:** We retrieved the medical charts of patients who referred to 30 European Oncological Institutes from 2008 to 2018. When patients with synchronous (up to 3 months of time interval in onset) or metachronous LC and OC were found, we collected detailed medical history, pathological features and clinical outcomes. Whenever available, formalin fixed paraffin embedded tumor tissue from both specimens was collected for centralized pathology revision with an immunohistochemical marker panel including TTF-1 and PAX-8. In ambiguous cases, a broader panel was performed (p40, CK-7, WT1, CA125, Calretinin, EMA, CEA, CgA, Vimentin, Napsin-A). Whenever tested, genetic alterations in LC and OC were also reported. **Result:** As of April 2018, among 30 European Oncological Centers (Italy, France, Slovenia), 11 retrieved in their series patients with a history of LC and OC, for a total of 18 cases in the last 10 years. Paired histological specimens were available in 6 cases. One patient was excluded, since pathology revision revealed that lung lesions were metastases from serous OC. Thus, analyses were performed on 17 patients. In 10/17 cases (58.8%), LC and OC were metachronous and, in 6/10 cases, OC preceded LC diagnosis, with a median interval of 4.5 years. Median age at diagnosis of the first malignancy was 62 years, the majority of patients (64.7%) were never-smoker, 6 had cancer familial history. Interestingly, 4 patients (23.5%) reported also a third or fourth malignancy. After a median follow-up of 6.5 years, 10 patients are alive. Regarding histology, most of LC were adenocarcinoma (14/17, 82.3%). Molecular status was available in 9/14 cases: 4 had EGFR mutation, 1 B-RAF mutation and 2 ALK translocation. OC were mostly high-grade serous (83,3%). BRCA status was available in 6 patients: 2 mutated, 2 wild-type and 2 affected by variants of unknown significance (USV). Moreover, one synchronous case presented both BRCA-USV and B-RAF mutation. **Conclusion:** In our series, synchronous and metachronous LC and OC were often driven by genetic alterations. Further genetic analysis with next generation sequencing technology has already been planned.

Keywords: lung ovarian cancer women

P2.09-22 RELEVANCE OF RESULTS OF INTRAOPERATIVE PLEURAL LAVAGE CYTOLOGY AND HISTOLOGICAL SUBTYPE IN LUNG ADENOCARCINOMA

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Background: Pleural lavage cytology (PLC) can be simply and easily performed on patients undergoing surgery for primary lung cancers. Although clinical factors related to tumor progression, such as lymph node metastasis and pleural invasion, are reportedly risk factors for positive PLC, the association between PLC and histological subtype remains unknown. The present study aimed to evaluate the impact of a micropapillary pattern (MPP) in lung adenocarcinomas on results of PLC and assess the complementary role of these two factors as prognostic predictors and their significance in a clinical setting. **Method:** We retrospectively reviewed 600 consecutive patients with surgically resected pulmonary adenocarcinomas and investigated the relationship between PLC status and clinicopathological factors including a histologically identified MPP component. In cases of MPP observed ≥5% in a largest cut surface was defined as MPP-positive group. **Result:** Twenty-five patients (4.2%) had positive PLC results. Positive PLC was significantly associated with MPP (p=0.0001), lymph node metastasis (p=0.01), and pleural invasion (p<0.0001) according to multivariate analysis. Patients with other established predictive factors for positive PLC, such as large tumor size, lymph node metastasis, pleural invasion, and lymphovascular invasion, have an increased risk of positive PLC when their tumor include histological MPP. With regard to lymph node metastasis, two factors, MPP and positive PLC, were associated with a higher incidence of occult N2 lymph node metastases. Among 25 patients with positive PLC, 18 (72%) were upstaged in postoperative pathologic examination whereas 139 of 575 (24%) patients with negative PLC were upstaged postoperatively. The prognosis of adenocarcinomas with MPP or positive PLC was significantly worse than that of patients without these features. Moreover, the survival rate of MPP and positive PLC group (MPP+ PLC+) was significantly worse than that of MPP and negative PLC group (MPP+ PLC−, p=0.03). Postoperative recurrences were found in 52% (13/25) of patients with positive PLC and 18% (103/575) of patients with negative (p<0.001). **Conclusion:** The presence of MPP in lung adenocarcinoma can be an independent predictor of positive PLC. These two factors have complementary and synergistic roles as prognostic factors. Detailed pre- or intra-operative examination of histological subtype and intraoperative PLC findings may provide important information for prediction of tumor progression and decisions regarding surgical procedure.

Keywords: Adenocarcinoma, pleural lavage cytology, micropapillary pattern

P2.09-23 A COMBINATION OF PODOPLANIN AND E-CADHERIN EXPRESSION IN LUNG SQCC MAY BE A POOR PROGNOSTIC INDICATOR: A PROPENSITY SCORE-MATCHED ANALYSIS.

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Background: The combination of clinicopathological prognostic factors for lung squamous cell carcinoma (SqCC) has not been still advocated. The aim of this study is to analyze the combination of prognostic markers of SqCC. **Method:** Retrospective chart review was performed to identify patients undergoing resection for SqCC between 2003 and 2015 (Ethical approval #: E2235). We examined the expressions of E-cadherin, vimentin, and podoplanin in cancer cells on tissue microarray to evaluate their prognostic value. Survival outcomes were analyzed with Kaplan-Meier method and log-rank test. To eliminate selection bias, propensity score-matched analysis on the basis of clinicopathological factors was performed. **Result:** Two hundred and two patients underwent complete resection with curative intent were identified (Median follow-up: 50.0 months, range: 0.67-150, 5y-OS: 67.5%, 5y-DFS: 53.4%). There was no significant difference in the prognosis of patients with low E-cadherin expression alone (OS: p=0.242 and DFS: p=0.401) and podoplanin-positive alone (OS: p=0.389 and DFS: p=0.874). However, OS and DFS in the combination of podoplanin-positive and low E-cadherin expression group was significantly lower than those in another group (OS; 75.0% vs 57.0%, respectively, p=0.034, DFS; 65.2% vs 44.2%, respectively, p=0.031.). **Conclusion:** A combination of podoplanin-positive and low E-cadherin expression in lung SqCC may be a poor prognostic indicator.

Keywords: Lung Squamous cell carcinoma, E-cadherin, podoplanin

P2.09-24 MERS67 IS A NOVEL ANTI-NAPI2B ANTIBODY AND DEMONSTRATES DIFFERENTIAL EXPRESSION PATTERNS IN LUNG CANCER HISTOLOGIC SUBTYPES

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Background: NaPi2b is a sodium-dependent phosphate transporter expressed in lung, ovarian, and thyroid cancers. Prior studies have suggested an enrichment of expression in lung adenocarcinoma (ACA).

XMT-1536 is a NaPi2b targeting ADC (Antibody Drug Conjugate) comprised of a humanized antibody (XMT-1535) conjugated with 10-15 auristatin F-HPA (AF-HPA) payload molecules via the Dolaflexin platform. AF-HPA is capable of controlled bystander-effect killing, resulting in efficacy in models with heterogeneous antigen expression, and is metabolized intra-tumorally to an active non-permeable metabolite to enable greater systemic tolerability. Previously, we demonstrated pre-clinical activity of XMT-1536 in human primary xenograft models of non-small cell lung cancer (NSCLC). MERS67 is a human-rabbit chimeric antibody derived from XMT-1535. MERS67 has been formatted for use as an immunohistochemical reagent by multiple methods and expression has been shown to correlate with response in an unselected series of primary ovarian cancer xenografts. (AACR-EORTC, 2017) We evaluated MERS67 to see if it would preferentially stain lung adenocarcinoma (ACA), as has been demonstrated using other NaPi2b antibodies. **Method:** An immunohistochemical assay for MERS67 was established on a Leica BondRx Instrument. The assay was performed on tissue microarrays (TMA), including NSCLC and small cell lung cancer (SCLC) cell line arrays, and a NSCLC human tumor array. Tumors in the NSCLC array had previously been classified based on morphologic features only. All arrays were scored based on the H-score method. To characterize the primary tumors further, the tumor TMA was stained with TTF-1 and p40, markers of ACA and squamous cell carcinoma (SqCC), respectively. Results of this staining were compared to MERS67 staining patterns. **Result:** H-Scores in the NSCLC cell line TMA ranged from 0-260, and from 0-100 in the SCLC TMA. Within the tissue microarray, 99 individual cases were evaluable. By morphologic classification 63 cases were SqCC, and 23 cases were ACA. Using an arbitrary cut point of H=50, there was a statistically significant difference in the number of NaPi2b positive ACA cases (19/23) vs SqCC (3/63). Among 43 cases where p40 and TTF-1 were evaluable and were in agreement with morphologic diagnosis, 7/7 cases of ACA were positive for NaPi2b, while 0/36 SqCC were positive. **Conclusion:** MERS67 is an anti-NaPi2b antibody that frequently demonstrates immunoreactivity in lung ACA. MERS67 is a chimeric antibody related to XMT-1536, a proprietary anti-NaPi2b ADC. Target expression using MERS67 is being evaluated in an ongoing XMT-1536 Phase 1 clinical trial enrolling non-squamous NSCLC patients.

Keywords: XMT-1536, NaPi2b, Adenocarcinoma

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-25 ABUNDANT TUMOR PROMOTING STROMAL CELLS IN LUNG ADENOCARCINOMA WITH HYPOXIC REGIONS

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Background: Carbonic anhydrase IX (CAIX) is a marker of hypoxia and its expression by cancer associated fibroblasts (CAFs) was reportedly associated with the poor prognosis of lung adenocarcinoma. This study aimed to characterize the hypoxic microenvironment containing CAIX (+) CAFs. **Method:** First, we evaluated the clinicopathological significance of CAIX expression by CAFs in 3 cm and above lung adenocarcinoma (n = 188). We then compared the expressions of E-cadherin, ezrin, ALDH1, CD44, EGFR, HSF-1, Glut-1, and PD-L1 in cancer cells, as well as those of CD204 and podoplanin in stromal cells between CAIX (+) CAFs and CAIX (−) CAFs cases (n = 25, each). **Result:** In total, 48 patients had CAIX (+) CAFs (26%). Multivariate analysis revealed that CAIX expression by CAFs could serve as an independent unfavorable prognostic factor for recurrence-free survival ($p < 0.05$). The staining score of hypoxia marker Glut-1 in cancer cells was significantly higher in cases with CAIX (+) CAFs than in those with CAIX (−) CAFs (median: 20 vs. 0, $p < 0.01$). In addition, the numbers of CD204 (+) tumor associated macrophages (TAMs) and podoplanin (+) CAFs were significantly higher in the CAIX (+) CAFs group than in the CAIX (−) CAFs group (TAMs: 31.5 vs. 17.0: $p < 0.01$, CAFs: 20 vs. 0: $p < 0.05$). The staining score of the other markers did not differ between the groups. **Conclusion:** Our results indicate that the presence of abundant tumor promoting stromal cells, CD204 (+) TAMs, and podoplanin (+) CAFs is characteristic of the tumor microenvironment containing CAIX (+) CAFs, which contributes to an increase in aggressive behavior in lung adenocarcinoma with hypoxic regions.

Keywords: tumor microenvironment, CAF, Hypoxia

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-26 CLINICAL SIGNIFICANCE OF SUBCELLULAR LOCALIZATION OF MASPIN IN PATIENTS WITH PATHOLOGICAL STAGE IA LUNG ADENOCARCINOMA

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Background: There were a lot of tumor-associated proteins before. Maspin is a tumor-suppressor protein and its prognostic value in lung adenocarcinoma has been reported. However, little is known about the clinical impact of subcellular localization of maspin in early-stage lung adenocarcinoma. We aimed to evaluate the clinical significance of subcellular localization of maspin in patients with pathological stage (p-stage) IA lung adenocarcinoma patients categorized by the new eighth edition TNM classification. **Method:** We immunohistochemically analyzed 181 tissue samples from p-stage IA1 (n=37), IA2 (n=92) and IA3 (n=52) lung adenocarcinomas using antibody for maspin. **Result:** The 181 cases fell into five predominant subtypes: lepidic (n=32), acinar (n=97), papillary (n=30), solid (n=20) and micropapillary (n=2). The frequencies of maspin staining were: cytoplasmic-only in 24.9%; pancellular (nuclear and cytoplasmic) in 8.8%; nuclear-only in 0.6%; no staining in 65.7%. Cytoplasmic-only staining significantly correlated with high pathological T-classification ($p=0.039$), lymphatic invasion ($p=0.002$) and poorer tumor differentiation ($p=0.002$). The patients were followed up for 12-151 months (median=74 months), and the cytoplasmic-only staining significantly correlated with shorter disease-free survival (DFS) ($p=0.034$) and disease-specific survival (DSS) ($p=0.036$) by log-rank tests. In Cox's multivariate analysis, lymphatic invasion had the most significant effect on shorter DFS and DSS. **Conclusion:** The expression of maspin in the cytoplasm alone could be useful for predicting unfavorable prognoses in patients with p-stage IA lung adenocarcinoma.

Keywords: Adenocarcinoma, Immunohistochemistry, Maspin

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-27 PROGNOSTIC SIGNIFICANCE OF VASCULAR INVASION IN PATHOLOGICAL STAGE IA LUNG ADENOCARCINOMA ACCORDING TO THE 8TH EDITION OF THE TNM CLASSIFICATION

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Background: Vascular invasion, including blood vessel invasion (v) and lymphatic vessel invasion (ly), is not a prognostic factor according to the 8th Edition of the Tumor-node-metastasis (TNM) Classification, and the prognostic impact of vascular invasion remains unclear. We reported the prognostic significance of vascular invasion classified according to the previous 7th Edition in patients with stage I non-small cell lung cancer (Diagn Pathol. 2015;10:17). The aim of the present study was to clarify whether vascular invasion classified in the 8th Edition has a prognostic impact on patients with pathological stage IA lung adenocarcinoma and should thus be adopted as an upstaging factor. **Method:** We reviewed 314 patients with pathological IA (T1a-1bN0 according to the UICC-TNM Classification of Malignant Tumours, 7th Edition) lung adenocarcinoma completely resected between 2000 and 2005. We excluded patients with mucinous adenocarcinoma. The pathological invasive size was measured on the maximal cut surface of the primary tumor, stained with hematoxylin-eosin (HE) and elastica van Gieson (EVG), in all cases. We evaluated blood vessel invasion using specimens stained with HE and EVG, and lymphatic vessel invasion using specimens stained with HE and anti-podoplanin antibody. Blood vessel invasion and lymphatic vessel invasion together represented tumor vessel invasion (TVI). Survival curves were plotted using the Kaplan–Meier method, and the statistical significance of differences between the groups was determined by the log-rank test. **Result:** The patients were stratified according to the 8th edition into Tis (N = 46), T1mi (N = 69), T1a (N = 82), T1b (N = 99), T1c (N = 18). The median follow-up period was 98.0 months. The recurrence-free survival rate at 5 years was 100%, 100%, 88.9%, 94.7%, 80.3%, 66.7%, and 66.7% in stage 0, IA1(TVI-), IA1(TVI+), IA2(TVI-), IA2(TVI+), IA3(TVI-), and IA3(TVI+), respectively. The lung cancer-specific survival rate at 5 years was 100%, 100%, 88.9%, 98.2%, 87.4%, 66.7%, and 66.7% in stage 0, IA1(TVI-), IA1(TVI+), IA2(TVI-), IA2(TVI+), IA3(TVI-) and

IA3(TVI+), respectively. The presence of TVI was a poor prognostic factor in stage IA1 and IA2, but not in stage IA3. **Conclusion:** TVI is a prognostic factor in patients with lung adenocarcinoma measuring 20 mm or less in the pathological invasive size. Stage IA1 lung adenocarcinoma without TVI can possibly be classified as minimally invasive, because patients with stage IA1 lung adenocarcinoma have 100% recurrence-free survival and lung cancer-specific survival.

Keywords: blood vessel invasion, lung adenocarcinoma, Lymphatic vessel invasion

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-28 DETECTION OF ISOLATED TUMOR CELLS IN REGIONAL LYMPH NODES FROM PN0LUNG CANCER BY NEGATIVE SELECTION USING IMMUNOMAGNETIC BEADS

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Background: Isolated tumor cells (ITC) referred to single tumor cells or small clusters of cells detected by routine hematoxylin and eosin stains or immunohistochemiry. Early detection of ITC in regional lymph nodes could identify a subset of N0 patients with potential risk of disease relapse. This study aimed to establish a new method to detect ITC based on a combination of immunomagnetic bead enrichment, immunofluorescence (IF) and immunofluorescence in situ hybridization (iFISH). **Method:** Lymph nodes were obtained from lung cancer patients intraoperatively. After immunomagnetic negative enrichment, tumor cells were identified using IF and iFISH, respectively. P53+/DAPI+/CD45- cells or CEP8+/DAPI+/CD45- cells were judged as positive cells. By comparing pathologically proved metastatic lymph nodes with those from non-invasive adenocarcinoma as control, the best cut-off values of the positive cells number was determinated using the receiver operating characteristic (ROC) curve to predict ITC. Single cell sequencing technology was employed to detect p53+/DAPI+/CD45- cells for TP53 mutation. Pathologically negative lymph nodes were detected for ITC using this newly established method. **Result:** Eleven metastatic lymph nodes from ten patients with NSCLC and eighteen lymph nodes from nine patients with non-invasive adenocarcinoma were collected for ROC curve analysis. p53+/DAPI+/CD45- cells were detected in 90.9% metastatic lymph nodes and 44.4% in the control group(P<0.001). The optimal cut-off value for the diagnosis of ITC by IF was 3 positive cells according to ROC curve analysis. The sensitivity and specificity were 81.82% and 94.44%, respectively. Four p53+/DAPI+/CD45- cells were tested using single-cell sequencing technique. All these cells were present with TP53 gene mutations. CEP8+/DAPI+/CD45- cells were detected in 60% metastatic lymph nodes and 6.25% lymph nodes in the control group(P=0.002). The optimal cut-off value for the diagnosis of ITC by iFISH was 1 positive cell. The sensitivity and specificity were 60% and 93.75%, respectively. Combining the two detection techniques, the sensitivity and specificity increased to 90% and 93.75%, respectively. Sixty lymph node samples from thirty patients with invasive NSCLC and pN0 disease were enriched by immunomagnetic beads, detected for ITC by IF, and iFISH. ITC were detected in 18.3%(11/60)of the pN0 lymph node samples. The pN0 status was reclassified as N0(mol+) in 33%(10/30) patients based on the recommendation of the American Joint Committee for Cancer. **Conclusion:** We established a new method to identify ITC in the regional lymph nodes by a combination of negative enrichment by immunomagnetic bead, IF and iFISH techniques, which could improve the detection of ITC compared with routine pathological examination.

Keywords: Lung cancer, Immunomagnetic bead negative method, Lymph node micrometastases

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-29 AUTOMATIC LUNG CANCER STAGING FROM MEDICAL REPORTS USING NATURAL LANGUAGE PROCESSING

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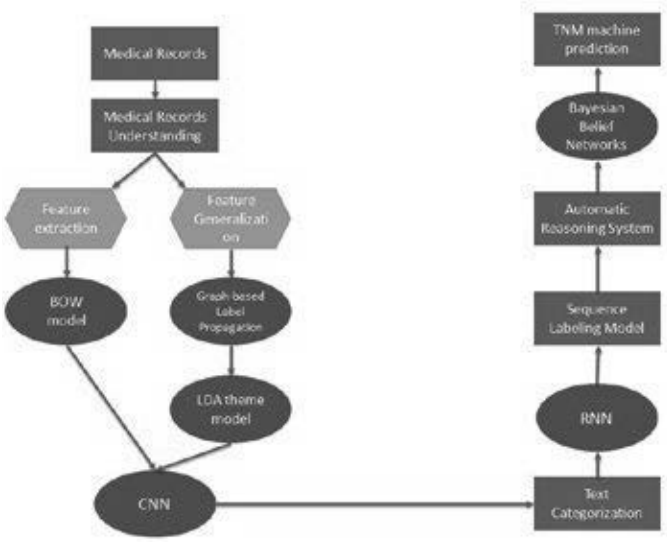
Background: Accurate TNM staging plays an important role in the diagnosis, treatment, and prognosis of lung cancer. In current clinical practice,the staging of lung cancer is usually decided by physicians. We aim to develop an automated lung cancer staging system using machine learning and verify the staging correctness. **Method:** In this work, we constructed a feature generalizing and automatically extracting model using NLP techniques. The parameters required for Tumor (T), Lymph nodes (N) and Metastases (M) categories of the eighth edition of the International Lung Cancer Research Association (IASLC) TNM staging system were automatically extracted from de-identified electronic medical records of pathology, operation note, CT scan, PET/CT scan, cranial MRI, bone scan, and ultrasound. A technical solution using Bayesian reasoning network was developed for automated staging. The stage was automatically predicted while the reasoning basis was given. All the reports were reviewed by thoracic surgeons to obtain the gold standard for evaluation.



Result: Five hundred de-identified reports were collected as training dataset to construct the model by learning from stage given by physicians. Five hundred and thirteen de-identified reports were collected as validation dataset. The current overall recall rate was 96.88%, and the agreement rate between machine prediction and physicians's diagnosis was 93.70%. **Conclusion:** Natural language processing is a useful technique for encoding medical reports in order to detect the TNM descriptors. Automatic lung cancer staging process using Bayesian reasoning network achieve acceptable accuracy. This system is extendable and can be applied to large database processing.

Keywords: lung cancer, TNM stage, natural language processing

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-30 CLINICOPATHOLOGICAL INVESTIGATION OF FOUR RESECTED CASES FOR PLEOMORPHIC CARCINOMA OF THE LUNG

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Background: Pleomorphic carcinoma (PC) of the lung has a poor prognosis and no established standard treatment. Particularly, cases of recurrence after surgery often result in death within one year of recurrence. At our hospital, we experienced four cases of PC, and all these patients remain alive, including those with recurrence. We report these cases of PC together with our histopathological findings. **Method:** We examined four patients with PC who underwent thoracoscopic lobectomy and mediastinal lymph node dissection between October 2014 and March 2017. The histopathological findings were expression of programmed death ligand 1 (PD-L1) and CD8-positive tumor-infiltrating lymphocytes ($CD8^+$TILs), which were examined for their relationship with prognosis. The expression of $CD8^+$TILs was evaluated using the ratio of $CD8^+/CD45^+$ (leukocyte common antigen) TILs. **Result:** While all patients survived, two of four patients experienced recurrence. Case 1 experienced recurrence 5 months after surgery and remains currently alive 35 months after recurrence using radiation therapy alone. Case 2 developed pleural dissemination and recurrence 10 months after surgery and remains alive 29 months after recurrence with a good partial response to chemotherapy and immune checkpoint inhibitors (nivolumab). Case 3 and 4 are both alive without recurrence 28 months and 12 months after surgery, respectively. All cases have high PD-L1 expression (tumor

proportion score >50%) and the CD8⁺/CD45⁺TILs ratio demonstrated a trend toward a higher expression in intratumor than invasive margin. Case 2 showed a good response to immune checkpoint inhibitors, despite the expression of CD8⁺TILs was the lowest of four patients. Case 4 had high expression of CD8⁺TILs, which might be associated with good prognosis in spite of locally advanced cancer.

Table. Pathologic characteristics in each patients

Case	1	2	3	4
Age/Sex	82/M	69/M	77/M	73/F
Initial recurrence	mediastinal lymph node	pleural dissemination, chestwall	-	-
pTNM/pStage(8th edition)	T3N2M1a/IVA	T2aN1M0/IIB	T2aN0M0/IA3	T2aN2M0/IIIA
Histology of carcinomatous portion	PC with SqCC	PC with ADC	PC with ADC	PC with ADC
PD-L1 (22C3)	90	90	70	80
CD8⁺/CD45⁺TILs (%)				
invasive margin	8	4	18	29
intratumor	78	7	13	44

PC: pleomorphic carcinoma, SqCC: squamous cell carcinoma, ADC: adenocarcinoma, PD-L1: Programmed death ligand 1, TILs: tumor-infiltrating lymphocytes,

Conclusion: The expression of CD8⁺TILs may be associated with prognosis of PC. We plan to continue investigating how PD-L1 expression and the CD8⁺TILs ratio are related to recurrence and therapeutic response.

Keywords: Pleomorphic carcinoma, programmed death ligand 1, CD8-positive tumor-infiltrating lymphocytes

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-31 CISPLATINUM SUPPRESSED METASTASIS OF NSCLC BY INHIBITING MACROPHAGE M2-LIKE POLARIZATION

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Background: Although M2-like tumor-associated macrophages (TAMs) have been considered as a vital therapeutic target in cancer therapy due to their role in promoting tumor progression and metastasis by inducing expression of CCR2 and CX3CR1 through IL-10 secretion, few compounds have been identified to inhibit M2-like polarization of TAMs. **Method:** *In vitro* analysis of cisplatinum in preventing macrophage M2-like polarization was conducted. Expression of cell surface marker CD206 and *CDH1*, *CCR2, CCL2* and *CX3CR1* genes were detected.The migration of non-small lung cancer cells promoted by the conditioned medium from M2-like macrophages was conducted by Transwell migration assay. The percentage of M2-like macrophages in tumor and normal lung tissues were analysised after the administration of cisplatinum for one week. **Result:** Here, we showed that cisplatinum significantly prevented macrophage M2-like polarization induced by IL-10 *in vitro*, as illustrated by reduced expression of cell surface marker CD206 and *CDH1*, *CCR2, CCL2* and *CX3CR1* genes. Furthermore, the migration of non-small lung cancer cells promoted by the conditioned medium from M2-like macrophages could be restrained by cisplatinum. Furthermore, cisplatinum reduced the number of metastasis of lung cancer without affecting tumor growth. Both in tumor and normal lung tissues, the percentage of M2-like macrophages decreased after the administration of cisplatinum for one week. **Conclusion:** Taken together, these data suggest that cisplatinum is able to inhibit macrophage M2-like polarization, which plays a vital role in cisplatinum suppressed metastasis of NSCLC.

Keywords: M2-like polarization, NSCLC, TAM

P2.09 PATHOLOGY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.09-32 DETACHED EPITHELIAL CELL CLUSTER SIZE IN LUNG ADENOCARCINOMA IS A MARKER OF POOR PROGNOSIS

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Background: Various types of detached epithelial cell clusters (DECs) are occasionally seen within lung adenocarcinoma (L-ADC): small clusters containing a small number of tumor cells (type 1); medium-sized clusters comprising 5-20 tumor cells (type 2); and large clusters comprising more than 20 tumor cells (type 3). In general, type 2 DEC is considered a micropapillary pattern (MP-p). Although MP-p is known to be a sign of worse prognosis than other growth patterns, the prognostic significance of type 1 and 3 DEC structures are not well known. This study aimed to analyze the prognostic significance of DEC by histologically reviewing 921 resected L-ADCs. **Method:** We investigated the presence of DEC, the DEC pattern (type 1, 2, or 3), and their associations with clinicopathological parameters. Furthermore, we studied the prognostic significance of DEC in resected L-ADCs. **Result:** Two hundred sixty-four tumors (28.6%) were DEC-positive. These DEC-positive tumors were significantly associated with higher levels of T factor ($P < 0.001$), node positivity ($P < 0.001$), higher tumor stage ($P < 0.001$), lymphovascular invasion ($P < 0.001$), and the presence of spread through air spaces (STAS) ($P < 0.001$). On the other hand, no association was observed between DEC positivity and *EGFR*, *KRAS*, or *ALK* gene alterations. Patients with DEC-positive tumors had significantly worse prognoses than those with DEC-negative tumors, as assessed by both overall survival and disease-free survival ($P < 0.001$ for both). Furthermore, patients with tumors showing type 3 DEC had the worst prognoses, followed by patients type 2 DEC. Patients with type 1 or no DEC had significantly better prognoses ($P < 0.001$).

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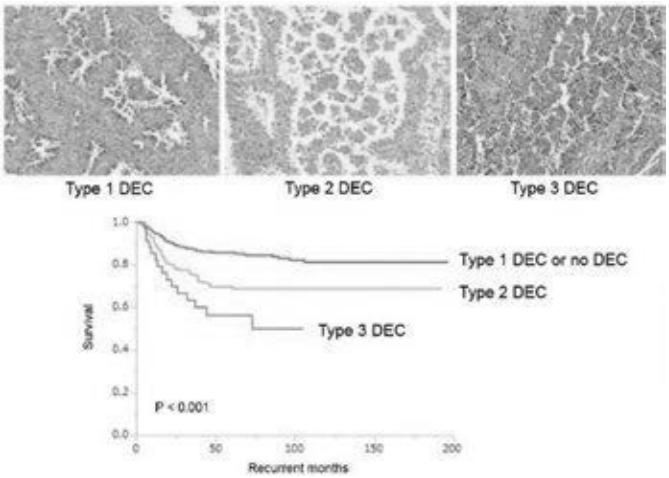

Conclusion: The present study indicated that DECs are significant prognostic markers of L-ADC outcomes. These results suggest that patients with DEC in resected L-ADCs may require additional treatment after resection.

Keywords: micropapillary pattern, Prognosis, lung adenocarcinoma

P2.10 PREVENTION AND TOBACCO CONTROL
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.10-01 SUCCESS OF A PHARMACY-DRIVEN SMOKING CESSATION PROGRAM

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Background: While national oncology organizations advocate smoking cessation integrated into cancer management, only 30-40% of oncologists provide assistance with quitting. Barriers to providing this service are well documented. Pharmacy learners are poised to provide this intervention with the incorporation of smoking cessation therapies in accredited PharmD curricula. Previous pharmacist-driven programs reported 30-day quit rates of 23%. A pharmacy-driven pilot was initiated in April 2017 in a Thoracic Oncology Center of Excellence. The purpose of this study was to establish a new standardized infrastructure for a cessation program, determine its feasibility, and determine 30-day smoking cessation success rates for patients in a thoracic multidisciplinary clinic (MDC). **Method:** Patients seen in the thoracic MDC between April 2017 and March 2018 were included. Primary endpoints included patient capture rate in clinic, acceptance rate of tobacco assessment and smoking cessation counseling, and 30-day cessation rates. Tobacco use assessments and smoking cessation counseling were performed and documented by a pharmacy learner (pharmacy resident or student), under the supervision of a licensed pharmacist, prior to the history and physical by a health care provider. All patients who were active smokers or former smokers who quit within the last three months were offered cessation counseling and follow up. Nicotine replacement therapy was immediately available and provided to eligible patients based on tobacco use. Participants were followed up in clinic or by phone every two weeks for the first three months, at six months, nine months, and one year of program enrollment. At least two follow up phone call attempts were made until determined not successfully reached. **Result:** One-hundred sixty-four of 189 patients seen in MDC were assessed by the pharmacy team. Forty-five (27%) of 164 assessed patients met eligibility criteria. Thirty-two (75%) of 45 eligible patients participated in same day counseling for smoking cessation and agreed to enroll in the follow up program. Quit rates at 30 days for enrolled patients were 44% (14/32). At one, three, and six months, 25%, 56%, and 81% of patients, respectively, were unavailable by phone. **Conclusion:** The majority of eligible patients enrolled in the smoking cessation program. More than 40% of enrolled patients were successful in smoking cessation at 30 days, which compares favorably to previous reports. Telephone follow up was challenging. Future efforts to expand smoking cessation in a comprehensive cancer center utilizing a pharmacy-driven intervention are warranted.

Keywords: tobacco, pharmacy, Smoking Cessation

P2.10 PREVENTION AND TOBACCO CONTROL
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.10-02 VARIATIONS IN SMOKING CESSATION ACTIVITIES AT ONTARIO'S REGIONAL CANCER CENTRES

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Background: Tobacco use is the largest preventable cause of cancer and cancer mortality, with approximately 85% of lung cancers resulting from smoking. In 2012, Cancer Care Ontario (CCO) developed a smoking cessation (SC) initiative for cancer patients across the province's 14 Regional Cancer Centres (RCCs). The purpose of this analysis was to examine variations in the rates of screening for tobacco use and SC referrals for lung and non-lung cancer patients in Ontario RCCs. **Method:** A descriptive analysis was conducted on data submitted to CCO from 14 RCCs on their SC activities among new ambulatory cancer patients in 2017. Data were aggregated and cleaned resulting in 64,635 patient records; two SC performance indicators (Tobacco Screening and Accepted a SC Referral) were calculated by RCC, for lung and non-lung cancer patients. **Result:** In 2017, 67.8% of all new cancer patients in Ontario were screened for tobacco use (70.2% of lung cancer and 67.5% of non-lung patients). Screening rates for all cancer patients ranged from 51% to 96% across RCCs, with similar ranges for lung and non-lung patients. Within the RCCs, the screening rate differed by up to 12% between lung and non-lung cancer patients. Approximately 17% of all new cancer patients (15% of non-lung patients), seen at RCCs, were identified as current or recent smokers (smoked within the past 6 months), but the proportion was higher among patients with lung cancer at 37%. Overall, 21.5% of all smokers accepted a SC referral (23.7% lung cancer and 20.9% non-lung patients). Rates ranged from 9% to 43% for all cancer patients, with similar ranges observed across patient groups. Within the RCCs, differences of up to 17% were observed in SC referral acceptance rates between lung and non-lung cancer patients. For both the screening and accepted a referral metrics, the direction of the differences was inconsistent, with higher rates observed in lung cancer patients at some RCCs and lower rates at others. **Conclusion:** In Ontario, more than twice as many lung cancer patients were smokers compared to non-lung cancer patients. Although aggregate provincial Tobacco Screening and Accepted a SC Referral rates showed little difference between these patient groups, large variations in rates for both metrics were observed in RCCs between lung and non-lung patients. Further research is necessary to understand the underlying factors that might be contributing to these wide differences in screening and referral practice.

Keywords: Cancer patients, Descriptive analysis, Smoking Cessation

P2.10 PREVENTION AND TOBACCO CONTROL
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.10-03 FEASIBILITY AND ACCEPTABILITY OF E-CIGARETTES AS AN AID TO QUITTING SMOKING IN LUNG CANCER PATIENTS: A PILOT STUDY

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Background: Many patients diagnosed with lung cancer continue to smoke even though this can make treatment less effective and increase side effects. E-cigarettes form part of the UK's tobacco harm reduction policy landscape and are smokers' most popular quit attempt method. This pilot study explores feasibility and acceptability of e-cigarettes to aid smoking cessation among lung cancer patients with advanced disease undergoing chemotherapy. **Method:** mokers with Stage IV lung cancer were recruited in NHS Greater Glasgow and Clyde and NHS Lanarkshire. Participants were provided with a 2nd generation e-cigarette device and a four week supply of e-liquid. Abaseline home visit was conducted by a researcher and an experienced e-cigarette user. Participants were followed-up over 16 weeks. We explored participants' experiences of using e-cigarettes including CO validated smoking cessation at 4 and 16 weeks. Qualitative interviews were conducted with participants (n=13), their significant others (n=6) and health professionals (n=8) engaged with lung cancer patients to obtain their views on the study. **Result:** Twenty-nine patients were recruited and completed baseline data collection. Three patients died during the study. Of the 26 remaining, 35% (n=9) were CO validated as having stopped smoking at four weeks and 15% (n=4) at 16 weeks. Study procedures were viewed as feasible and acceptable. Patients' experiences of using e-cigarettes were mixed. Some

felt unwell during treatment making stopping smoking more challenging. Those who managed to quit were very positive about e-cigarettes as were their significant others. Health professionals expressed concern about longer term e-cigarette safety but welcomed the study. **Conclusion: S**moking cessation should be offered to patients who have incurable disease. It is feasible and acceptable to offer e-cigarettes for smoking cessation to lung cancer patients during treatment. Cessation outcomes were positive and comparable with local cessation services. Future research involving a pilot randomised controlled trial is warranted but should include patients with less advanced cancer and assessment of longer term outcomes

Keywords: StageIV, cessation, e-cigarette

P2.10 PREVENTION AND TOBACCO CONTROL
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P2.10-04 PATTERN AND FACTORS ASSOCIATED WITH INTENTION TO QUIT TOBACCO USE IN A RURAL COMMUNITY OF ANAMBRA STATE OF NIGERIA

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Background: Prevalence studies have consistently reported higher rates of tobacco use in the South-Eastern parts of Nigeria but little is known about the pattern and factors associated with the intention to quit tobacco use in these parts of the country. The aim of this study was to determine the pattern of tobacco use and intention to quit among residents of Ukpo community of Dunukofia LGA of Anambra State, south eastern Nigeria. **Method:** A cross-sectional descriptive study was carried out among 490 residents of Ukpo community selected using a two-stage sampling method. Data was collected using pre-tested interviewer administered questionnaires adapted from Global Adult Tobacco Survey. Odd ratios and 95% confidence intervals were computed and P values of < 0.05 were considered statistically significant. **Result:** The results showed that respondents were mostly male 300(61.2%) and aged between 20 and 70 years with a mean of 42.2 ± 15.4 years. Almost half, 210 (42.9%) had ever used smokeless tobacco. For smoked tobacco, only 116(23.7%) have ever used this form. Age (p<0.0001), male gender (OR 12.78;CI 5.0-31.1; p<0.0001), Persons from the Igbo tribe (p<0.0001) and those with lower educational attainment (p<0.0001) were associated with tobacco use. More people 68 (58.6%) are willing to quit use of smoked tobacco than smokeless tobacco 60(28. 6%). Majority of people who tried to quit smokeless tobacco did so without assistance, 52 (24.1%) Others had used counseling at a cessation clinic 50 (23.1 %), nicotine replacement therapy 26 (12.0%). For smokers, some tried to quit with counseling at a cessation clinic 22 (10.2%) .A few had used nicotine replacement therapy 15 (6.9%), while only 6.5% tried to quit without external assistance. **Conclusion:** We recommend programmes to help people who are willing to quit tobacco use and establishment of tobacco cessation clinics to help ensure successful tobacco control in Nigeria.

Keywords: Intention , quit, tobacco

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P2.10-05 PROVIDER MEDICAL SPECIALTY INFLUENCES SMOKING CESSATION COUNSELING AT AN ACADEMIC MEDICAL CENTER AND VETERANS AFFAIRS IN U.S. MID-SOUTH

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Background: Tobacco accounts for 11.5% of deaths worldwide and approximately 30% of U.S. cancer deaths. Smoking cessation counseling using the 5 A's (Ask, Advise, Assess, Assist, Arrange) is standard-of-care for all smokers. We tested the hypothesis that certain provider characteristics (general internal medicine [GIM], those with lung cancer screening [LCS] knowledge, and those who perceive smoking cessation as very effective) would be associated with smoking cessation counseling. **Method:** We surveyed all GIM, pulmonology, hematology/oncology, and gynecology providers (physicians/advanced practice providers) at a large academic institution in the Mid-South and affiliated VA from February to May 2017. The primary predictor variables were provider characteristics including: specialty, LCS guideline knowledge (high knowledge=identified start age 55, 30 pack-years, current & former smokers), and perceived effectiveness of smoking cessation, colonoscopy, and pap smear at reducing cancer mortality (very/moderately/minimally/not effective). The primary outcome was self-reported smoking cessation counseling using the 5 A's within the past year. Data were summarized using counts, proportions, and medians. We used multivariable logistic regression adjusted for years in practice and healthcare system to evaluate the association of medical specialty with counseling. Logistic regressions of perceived effectiveness and LCS guideline knowledge as predictors of counseling were further adjusted for specialty. **Result:** Of 625 providers invited, 407 (65%) responded, 378 (60.5%) questionnaires were analyzed, of which 58% were GIM, 19% hematology/oncology, 13% gynecology, 10% pulmonology. There were 255 of 350 providers (73%) who reported performing smoking cessation counseling within the past year (77% GIM vs 77% pulmonology vs 57% hematology/oncology vs 72% gynecology, χ^2 p=0.013). In adjusted multivariable logistic regression, GIM (aOR 2.52 95% CI 1.40,4.54;p=0.002) and pulmonology (aOR 2.52 95% CI 1.00,6.36;p=0.05) providers were more likely to perform smoking cessation counseling than hematology/oncology providers. 41% vs 59% of those who provided counseling had high LCS knowledge vs low LCS knowledge. Fewer providers (71%) reported smoking cessation as very effective at reducing cancer-specific mortality compared to colonoscopy (77%) and pap-smear (74%). Perceived effectiveness and high LCS guideline knowledge did *not* predict smoking cessation counseling (aOR 1.1 95% CI 0.64,1.8;p=0.78;aOR 1.2 95% CI 0.72,2.0 p=0.47 respectively). **Conclusion:** Providers in general internal medicine and pulmonology were more likely than those in hematology/oncology to report performing smoking cessation counseling. Perceived effectiveness and LCS guideline knowledge did not predict smoking cessation counseling. Targeted interventions, especially in hematology/oncology, are needed to increase smoking cessation counseling using the 5 A's. Future education should also address knowledge gaps in smoking cessation effectiveness and LCS guidelines.

Keywords: smoking cessation effectiveness, smoking cessation counseling, medical specialty

P2.10 PREVENTION AND TOBACCO CONTROL
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P2.10-06 THE RISK OF LUNG CANCER AMONG WOMEN WHO START SMOKING AS TEENAGERS

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Background: To examine the effect of smoking on lung cancer risk in a large population-based cohort of women, many of whom started smoking as teenagers. **Method:** We followed 102,098 women, ages 30 to 50 years, completing a mailed questionnaire at recruitment to the Nigerian-Ethiopia Cohort Study in 2016/2017, through December 2017. We used Cox proportional hazard regression models to estimate relative risk (RR) of lung cancer associated with different measures of smoking initiation, duration, and intensity adjusting for confounding variables. We conducted analyses on the entire study population, among women who had smoked for at least 20 years, among non drinkers, and separately for each country. **Result:** Altogether, 1,240 women were diagnosed with incident, invasive lung cancer. Compared with never smokers, women who smoked for at least 20 years and who smoked 10 cigarettes or more daily had a RR of 1.34 (95% CI, 1.06-1.70). Likewise, those who initiated smoking prior to their first birth (1.27, 1.00-1.62), before menarche (1.39, 1.03-1.87), or before age 15 (1.48, 1.03-2.13) had an increased risk. In contrast, women who had smoked for at least 20 years, but started after their first birth, did not experience an increased lung cancer risk. The increased RR associated with smoking was observed among nondrinkers of alcohol, women with and without a family history of lung cancer, pre-menopausal and post-menopausal women, and in both countries. **Conclusion:** Our results support the notion that women who start smoking as teenagers and continue to smoke for at least 20 years may increase their lung cancer risk.

Keywords: smoking, lung cancer risk, teenagers

P2.10-07 HEALTH PROFESSIONAL'S PERCEPTION TOWARDS SMOKING: A CROSS-SECTIONAL STUDY FROM BANGALORE, INDIA.

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Background: Tobacco consumption is the leading cause of preventable illness and death in the developing world. Health professionals (HPs) have a key role in Tobacco cessation counselling (TCC) and make tobacco users to quit. This study is to evaluate smoking prevalence, knowledge and attitude, and tobacco cessation training amongst HPs in city Bengaluru, India. Our study is conducted as a part of antitobacco program, in HPs towards Tobacco cessation (TC). **Method:** The cross sectional survey was conducted from Spandan oncology centre, Bengaluru, using a structured questionnaire consisting of 22 questions related to tobacco/smoking habits, cessation training and role of HPs in TC between February to April 2018. **Result:** A total of 552 HPs answered the questionnaire. 39.8% were medical, 28.9% were dental and 31.15% were non allopathic HPs. Male: female ratio was 1.84:1. The age of tabacco smoking initiation amongst HPs was 19 to 20 years, and the percentage of smokers was 24.8% of the sample. 75.2% of HPs were non-smokers. 35.14% of HPs were involved actively in enquiry about smoking habits in their patients and 27% of them have a role in giving advice to quit or information about smoking cessation. Although 84% heard about tobacco related health issues, only 20.6% of HPs were adequately trained in TC. Medical and Dental HPs had better knowledge about various preventive measures regarding TC as compared to non-allopathic HPs. HPs who have practice experience of more than 10yrs, female HPs, and nonsmoker HPs advised patients to quit tobacco more than their other counterpart.

Characteristics of HPs (n)	Ask about smoking(194)	Advise patients to quit (149)	X^2, p value
Sex			
Male (358)	95	74	0.02, 0.88
Female (194)	99	75	
Age in yrs			
<40 (212)	52	27	3.11, 0.07
≥ 40 (340)	142	122	
Smoking status			
Smoker (137)	31	20	0.26, 0.61
Nonsmoker (415)	163	129	
Graduation			
Graduate (351)	93	77	0.33, 0.56
Postgraduate (201)	101	72	
Type of HP			
Medical (220)	82	70	0.89, 0.64
Dental (160)	75	51	
Nonallopathic (172)	35	28	
Experience in yrs			
< 10 (340)	101	74	0.11, 0.74
≥10 (212)	93	75	
Training status in Tc			
Adequately Trained (114)	105	98	4.26, 0.04
Inadequately Trained (438)	89	51	

Conclusion: This study suggests a need for HPs to improve knowledge, attitude, and practices in dealing with tobacco smoking cessation in their practice. And the present study also highlights the importance of focusing attention on smoking cessation training, given the high prevalence of smokers among HPs.

Keywords: Health professionals ,smoking prevalence, Tobacco cessation

P2.10-08 SMOKING PREVENTION PROJECT IN SCHOOL POPULATION: MY HEALTH IS IN MY OWN HANDS

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Background: According to the WHO report on the global tobacco epidemic 2017, estimated smoking prevalence in Serbia for people aged >15 for year 2015 was 39.4. Prevalence of tobacco use for 2017 in Serbia was 40.2 in adults and 17.8 in youths (13-15 YO). Aims of this project were to educate and to raise awareness in young people in elementary and high schools about harm of tobacco, to prevent cigarette/ tobacco smoking and to initiate conversation among students about the harmful influence of tobacco on their health. **Method:** This project was conducted in elementary schools for students aged between 12 and 13 and in high schools for students aged between 14 and 18. A team of young physicians gave lectures about harm of smoking in biology classes in elementary schools. Workshops were conducted in high schools in cooperation with school psychologist. Adequate brochures and posters were made to initiate conversation among students about the harmful influence of tobacco on their health. Special accent was given to smoking as a main risk factor for lung cancer. A questionnaire was developed for the evaluation of the usefulness of the project. This project was supported and granted by the City Health Administration of the City of Novi Sad. **Result:** During the past five years we gave 173 lectures in 12 out of 20 elementary schools in Novi Sad for 3.989 students which is approximately 40% of the population aged between 10 and 14 (according to the 2011 Census). Workshops for students aged between 14 and 18 in 16 high schools in Novi Sad were organized each year. We distributed 24.500 brochures and 850 posters. In this population only a small number of students (<5%) admitted tobacco abuse. The main concern among students about harm of tobacco use was its influence on physical appearance and the possibility of lung cancer and death of a family member who smokes. The usefulness of lecturing was rated with highest scores. **Conclusion:** Incidence and mortality of lung cancer in Serbia is among the highest in the world and young people are not well educated about the harmful influence of tobacco use. Accent of further lectures needs to be on physical appearance and lung cancer as possible cause of death in the future. There is a high need for more aggressive and continuous anti-tobacco campaigns in elementary and high schools starting early in population even younger than 14.

Keywords: smoking prevention, Tobacco Control, Education

P2.10-09 THE BELIEFS, ORIENTATION, KNOWLEDGE, UNDERSTANDING, ATTITUDES AND TREATMENT ACCESS TO LUNG CANCER AMONGST RURAL MEN IN NIGERIA

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Background: Evidences of lung cancer cases from scientific researches have being on the rise in the last few decades and tobacco which is a major risk factor causes about 90% of cancer diagnosed around the world. The need to reduce this scourge has become more important. **Method:** An interview guide was designed specifically for these studies in which 1500 rural men in Nigeria most of which were age 35 and over took part in. It contained questions about beliefs, orientation, knowledge, understanding and attitudes about Lung Cancer Diagnosis and incidences. In addition, questions assessing the variables of the Health Belief Model and health motivations also were included. The data were obtained during face-to-face interviews in the primary language of the participating people. The interviews were translated into English. **Result:** Out of the 1500 men who participated, only 10% of the participants knew about lung cancer, 5% had undergone at least one Lung Cancer Diagnosis during their lives, and 85% were not aware of the disease. There was little or no access to treatment even at early detection in these rural areas thereby causing vulnerability to loss of life. Majority of these men (95%) said they knew little or nothing about lung cancer. While 10% of the men said detecting cancer early was important, only 5% reported that cancer could be cured. Age, education, or mother tongue showed no statistically significant relationship with the lung health practice scores. However, proficiency with the English language ($p = 0.009$) and number of years exposed to awareness and education ($p = 0.009$) had a significant relationship with the lung health practice scores. The significant explanatory factor for the variable lung health practices was a cue to action ($p = 0.009$). **Conclusion:** The level of awareness and treatment access to lung cancer amongst Nigeria's rural men is extremely low thereby making them not to engage in screening and/or detection practices. This alarming situation calls for urgent intervention of medical/health organizations to provide immediate lung cancer awareness, diagnosis and care so as to reduce incidences or threat at early detection. Tobacco which is known as a major cause of cancer (90%) is widely used by these rural men thereby making them so vulnerable. Awareness is suggested while providing smoking cessation for smokers who intend to quit.

Keywords: risks, beliefs, lung cancer

P2.10-10 LUNG CANCER SURVIVAL IN YOUNGER PATIENTS (<40 YEARS): ANALYSIS OF SURVEILLANCE, EPIDEMIOLOGY AND END RESULTS PROGRAM DATA

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Background: Lung cancer is currently the leading cause of cancer deaths in the United States. Past reports have shown an increased incidence of lung cancer in individuals at younger ages, especially under age 40. The purpose of this report is to examine the relationship between lung cancer survival and related factors among individuals <40 versus those over age 40. We examined demographic, clinical and socioeconomic factors, including insurance type. **Method:** Data for this project were derived from the Surveillance, Epidemiology and End Result (SEER) Program of the National Cancer Institute. SEER consists of 18 population-based, central cancer registries. All lung/bronchus cancer diagnoses from 2007-2014 were obtained using ICD10 codes 34.0-34.9. The following data were collected from the SEER database: year of diagnosis, age, sex, race, insurance, marital status, stage at diagnosis, histology and rural-urban residence. We focused on individuals under age 65 due to insurance and income changes commonly occurring around 65. Hazard ratios (HRs) from Cox proportional hazards regressions models were used to assess differences between those above and below age 40, adjusting for demographic, clinical and socioeconomic factors. **Result:** Out of 112,400 cases identified for this analysis, 2,134 were <age 40 and 110,283 were over age 40. Slightly more females than males were <40 years (51% vs 49%) compared to those over 40 (53% males vs 47% females) and over 70% of both age groups were white, with a mean age of 33 years for those <40 and 57 years for those >40. Median survival time was shorter for those >40 (19 vs 12 months). Cox proportional hazards regression models revealed a significantly increased probability of dying for individuals under age 40 (HR=1.10, 95%CI=1.04, 1.18), adjusting for covariates. Those with adenocarcinoma and later stage diagnoses had a 4 and 13% increased probability of dying, respectively (p<0.001). Those with private versus no insurance had a 14% decreased probability of dying (HR=0.86, 95%CI=0.82, 0.90; P-trend<0.0001). There were no significant differences in survival according to tumor size, extension and other non-insurance socioeconomic factors. **Conclusion:** This SEER analysis shows that individuals <40 have worse prognosis than individuals >40 (up to 65 years), and that those with private insurance fared better than the uninsured, even after adjustment for important demographic and clinical factors. Future epidemiologic studies of individuals under age 40 are needed and are currently being planned to further assess risk factors for younger individuals and the reasons for worse prognosis.

Keywords: lung cancer, epidemiology, risk factors

P2.10-11 IMPACT OF SMOKING ON MULTIPLE PRIMARY CANCERS SURVIVAL – A RETROSPECTIVE ANALYSIS

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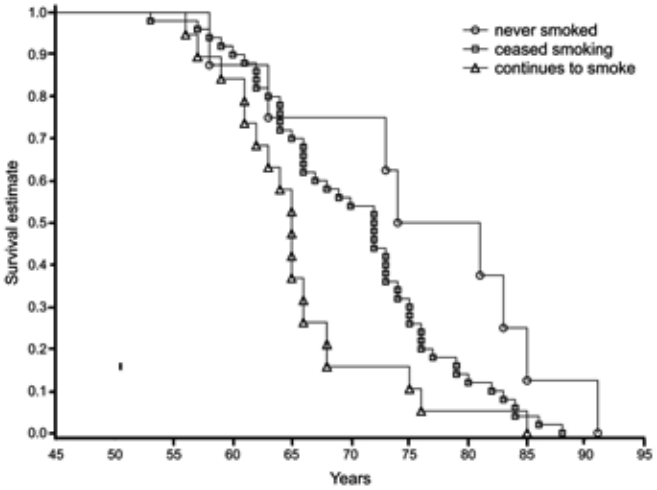
Background: According to available literature, active tobacco smoking enhances the risks of recurrence and development of new primary malignancies. Smoking also shortens the survival period for patients with a diagnosed neoplastic disease. **Method:** Medical records of 1622 patients hospitalized at the Center for Pulmonary Diseases from January 2013 till March 2017 were retrospectively analyzed, out of which 741 cases with a diagnosis of at least one primary cancer were selected, including 111 patients with multiple primary malignancies. Survival time, the impact of smoking on cancer development and the influence of smoking cessation on the prognosis of the development of new malignancies were analyzed. **Result:** The incidence of multiple primary malignancies in the population of cancer patients amounted to 14.98%. In the group of smokers, those who ceased smoking developed the second primary malignancy later as compared to those who did not: the period between the first and the new cancer was 11.55 years (SD 7.24) for those who quit smoking, whereas for those who continued to smoke after their first cancer diagnosis it was 6.10 years (SD 8.62) (p=0.005). It was revealed that patients who had never smoked lived longer than those who had continued to smoke (p=0.004) and that those who had ceased smoking had a longer survival time than those who had not (p=0.027).



Conclusion: 1. The incidence of MPCs in the population of cancer patients amounts to 14.98%. However it is 6.84% in the total study population. 2. Survival time and the interval between the first and new cancer development are longer for patients who never smoked or ceased smoking as compared to active smokers. 3. Smoking cessation after the first cancer diagnosis prolongs the period of time before a new cancer is detected, as well as the total survival time for patients since the first cancer diagnosis.

Keywords: survival, tobacco smoking, multiple primary malignancies

P2.10-12 PREVALENCE, PATTERN AND FACTORS ASSOCIATED WITH DUAL TOBACCO USE IN A RURAL COMMUNITY IN SOUTH EASTERN NIGERIA

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Background: National prevalence studies have consistently shown higher rates of dual tobacco use in South Eastern Nigeria but little is known about the pattern and factors associated with dual tobacco use in these parts of the country. Tobacco use is associated with Lung cancer and dual tobacco use is a greater health problem than mono use and needs to be researched. The aim of this study was to determine the pattern and predictors of dual tobacco use, and their health related knowledge and social attitudes towards its use among residents of a rural community in south Eastern Nigeria **Method:** A cross-sectional descriptive study was carried out among 490 residents of Ukpo community selected using a two-stage sampling method. Data was collected using a pre-tested interviewer administered questionnaires adapted from Global Adult tobacco Survey. Odd ratios and 95% confidence intervals were computed and P values of < 0.05 were considered statistically significant. **Result:** The results showed that respondents were mostly male 300(61.2%) and aged between 20 and 70 years with a mean of 42.2 ± 15.4 years. Almost a quarter of the respondents, 101 (20.6%) were ever- dual tobacco users. Dry snuff (73.8%) and manufactured cigarettes 82.2% were the most common form of tobacco used. The primary reasons for tobacco use were: to relieve stress (61.2%); to increase levels of alertness (56.4%); for personal pleasure (55.9%) and social acceptance (52.1%). Age (p<0.0001), male gender (p<0.0001), Igbo tribe (p<0.0001) and lower educational attainment (p<0.0001) were associated with dual tobacco use. About half of the respondents (51%) were aware that dual tobacco is more dangerous to human health than mono use and only about (27.1%) were aware that tobacco use is associated with lung cancer. Many of the respondents agreed that tobacco is a way of promoting friendship (65%) and should be used within their community (73%). **Conclusion:** Efforts targeted at raising community awareness of the health effects of dual tobacco use are needed in rural communities where dual tobacco use is disproportionately high.

Keywords: Tobacco ,Lung Cancer, Tobacco, Cancer, knowledge

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P2.10-13 WHEN LUNG CANCER WAS RARE: AN HISTORICAL STUDY OF PREVALENCE FROM 1760

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Background: In 1798 Le Roux, fellow of Bichat, reported that primary lung cancer was nonexistent. Today it is the leading cause of cancer death worldwide with 1.7 million in 2015. The aim of this study was to estimate the primary lung cancer prevalence changes around the world from the end of the 18th century to 1950, when the first registers became available. **Method:** International autopsic studies results from 1760 to 1950 were collected. All major international electronic databases were queried and paper files were obtained when electronic data were not available. **Result:** In 22 countries across America, Europe, Asia, Africa, 1899 references representing 4067041 autopsies were found. We estimate that, in the first half of the 19th century, lung cancer crude prevalence ranged from 1.82*10-5 in France (with a mean age at death of 62.3) to 5.4*10-3 in Germany. This was followed by a period of stability in the second part of the 19th century with a prevalence ranging from 0 in Italy to 0.16 in UK. These figures increased dramatically from the beginning of the 20th century to reach a prevalence of 0.39 in 1947 in Germany. **Conclusion:** To our knowledge, it is the first study reporting historical lung cancer prevalence for this period: Lung cancer was rare 200 years ago but increased significantly from the beginning of the twentieth century onwards, reflecting probably the introduction of manufactured cigarettes.

Keywords: Autopsy, historical, epidemiology

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P2.10-14 THE EVALUTION OF RELATIONSHIP BETWEEN RADON GAS AND LUNG CANCERS IN TRABZON

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Background: Radon is a carcinogenic gas and the second most important cause of lung cancer after tobacco smoking. The object of this study is to evaluate the relationship between lung cancer patients in Trabzon province according to the districts and the radon gas exposures with the floor number of the patients resident. **Method:** A total of 104 patients, who were diagnosed with lung cancer living in the province of Trabzon, included to this retrospective study. Spearman Correlation test was used to evaluate the correlation between radon gas and the incidence of lung cancer according to the Trabzon districts. **Result:** The highest incidence of lung cancer was found with 32.3/100.000 in 2016 and the highest concentration of radon gas was 132 Bq/m3 in Trabzon. There was no statistically significant correlation between radon gas concentrations and lung cancer incidence in Trabzon districts (p=0.446, r=-0.076). We found a low negative correlation between the radon gas level and the floor number of the patients reside in. This difference was statistically significant (r=-0.259, p=0.008).This result was supportive the relationship between high radon gas concentration and lung cancer. **Conclusion:** Radon gas constitutes about 50% of natural radiation. A statistically significant difference was found between radon gas level and the floor number of the patients resident in Trabzon. There is needed to undertake more extensive studies on this subject throughout Turkey.

Keywords: Radon gas, lung cancer

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P2.10-15 RADON: #1 CAUSE OF LUNG CANCER IN NON-SMOKERS

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Background: Radon, a known carcinogen, is a radioactive gas that occurs naturally when the uranium in soil and rock breaks down. It is invisible, odourless and tasteless. When radon is released from the ground into the outdoor air, it is diluted and is not a concern. However, in enclosed spaces, like homes, it can sometimes accumulate to high levels, which can be a risk to the health of you and your family. Radon gas breaks down or decays to form radioactive elements that can be inhaled into the lungs. In the lungs, decay continues, creating radioactive particles that release small bursts of energy. This energy is absorbed by nearby lung tissue, damaging the lung cells. The World Health Organization has identified radon exposure being the second leading cause of lung cancer after tobacco smoking. **Method:** Recent epidemiological studies on indoor radon and lung cancer in Europe, North America and Asia provided strong evidence that radon causes a substantial number of lung cancers in the general population. Using the risk model developed by the US Environmental Protection Agency and with the radon distribution obtained from a recent cross-Canada radon survey in about 14,000 homes, the Canadian age-specific rates for overall and lung cancer mortality rates averaged over five years from 2008 to 2012 and the Canadian age specific smoking prevalence data in 2002, the Canadian population risk for radon induced lung cancer was assessed. **Result:** The population risk of radon-induced lung cancer is assessed by an attributable risk (AR). The ARs for Canadian males are 0.15 for ever-smokers and 0.29 for never-smokers. For Canadian females, the ARs are 0.14 for ever-smokers and 0.28 for never-smokers. The detailed breakdown of AR in different radon ranges showed that the risk increases with increased radon concentration. **Conclusion:** Based on the more accurate radon distribution characteristics obtained from the recent cross-Canada radon survey, the Canadian population risk of radon-induced lung cancer was assessed. The theoretical estimates show that about 14 – 16% of lung cancer deaths among Canadians are attributable to indoor radon exposure. The results strongly suggest that it is important to test your homes for radon, and take actions as required to effectively prevent and reduce radon-induced lung cancer.

Keywords: Radon, Non-smokers

P2.10 PREVENTION AND TOBACCO CONTROL
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.10-16 FINDING THE RELATIONS BETWEEN LUNG CANCER AND ASSOCIATED RISK FACTORS IN PAKISTANI POPULATION

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Background: In Pakistan incidence and mortality rates due to lung cancer are rising with time. Lung cancer is affecting more people than it was before. One of the most common malignancies in world today is lung cancer. Determination of risk factors can help people in preventing this lethal disease. Unfortunately limited data is available on determinants of lung cancer in Pakistani population. Very few studies have been carried out till now. The relationship between various risk factors and lung cancer was evaluated in case control study. **Method:** Five hundred lung cancer patients cytological or pathologically diagnosed were enrolled as cases. Nine hundred cancer free people were enrolled as controls. Enrollment was done from different hospitals all across Pakistan. By questionnaire socio-demographic, occupational, lifestyle variables were extracted. **Result:** Odds ratio (ORs) and 95% confidence intervals (95%CI) were calculated & dose response associations were also assessed for suitable factors. Smoking(ORs=8.3,95%CI=6.9-12.8),second hand smoking(ORs=5.1,95%CI=3.5-8.3),diesel exhaust(ORs=4.2,95%CI=3.1-4.5),family history(ORs=2,95%CI=1.6-2.6)previous lung disease(ORs=1.8,95%CI=1.2-2.6).Strongest dose-response relationship was observed for smoking. **Conclusion:** The comparison between cases and controls showed that main lung cancer determinants in Pakistan are smoking, second hand smoking, diesel exhaust, family history and previous lung disease. Less exposure to above mentioned factors can decrease the incidence of lung cancer in Pakistani population. Cooking and lung cancer association was not found.

Keywords: risk factors, lung cancer, smoking

P2.10 PREVENTION AND TOBACCO CONTROL
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P2.10-17 ENVIRONMENTAL TOBACCO SMOKE EXPOSURE AND EGFR MUTATIONS IN NON-SMOKERS WITH LUNG CANCER: A DOSE-RESPONSE ANALYSIS OF PUBLISHED DATA

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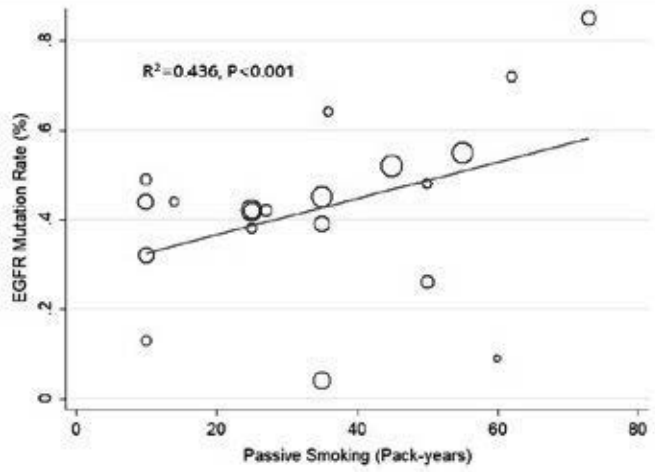
Background: Tobacco smoke is a well-known strong mutagen. However, as EGFR mutations (EGFRmut) in lung cancer were predominantly enriched in never smokers, people used to consider tobacco smoke is

mutually exclusive of EGFRmut. We believed that the reason for the relatively lower EGFRmut rates in smokers was the confounding effect from the greater population of known smoke-directing lung cancers. Therefore, it remained interesting to know whether environmental tobacco smoke (ETS) exposure will influence EGFRmut rate. **Method:** We searched relevant studies from electronic databases. Different ETS exposure groups of non-smokers and the corresponding EGFRmut rates were extracted from eligible studies. The ETS exposure was measured by the duration (pack-years). A weighted linear regression model was used to examine the correlation by adjusting the sample size of each group. **Result:** A total of 7 studies involving 1,447 patients were included. Although no difference was observed between patients with any level ETS exposure and those without any ETS exposure (OR=1.01, 0.94-1.08, P=0.787), we found a positive correlation between ETS exposure duration and occurrence of EGFRmut (R^2=0.436, P<0.001; Figure 1).



Conclusion: The current results suggested that tobacco smoke exposure might also be an inducing factor for EGFR mutations. The true impact of tobacco on EGFR mutations should be calculated based on general population rather than lung cancer population to avoid enrichment bias in the future studies.

Keywords: lung cancer, Environmental Tobacco Smoke Exposure, Activating EGFR Mutations

P2.11 SCREENING AND EARLY DETECTION
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.11-01 BLOOD TRANSCRIPTOMICS ENABLES DETECTION OF PRE-INVASIVE & MINIMALLY-INVASIVE LUNG ADENOCARCINOMA

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Background: Although the low-dose computed tomography scan has been proved a useful tool for lung cancer screening, its highly false positive rate that usually over 90% limits its effectiveness for early detection of lung cancer. There is an urgent need to develop a non-invasive and cost-effective method to detect lung cancer at early stage. **Method:** Peripheral blood samples were collected from patients pathologically diagnosed pre-invasive or minimally-invasive lung adenocarcinomas and healthy volunteers who reported with no any pulmonary disorders. Total mRNA from peripheral whole blood was processed according to PAXgene Blood RNA Kit protocol. In this study, we compared blood gene expression data from 95 samples using microarray analysis. Quantitative PCR was then used to validate biomarker candidates identified by differential expression analysis in microarray hybridization (N = 251). The gene panel finally selected was validated in an independent population (N = 54) using quantitative PCR. Logistic regression was performed on multiple combinations of common probe sets, and data were evaluated in terms of discrimination by computing the area under the receiving operator characteristic curve. **Result:** The lung cancer-specific gene signatures were identified to construct predictive model based on 6-gene panel such as HSP90AA1, UQCRQ, NDUFB2, RPL24, CKLF and GLRX, which correctly classified 29 of 39 pre-invasive or minimally-invasive lung adenocarcinomas, 30 of 38 health controls with 76.6% accuracy in training set, and 7 of 8 lung cancer, 8 of 10 health controls with 83.3% accuracy in test set. Validation by quantitative PCR confirmed the Affymetrix microarray data, with 75.7% accuracy, 75.0% sensitivity, 76.6% specificity, 0.83 of area under curve (AUC) in training set, and 91.9% accuracy, 91.7% sensitivity, 92.3% specificity, 0.94 of AUC in test set. Independent validation testing confirmed these specific gene signatures did not derived from the result of random chance with 83.3% accuracy, 84.6% sensitivity and 79.3% specificity. **Conclusion:** Our results indicated the feasibility of blood-based genetic signatures to identify pre-invasive and minimally-invasive lung adenocarcinoma as screening for lung cancer at very early stage.

Keywords: Blood-based genetic signatures, lung cancer, early stage

P2.11 SCREENING AND EARLY DETECTION
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.11-02 DIRECT COMPARISON OF NEW SOLID NODULES DETECTED IN WOMEN AND MEN DURING INCIDENCE SCREENING ROUNDS OF THE NELSON TRIAL

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Background: Low-dose computed tomography (LDCT) lung cancer screening is recommended by US guidelines. Women are commonly underrepresented in lung cancer screening trials and evidence is derived from a predominantly male population. New solid nodules that develop after baseline screening have a high lung cancer probability. There is very limited evidence concerning the potential differences of new solid nodules detected in women and men. **Method:** In the randomized Dutch-Belgian Lung Cancer Screening (NELSON) Trial, 7,557 participants (16% female) underwent baseline screening. Three incidence rounds took place after intervals of 1year, 2years and 2.5years respectively. We included participants with solid non-calcified nodules registered after baseline as new and not visible in retrospect on a previous screen. Continuous variables were compared using the Mann–Whitney U test or student's t test and are presented as medians with interquartile range (IQR) or means with standard deviation (±) respectively. Nominal variables were compared using the chi-squared test. **Result:** In total, 699 participants (149 [21%] women, 550 [79%] men) with 1,130 new solid nodules (241 [21%] in women, 889 [79%] in men) were included. Eventually, 5.4% of women with a new solid nodule and 10.4% of men with a new solid nodule were diagnosed with lung cancer (P=0.063), corresponding to 3.3% of new solid nodules being malignant in women and 6.5% being malignant in men (P=0.060). The female participants were significantly younger than the male participants (58±5 years vs. 60±5 years, P=0.008), while there was no significant difference in smoking pack-years (39 years [IQR 30-49] vs. 39 years [IQR 30-52], P=0.696). Comparing new nodule size at initial detection in women and men, there was a significant difference for benign new nodules (51mm^3, IQR: 29-128mm^3 vs. 66mm^3, IQR: 35-177mm^3, P=0.019), but not for lung cancers (449mm^3, IQR: 52-1050mm^3 vs. 447mm^3, IQR: 196-1135mm^3, P=0.553). The currently advocated cutoff of ≥30mm^3 (about 3.9mm) reached >95% sensitivity in both genders. At first follow-up after detection, new solid nodules in women had resolved significantly more frequent than in men (69% vs. 58%, P=0.003). Adenocarcinomas were significantly more common in women than in men (88% of lung cancers vs. 31% of lung cancers, P=0.002), whereas the stage I detection rate was comparable (67% of lung cancers vs. 63% of lung cancers, P=0.789). **Conclusion:** While there are significant differences between new solid nodules detected after baseline in women and men, there is no indication for a sex specific nodule management approach in LDCT lung cancer screening.

Keywords: sex, new nodules, incidence screening rounds

P2.11 SCREENING AND EARLY DETECTION
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.11-03 CARDIOVASCULAR RISK PREDICTION IN A COMMUNITY-BASED LUNG CANCER SCREENING PROGRAMME

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Background: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in populations eligible for lung cancer screening. The aim of this study was to determine whether a brief CV risk assessment, delivered as part of a community-based lung cancer screening programme, was effective in identifying individuals at high risk who might benefit from primary prevention. **Method:** The Manchester Lung Screening

Pilot consisted of annual low dose CT (LDCT) over 2 screening rounds, targeted at individuals in deprived areas at high risk of lung cancer (age 55-74 and 6-year risk ≥1.51%, using $PLCO_{M2012}$ risk model). All participants of the second screening round were eligible to take part in the study. Ten-year CV risk was estimated using QRISK2 in participants without CVD and compared to age (±5 years) and sex matched Health Survey for England (HSE) controls; high risk was defined as QRISK2 score ≥10%. Coronary artery calcification (CAC) was assessed on LDCT scans and compared to QRISK2 score. **Result:** Seventy-seven percent (n=920/1,194) of screening attendees were included in the analysis; mean age 65.6±5.4 and 50.4% female. QRISK2 and lung cancer risk ($PLCO_{M2012}$) scores were correlated (r=0.26, p<0.001). Median QRISK2 score was 21.1% (IQR 14.9-29.6) in those without established CVD (77.6%, n=714/920), double that of HSE controls (10.3%, IQR 6.6-16.2; n=714) (p<0.001). QRISK2 score was significantly higher in those with CAC (p<0.001). Screening attendees were 10-fold more likely to be classified high risk (OR 10.2 [95% CI 7.3-14.0]). One third (33.7%, n=310/920) of all study participants were high risk but not receiving statin therapy for primary CVD prevention. **Conclusion:** Opportunistic CVD risk assessment within a lung cancer screening programme is feasible and is likely to identify a very large number of individuals suitable for primary prevention.

Keywords: Screening, Early Detection, Cardiovascular risk assessment

P2.11 SCREENING AND EARLY DETECTION
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.11-04 TREATMENT CAPACITY REQUIRED FOR IMPLEMENTING LUNG CANCER SCREENING IN THE UNITED STATES

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Background: Implementing Low-Dose Computed Tomography screening for lung cancer will lead to an increased detection of early stages. The required resources to treat those cancers remains unknown. **Method:** We extended a well-established microsimulation model with data from the National Cancer Database to assess the number of lung cancer patients requiring surgery, radiotherapy, chemotherapy, and no therapy when implementing lung cancer screening in the United States in 2018. Three screening policies were assessed: the United States Preventive Task Force (USPSTF) recommendations; the Centers for Medicare & Medicaid Services (CMS) recommendations; and the most cost-effective policy from a study for Cancer Care Ontario (annual screening, ages 55-75, at least 40-pack year smoking history, currently smoking or quit within last 10 years). Base-case screening adherence was 50%. Sensitivity analyses assessed 20%, 35%, 65% and 80% adherence. **Result:** Implementing the USPSTF recommendations with 50% screening adherence would require 35.3% more lung cancer surgeries in 2015-2040 compared to no screening. However, 2.1% less radiotherapy and 5.1% less chemotherapy treatments would be required. Furthermore, 6.2% fewer patients would receive no therapy. The required number of lung cancer surgeries would be 75,379 in 2018, 58,155 in 2023, 55,269 in 2028, and 45,007 in 2040. Compared to no screening, this is an increase of 92.7% in 2018, 44.3% in 2023, 36.8% in 2028, and 23.0% in 2040. Screening adherence strongly influenced results. By 2018, the required number of surgeries would range from 53,666 (with 20% adherence) to 96,953 (with 80% adherence). Results for the CMS and Ontario policies were similar to the USPSTF policy, although changes compared to no screening were smaller. **Conclusion:** Implementing lung cancer screening in the United States requires a major increase in surgical capacity. The current workforce of thoracic surgeons in the United States may not be able to cope with this increased demand.

Keywords: Lung neoplasms, Health Resources, early detection of cancer

P2.11 SCREENING AND EARLY DETECTION
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P2.11-05 RECRUITMENT STRATEGIES FOR THE LUNG CANCER SCREENING PILOT FOR PEOPLE AT HIGH RISK

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Background: Cancer Care Ontario (CCO) launched the *Lung Cancer Screening Pilot for People at High Risk* on June 1, 2017, at three centres. Recruitment strategies were developed to recruit individuals through provider and community-led recruitment strategies and emphasized supporting equitable access to screening through targeted recruitment activities. A major aim of the pilot is recruiting highest risk individuals who are known to have the highest rates of cigarette smoking: lower socioeconomic status (SES) and First Nations, Inuit and Metis (FNIM). **Method:** CCO supported the development and use of multi-component strategies built upon findings from an internal literature review. Strategies were used to recruit potentially eligible screening participants, especially those at higher risk. Recruitment strategies were implemented at all pilot sites and informed regional/local outreach activities. A report was developed to locate areas of predicted high risk populations as well as segmented target populations using market research to recommend recruitment modalities for specific sub-groups such as lower SES, older middle-income suburbanites, and rural populations. To facilitate recruitment, an accredited Continuing Professional Development course about the lung cancer screening pilots was developed for primary care leads and collaborative educational sessions were held with primary care providers and FNIM provider groups. CCO collected recruitment related data from each pilot site quarterly, and collected patient-level data (e.g., provider-referred vs self-presenter, number of people found eligible for screening) monthly. Recruitment events were also tracked. **Result:** Based on early results, June to November 2017, 1038 eligible individuals were recruited across the three pilot sites. The leading methods of recruitment were physician referrals, newspaper advertisements, word of mouth and nurse practitioners. The majority of individuals, 60.4%, were referred by family doctors. 13.2% indicated newspaper advertisements as source of recruitment. 6.3% were recruited through word of mouth and 6.0% were recruited through nurse practitioners. Approximately 27% of eligible individuals were recruited from low income postal codes (average annual household income < $70,000 CAD). 6.3% of eligible individuals identified as FNIM. Updated data will be presented at the conference. **Conclusion:** Early results have shown that provider-led recruitment strategies have been an effective method in enlisting individuals and is the primary source of recruitment for the pilot. However, recruitment of higher risk individuals such as FNIM and those with a lower socioeconomic status remains low. CCO is working with pilot sites and organizational partners to better understand how to engage and recruit these higher risk individuals.

P2.11 SCREENING AND EARLY DETECTION
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P2.11-06 A NEW HISTOPLASMOSIS ANTIBODY ENZYME IMMUNOASSAY FOR THE DIAGNOSIS OF LUNG BENIGN NODULES

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Background: Granulomas caused by infectious lung diseases often present as indeterminate pulmonary nodules on radiography. Newly available antibody enzyme immunoassay (EIA) test for histoplasmosis has not been studied for the evaluation of lung nodules suspicious for cancer. This study investigates serum biomarkers for histoplasmosis measured by a new CLIA-certified test as a response to exposure when positive and as a predictor of benign disease in indeterminate pulmonary lung nodules from a highly endemic region. **Method:** 376 serum samples from our biorepository of patients presenting with pulmonary nodules ≤30mm in maximum diameter were analyzed for histoplasmosis by the IgG and IgM EIA. Manufacturer-suggested levels for histoplasmosis diagnosis was used to indicate a positive test for antibodies. Final diagnosis was determined pathologically or by radiographic follow-up. Diagnostic test characteristics with 95% confidence intervals (CI) for benign lung disease were estimated. **Result:** Cancer prevalence was 59% (n=223). Seventy-seven (20%) samples were positive for IgG anti-*Histoplasma* antibodies (Table 1). Twenty-one (5.6%) were IgM antibody positive and 84 (22%) were positive for either antibody. Positive diagnostic likelihood ratios (DLR) for benign disease were 3.22 (95%CI: 2.08,4.98) for IgG antibodies, 6.19 (95%CI: 2.13,18.1) for IgM antibodies each separately, and 2.92 (95%CI: 1.95,4.37) if either IgG or IgM were positive. When both IgG and IgM antibodies were positive then DLR was 42.2 (95%CI: 2.54,702). When both IgG and IgM were found (n=14), no nodules were cancerous. Only a positive EIA test offered clinically informative results. **Conclusion:** A positive EIA test for both IgM and IgG strongly suggests benign granuloma and ruled out lung cancer for 9% of benign nodules arising from a highly endemic area of the country. The new EIA test may improve the diagnostic evaluation of indeterminate pulmonary nodules and avoid harmful invasive biopsies. Additional investigation in conjunction with other non-invasive cancer biomarker tests is warranted.

Keywords: Benign Biomarker Diagnosis

P2.11-07 LUNG CANCER IN A TERTIARY CARE SETTING: SO NEAR, YET SO FAR

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Background: Lung cancer patients usually present in advanced stage. Once diagnosed, these patients do not take treatment/tend to leave it in-between, because of various financial and psychosocial problems, and issues related to administration of chemotherapy and side effect profile. If diagnosed at an early stage, lung cancer has a high overall 5 year survival. In developing countries, with a high burden of lung cancer and its associated morbidity and mortality, there is a need to screen the 'at risk' population, thus facilitating early diagnosis. Lung cancer patients were hence studied at presentation and followed upto 10-12 weeks after diagnosis. The utility of a biomarker, Heat shock protein 90-beta (Hsp 90-beta) was assessed alongwith. **Method:** 60 individuals were included: 20 histologically/cytologically proven patients of lung cancer before treatment initiation(Group A), 20 patients with benign lung diseases(Group B) and 20 apparently healthy individuals(Group C). After thorough investigations and staging(TNM classification), patients of Group A were administered chemotherapy (NCCN guidelines), and followed upto 10-12 weeks after diagnosis. Also, 5ml of venous blood was collected from all individuals for Hsp90-beta evaluation by ELISA. **Result:** In Group A,1/20 patient was diagnosed with stage 3, rest 19/20 patients were diagnosed with stage 4 lung cancer. Predominant histopathological type was squamous cell carcinoma(14/20 patients), followed by adenocarcinoma(4/20) and small cell carcinoma(2/20). At follow up, 35% (7/20) patients were dead/lost to follow up. 13 patients were given chemotherapy, 10/13had partial response and 3/13 had progressive disease(RECIST Criteria). The 3groups were age and gender matched. Mean serum Hsp90-beta levels were 242.850, 129.825 and 107.150ng/ml in group A,B and C respectively. Group A had significantly higher levels ($p<0.0005$, cut off value:146.5ng/ml, 95%sensitivity and specificity). The levels did not differ with histological type/stage of cancer. At follow up, in 13 patients of Group A, mean Hsp90-beta levels showed an increase. **Conclusion:** Majority of the patients presented in stage 4 signifying the urgent need of a diagnostic/screening tool for detection in early stages. Also, various factors which could be responsible for a high attrition rate due to death/lost to follow up need to be studied, so that specific interventions can be planned. Serum Hsp90-beta could be a valuable biomarker in diagnosis/screening of lung cancer. However, its prognostic role needs elucidation. Detailed studies with larger sample size, different histologies and different stages are required to establish various strategies for early diagnosis and timely comprehensive management, so as to drive the final treatment outcomes in a positive direction.

Keywords: lung cancer, staging, diagnosis

P2.11-08 TUMOR AUTOANTIBODY PANEL CAN IMPROVE THE ACCURACY OF EARLY DIAGNOSIS IN LUNG CANCER PRESENTING WITH GGNS /SOLID NODULES

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Background: Autoantibody is an attractive diagnostic approach for early detection of malignant tumors. We performed this study to validate the performance of an autoantibodies (TAAs) panel (p53,PGP9.5,SOX2,GAGE7,GBU4-5,MAGE A1,CAGE) to aid early diagnosis of lung adenocarcinoma with ground-glass nodules (GGNs) and/or solid nodules in Chinese population and to find an effective simple blood test which can be used in further assessing the risk of lung cancer being present GGNs and/or nodules. **Method:** A prospective audit was conducted on 540 individuals known to have GGNs and/or lung nodules. These patients included 311 pulmonary malignant or borderline lung diseases, 229 lung benign GGNs and/or nodules. We detected TAAs quantitation by ELISA method. **Result:** The sensitivity and specificity of autoantibody assay were 48.6% and 92.7% respectively. In lung invasive adenocarcinoma, the sensitivity of autoantibody assay was 51.9%. When the seven-autoantibody panel test was combined with CT imaging in patients with GGNs and/or nodules, the accuracy was increased to 90.42%.

Table Sub-analysis in lung malignant or borderline diseases

	TAAs-	TAAs+	P value	MiRNA-	MiRNA+	P value	Total-	Total+	P value
Gender, *n* (%)									
Male	181 (63.7%)	107 (57.5%)	0.208	180 (64.5%)	108 (56.5%)	0.084	152 (65.0%)	136 (57.6%)	0.108
Female	103 (36.3%)	79 (42.5%)		99 (35.5%)	83 (43.5%)		82 (35.0%)	100 (42.4%)	
Age, *n* (%)									
≤70	238 (83.8%)	153 (82.3%)	0.706	234 (83.9%)	157 (82.2%)	0.707	195 (83.3%)	196 (83.1%)	1.000
>70	46 (16.2%)	33 (17.7%)		45 (16.1%)	34 (17.8%)		39 (16.7%)	40 (16.9%)	
Smoke status, *n* (%)									
Smoker	152 (53.5%)	102 (54.8%)	0.850	140 (50.2%)	114 (59.7%)	0.048	118 (50.4%)	136 (57.6%)	0.139
Non-smoker	132 (46.5%)	84 (45.2%)		139 (49.8%)	77 (40.3%)		116 (49.6%)	100 (42.4%)	
GGNs size, *n* (%)									
≤8mm	141 (49.6%)	78 (41.9%)	0.109	154 (55.2%)	65 (34.0%)	<0.001	138 (59.0%)	81 (34.3%)	<0.001
>8mm	143 (50.4%)	108 (58.1%)		125 (44.8%)	126 (66.0%)		96 (41.0%)	155 (65.7%)	
Number of GGNs, *n* (%)									
≤3	229 (80.6%)	122 (65.6%)	<0.001	219 (78.5%)	132 (69.1%)	0.024	191 (81.6%)	160 (67.8%)	0.001
>3	55 (19.4%)	64 (34.4%)		60 (21.5%)	59 (30.9%)		43 (18.4%)	76 (32.2%)	
GGN Type, *n* (%)									
Pure GGN	114 (40.1%)	56 (30.1%)	0.031	113 (40.5%)	57 (29.8%)	0.019	102 (43.6%)	68 (28.8%)	0.001
Mixed GGN	170 (59.9%)	130 (69.9%)		166 (59.5%)	134 (70.2%)		132 (56.4%)	168 (71.2%)	

Conclusion: The greatest impact of using the new seven-autoantibody panel was the highly significant improvement in the sensitivity and specificity of the test in the clinical setting. Our study suggested that the seven-autoantibody panel can be combined with CT imaging to aid diagnosis of lung cancer with GGNs and/or solid nodules.

Keywords: early diagnosis, tumor autoantibody panel, lung cancer, ground-glass nodules (GGNs)

P2.11-09 UNCOMMON EGFR MUTATION ANALYSIS FROM URINE OF LUNG CANCER PATIENTS

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Background: Lung cancer is a type of cancer with a very high mortality rate, mostly caused by misdiagnosis of the cancer during early stage when most of the treatment are supposed to be adequate. A type of medical diagnosis known as molecular diagnosis has been developed to alleviate this problem. One example of this diagnosis method is targeted therapy on specific DNA for biomarking. In Non-Small Cell Lung Cancer (NSCLC), mutation in EGFR gene will activate Tyrosine Kinase response and the decay of auto inhibitor system. The standard method to identify EGFR mutations is tissue biopsy that requires the sampling of tissue. A secondary method using molecular diagnosis has been developed to increase the succes rate of the lung cancer diagnosis. Plasma circulating tumor DNA (ctDNA) is a DNA fragment which contains tumor-specific alteration, mostly found in body fluids such as blood, urine, saliva, sputum, and pleura. ctDNA fragments in urine can easily be sampled for biopsy, a type of molecular analysis on the urine to look for these altered DNAs can be used as another option for lung cancer detection as well. **Method:** A total of 30 frozen urine sample were collected from NSCLC patients. The patients were diagnosed with positive EGFR mutation from the cell line. The exon 18 and 20 of EGFR were the target for mutational analysis, ctDNA from urine was amplified using polymerase with original primer for sequencing. **Result:** Among 30 samples, 6% was detected as G719X mutations, 50% detected as T790M mutations, 60% was detected as Q787Q mutations. Urine samples was determined as viable testing methods like DNA direct sequencing from tissue. **Conclusion:** Lung cancer harboring exon 18 and exon 20 mutations can be detected using DNA direct sequencing method. The use of urine biopsy was proven to be viable as an alternative to tissue biopsy when tissue isn't available for molecular testing.

Keywords: ctDNA, EGFR mutation, urine liquid biopsy

P2.11-10 POTENTIAL UTILITY OF A POSITIVE EARLYCDT®-LUNG BLOOD BIOMARKER TEST IN INDETERMINATE PULMONARY NODULES

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Background: EarlyCDT®-Lung is a blood-based biomarker of risk for lung cancer and is able to detect early stage disease. Indeterminate pulmonary nodules (IPN) of 8-20 mm are a common clinical problem. Approximately 20% of IPNs are malignant in many series, but determining which ones are malignant versus benign is a dilemma. The ACCP guidelines recommend surgical resection for IPN of high risk for malignancy (>65%). A moderate positive EarlyCDT-Lung (sensitivity 40%; specificity 93%) has been shown to increase the risk of malignancy in IPNs of intermediate risk (10-65%) (Massion et al J Thorac Oncol 2017). **Method:** We evaluated 48 patients from a clinical audit with an IPN and a calculated risk of malignancy of >30% based on the Mayo/Swensen calculator. **Result:** Twenty-five patients had benign nodules and 23 were proven to be lung cancer. The positive predictive value (PPV) of the calculator alone was 48%. The biomarker test was positive in 23% (11 of 48) of the population (>30% risk). Ten of these 11 were proven to be lung cancer and one was benign; PPV of 91%. This 9% rate for benign disease is a marked improvement from the average resection rate of 20-25% for benign disease that has been reported in multiple lung cancer screening trials (24% in NLST). **Conclusion:** Combining the EarlyCDT-Lung blood test with calculated risk of IPNs of >30% resulted in a high PPV and would result in a resection rate of IPNs for benign disease of <10%. A prospective clinical utility study with EarlyCDT-Lung and IPNs is planned.

Keywords: indeterminate pulmonary nodules, Blood Biomarker, lung cancer

P2.11-11 IDENTIFICATION OF THE GENETIC DETERMINANTS OF SUSCEPTIBILITY TO LUNG CANCER IN A MOROCCAN COHORT

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Background: Lung cancer is the most common cause of death from cancer worldwide, estimated to be responsible 1.59 million deaths, representing 19.4% of all cancer types. Representing 80–85% of all cases non-small cell lung cancer (NSCLC) is the most predominant type of lung cancer. Lung cancer has been recognized as a complex multifactorial disease resulting from the interactions between various genetic and environmental factors. Identification of genes involved in the occurrence and development of lung cancer could contribute to further understanding of the underlying mechanisms, and even a very important additional appropriate prevention strategies and targeted treatments for reducing lung cancer burden. Many studies have suggested that key cytokines in inflammation pathways may exert important roles in the etiology of lung cancer. The aim of this study was to investigate whether common variants in inflammatory and immune response genes influence lung cancer risk in Moroccan patients. **Method:** Using a candidate gene approach, 9 single nucleotide polymorphisms (SNPs) in 5 genes were assessed in 308 controls and 120 lung cancer patients. Genotyping was performed with the TaqMan® allelic discrimination technology. The results were analysed using SPSS 24.0 software. **Result:** Among the 5 studied genes, we found a significant association for the IL17A (rs7747909) polymorphisms, IL-6_rs2069840a trend of association was observed for without reaching the significance level. No significant association was observed for the remaining SNPs in the following genes: MIF_rs755622, IL-6R_rs2228145, IL6ST_rs2228044, TYK2_(rs2304856, rs34536443, rs35018800), STAT3 rs2293152. **Conclusion:** The results founded suggest the important role of genetically determined high inflammatory response in the pathogenesis of lung cancer in the Moroccan population.

Keywords: lung cancer risk, Inflammatory system, Moroccan population

P2.11-12 METABOLOMIC ANALYSIS IN LUNG CANCER FOR SCREENING AND EARLY DETECTION

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Background: Metabolomics, a simultaneous measurment technique for hundsleds of low weight molecules, generally called metabolites, is an effective technique to understand how metabolism is changed by various factors, including environment and diseases, particularly malignant diseases. Body fluids, such as urine or saliva, harvested non-invasively have been used in this analytical technology, which yielded a potential of precise diagnosis of various cancers. Metabolomic analysis has begun to be reported based on the pattern information of metabolites. It can be used for practical clinical early detection of carcinoma of various organs. However, practical metabolomic analysis regarding lung cancer has not been repored yet. We used surgically resected specimen of lung cancer to analyze and clarify metabolomic profiles as an aspect of lung cancer. **Method:** We obtained blood and saliva from 110 patients with lung cancer after obtaining informed consent for this study and compared the metabolomic profiles of both blood and saliva in 83 who has neither pulmonary disease nor past history of any cancer in terms of various clinical aspects. Metabolomic analysis was performed by capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS) of metabolites of the blood and saliva, then analysed ionized sample which contained the most metabolites in primary pathways. **Result:** Analysis of serum and metabolite organization by CE-TOFMS revealed that the intermediate metabolite levels of several pathways changed markedly in lung cancer blood and saliva. We identified characteristic metabolomic patterns in advanced lung cancer with metabolomic clinical information by analysing the association with the overall metabolism profile. **Conclusion:** We identified metabolomic biomarkers which were characteristic of lung cancer using blood and saliva in this study. At present, we are analysing various body fluids for analysis of lung cancer cases including prognostic implications. Applications to non-invasive, simple, easy and low-cost cancer screening are expected in the future.

Keywords: metabolomics, lung cancer, Early Detection

P2.11-13 PRECISE EARLY DETECTION OF LUNG CANCER AND BLOOD CELL CIRCUIT

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Background: Significance of blood cell circuit in terms of early detection of lung cancer (LC) was investigated. **Method:** In trial (1987-2018) consecutive cases after surgery, monitored 115 LC patients (LCP) (m=100, f=15; lobectomies=115) with pathologic stage IA (tumor size=1.86±0.30 cm; squamous=51, adenocarcinoma=59, large cell=5; T1N0M0=115; G1=39, G2=42, G3=34, 5-year survival=100%) and 120 healthy donors (HD) (m=69, f=51) were reviewed. Variables selected for study were input levels of blood cell circuit, sex, age, TNMG. Differences between groups were evaluated using discriminant analysis, clustering, nonlinear estimation, structural equation modeling, Monte Carlo, bootstrap simulation and neural networks computing. **Result:** It was revealed that early detection of LC from HD (n=235) significantly depended on: leucocytes (abs, total), segmented neutrophils (%, abs, total), lymphocytes (%), monocytes (abs, total) (P=0.012-0.000). Neural networks computing, genetic algorithm selection and bootstrap simulation revealed relationships of early detection of LC and lymphocytes (rank=1), stick neutrophils (rank=2), monocytes (3), segmented neutrophils (4), leucocytes (5), eosinophils (6). Correct detection of early LCP was 100% by neural networks computing (error=0.000; area under ROC curve=1.0). **Conclusion:** Early detection of LC from HD significantly depended on blood cell circuit.

P2.11-14 MALIGNANCY ASSOCIATED CHANGE AND THE LUCED® TEST FOR DETECTION OF EARLY STAGE LUNG CANCER

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Background: Early detection remains the most reliable and effective strategy for curing lung cancer. Many approaches, however, are limited by poor sensitivity or specificity that increase health care costs and potentially risk patient health through unneeded procedures. The association between cell morphology and cancer has been established in the pathology literature. However, through the so-called field effect, cancer can introduce subtle morphological changes into non-cancerous cells that are proximal to the tumor site. The Cell-CT™ platform and LuCED® test represent a promising new method for detecting lung cancer with high (92%) sensitivity and (95%) specificity based on cytologically abnormal cells. In this research we investigate use of the Cell-CT to detect malignancy associated changes in normal cells near the cancer with a view towards enhancing LuCED test performance. **Method:** We present a study of 3D morphological alterations in non-cancer cells obtained from sputum of healthy subjects and biopsy confirmed lung cancer patients. Three major cell types were analyzed from 235 patients: bronchial epithelial columnar, squamous intermediate, and mature macrophages. We used the Cell-CT™ platform to measure over 700 different structural biomarkers for each cell. The measurements were used to define prominent clusters of cells through a hierarchical process that were then used under supervised learning, with case status as ground truth, to create classifiers that optimally separated cells from cancer vs. normal cases. **Result:** The table gives classifier development and performance characteristics:

Cell Type	Number of cells from cancer patients	Number of cells from normal patients	Cluster-based Supervised Learning – aROC
Squamous Intermediate	2316	684	0.94
Macrophages	4960	5040	0.94
Columnar cells	3227	3234	0.92

Conclusion: Our results indicate that the Cell-CT can discriminate cell features that are too subtle to distinguish by a human. The study suggests that detection of cells with Malignancy Associated Changes may be used to further enhance the LuCED test's performance beyond published levels.

Keywords: Cell-CT, The LuCED test, Early Detection

P2.11-15 IDENTIFYING PATIENTS FOR WHOM LUNG CANCER SCREENING IS PREFERENCE-SENSITIVE: A MICROSIMULATION STUDY

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Background: Many health systems are still exploring how to implement an effective, patient-centered low-dose computed tomography (LDCT) screening program. **Objective:** Examine factors that influence when LDCT screening is preference-sensitive. **Method: Design:** State-transition microsimulation model **Data Sources:** Two large randomized trials, published decision analyses, and the Surveillance, Epidemiology and End-Results cancer registry **Target Population:** US-representative sample of simulated patients meeting current US Preventive Services Task Force screening eligibility criteria **Time Horizon:** Lifetime **Perspective:** Individual **Intervention:** LDCT screening annually for 3 years **Outcomes Measures:** Lifetime quality-adjusted life-year gains and reduction in lung cancer mortality. To examine the effect of preferences on net benefit, we varied disutilities (i.e., negative feelings) quantifying the burden of screening and follow-up across a likely range. We also examined the effect of varying the rate of false-positive scans and overdiagnosis associated with screening. **Results of Base-Case Analysis:** Moderate differences in preferences about the downsides of LDCT screening influenced whether screening was appropriate for eligible persons with < 0.3% annual lung cancer risk or life-expectancy < 10.5 years. For higher-risk eligible persons with longer life-expectancy, roughly 50% of the study population, LDCT screening overcame even highly negative views about screening and its downsides. **Results of Sensitivity Analysis:** Rates of false-positive findings and overdiagnosed lung cancers were not highly influential. **Limitation:** The quantitative thresholds we identified may vary depending on the structure of the microsimulation model. **Conclusion:** Identifying circumstances under which LDCT screening is more vs. less preference-sensitive may help clinicians personalize their approach to discussing LDCT screening, tailoring to both preferences and clinical benefit. THIS ARTICLE HAS BEEN ACCEPTED FOR PUBLICATION IN THE ANNALS FOR INTERNAL MEDICINE. Given its relevance, we would like the opportunity to present our findings at the WCLC

Keywords: Preference sensitive, Risk-thresholds, CT screening

P2.11-16 COMPARISON OF TWO LUNG CANCER SCREENING PROGRAMS IN ONE MEDICAL CENTER - DOES EXPERIENCE OF THE SCREENING TEAM AND INDICATIONS AFFECT THE RESULTS?

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Background: Onset of lung cancer (LC) screening programs in Europe is expected in near future in form of stepwise process. Yet, several issues need improvement. We compared two screening programs performed in Gdańsk, Poland by one multidisciplinary team in over 14,000 individuals – Pomeranian Pilot Lung Cancer Screening Program (PPP) and Moltest Bis (MB). We assessed how do the indications and learning curve affect results. **Method:** Between 2009-2011, 8,649 healthy volunteers (aged 50-75, >20 pack-years) were recruited to PPP. Between 2016-2017, 5,534 healthy volunteers (aged 50-79, >30 pack-years) entered MB. Early MB results are presented as it will be closed in May 2018. Positive computed tomography's (LDCT) result in the first round led to secondary screening. Three rounds of LDCT screening in PPP and two rounds in MB were performed in suspected lung nodules. All positive results were assessed by this same multidisciplinary team. **Result:** Detection rates of lung nodules requiring follow-up were 34.7% of PPP and 17.6% of MB subjects (p<0.0001). LC was diagnosed in 107 (1.24%) PPP and 105 (1.90%) MB participants (p=0.0016). Three hundred (3.5%) PPP and 199 (3.6%) MB patients were referred for further diagnostic work-up (p=0.6890). Yet, more MB patients were sent for diagnostic work-up after first screening round - 85.9% vs 75.7% in PPP (p=0.0050). Fine needle aspiration biopsy was more often positive among LC subjects in MB (84.7% vs 54.0% in PPP; p=0.0002). Surgical resection was performed in 125 (1.5%) PPP and 80 (1.5%) MB patients (p=0.7385), with 19.2% and 15.0% of futile interventions, respectively. Lobectomies or segmentectomies were performed in 84.0% and 90.0% of LC patients in PPP and MB, respectively (p=0.2160). MB patients more often

underwent video-assisted thoracoscopic resections – 73.0% vs 24.0% in PPP (p<0.0001). Complication rates were comparable in both programs – 11.2% in PPP vs 17.1% in MB (p=0.0560). Majority of subjects with non-small cell lung cancer (NSCLC) had stage I or II – 86.4% in PPP and 83.4% in MB (p=0.442). Rate of stage I NSCLC within surgical group was higher in MB (86.0% vs 79.0% in PPP; p<0.001). **Conclusion:** Narrower inclusion criteria (>30 pack-years) and increased upper age limit (79 years) led to higher detection rate and number of operated early stage NSCLC patients. Experience gained in PPP has resulted in reduction of number of nodules requiring follow-up but not reduction of "unnecessary" diagnostic work up and surgical treatment. Minimally invasive surgery was applied significantly more often with broader experience.

Keywords: low-dose computed tomography, Screening, lung cancer

P2.11 SCREENING AND EARLY DETECTION
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.11-17 MICRORNAS IN EXHALED BREATH CONDENSATE AND BRONCHIAL BRUSHINGS AS BIOMARKERS FOR EARLY DIAGNOSIS OF LUNG CANCER

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Background: Lung cancer is one of the primary causes of death worldwide. According to Global Burden of Disease (GBD), highest prevalence and mortality of NSCLC is found in men in India. These typically may present as nodules or masses in the lung. The circulating microRNAs delineate stable and reproducible markers for lung cancer and may play important role in non-invasive diagnostic marker. We have previously discovered miRNA signatures in the exhaled breath condensate (EBC) that are suitable for early diagnostics of various lung diseases. Since miRNAs have roles in the pathogenesis of lung diseases, they can be potentially useful in the early diagnosis of lung cancer and may as well complement the other conventional investigative methods such as low dose computerized tomography (LDCT) to avoid high false positive rates. Due to paucity of thoracic surgeons and interventional bronchoscopists in India, the inaccessibility of the suspected tumor tissue for pathological diagnosis is a big challenge. All India Institute of Medical Sciences, New Delhi is one of the pioneer institutions that provides medical care to patients coming from different ethnic and socioeconomic backgrounds in India. Based on our previous work and expertise in this area along with emerging consensus in the field, this work is expected to yield promising outcomes. **Method: Exhaled Breath Condensate Collection:** Samples were collected from the suspected NSCLC patients during OPD by using RTube. miRNA isolation from c-DNA synthesis using Quantimir qPCR kit qPCR reaction setup for profiling **Bronchoscopy procedure:** Bronchial brushings were collected after obtaining written informed consent during routine diagnosis. miRNA isolation c-DNA synthesis by using Kit from Applied Biosystems qPCR reaction setup by using Kapafast SybrGreen **Result:** In this study, we found the pro tumorigenic miRNAs like miR-19a, miR-33b, miR-558 are found to be upregulated and anti-tumor miRNAs like let7b, miR-132 and miR-181c found to be downregulated in the exhaled breath of NSCLC patients. Further we validated these miRNAs in bronchial brushings samples taken from respected patients. Surprisingly; those miRNAs showed positive trend. **Conclusion:** In this study, we have found various differentially expressed MicroRNAs in the exhaled breath as well as bronchial brushings samples taken from diagnosed NSCLC patients. The known pro tumorigenic miRNAs were found to be upregulated and anti tumorigenic miRNAs were downregulated. Hence, these biomarkers could either be used as a preliminary non-invasive screening method for the diagnosis of NSCLC. Apart from this, these identified miRNAs could be novel therapeutic targets for the treatment of NSCLC.

Keywords: NSCLC, miRNAs, EBC

P2.11 SCREENING AND EARLY DETECTION
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.11-18 A COMPREHENSIVE LUNG CANCER SCREENING PROGRAM: 5 YEARS IN REVIEW

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Background: Lung cancer screening provides an opportunity for early detection, improved survival and tobacco cessation. The purpose of this report is to provide outcome measures and lessons learned during the first five years at Stony Brook's Center for Lung Cancer Screening and Prevention. **Method:** The screening programs' REDCap database was queried for the results. Demographic information, CAT scan data, lung cancer diagnoses, adherence rates, and tobacco cessation rates were computed. **Result:** TCLCSP has enrolled 825 patients. 26 patients (3.15%) were diagnosed with lung cancer.

Table 1:

DISTRIBUTION OF LUNG CANCER CELL TYPE AND STAGE. N=26 LUNG CANCERS OF 825 PATIENTS				
	Adenocarcinoma	Squamous Cell	Carcinoid	Small Cell Carcinoma
Number (%)	21 (80)	3 (12)	1 (3.5)	1 (3.54)
1A n(%)	16 (62)	3 (12)	1 (3.5)	1 (3.5)
1B n(%)	1 (3.5)	0 (0)	0 (0)	0 (0)
2A n(%)	3 (12)	0 (0)	0 (0)	0 (0)
2B n(%)	0 (0)	0 (0)	0 (0)	0 (0)
3A n(%)	1 (3.5)	0 (0)	0 (0)	0 (0)
3B n(%)	0 (0)	0 (0)	0 (0)	0 (0)
4 n(%)	0 (0)	0 (0)	0 (0)	0 (0)

Demographic, CAT scan, Adherence and Tobacco cessation rates are reported in *Table 2*. *Table 2: Demographic characteristics and results*:

Demographic Variable	% of patients
Gender – Male/Female	60%/40%
Current Smoker	42%
NCCN 1 Criteria	78%
NCCN 2 Criteria	22%
Mean Age	60
Number of Pack Years	46 mean +/- 24 SD
History of Lung Disease	23%
History of other cancer	27%
Family history of lung cancer	26%
LUNG RAD 1	28%
LUNG RAD 2	51%
LUNG RAD 3	15%
LUNG RAD 4	6%
CAT scan with incidental findings	45%
Screening patients diagnosed with LUNG CANCER	3.15%
Screening patients diagnosed with other (than lung) cancer	.36%
Adherence (CT done within 3 months of recommended date) Rates	86%
Tobacco Reduction (Self reported decreased smoking rates) Rates	55%
Tobacco Cessation (Self reported tobacco cessation for 6 months) Rates	35%

Lessons Learned: Program Growth and Maintenance: Program growth has a direct relation to advertisement, community education and satisfactory reviews from PCPs. Low cost poster and brochure advertisements are effective. Database is key. *Adherence:* Successful adherence requires education, positive experience, distress management and a patient coordinator. *Tobacco Cessation:* Tobacco cessation counseling success is dose dependent & telephone counseling provides added opportunities. Tobacco reduction plans are a viable option. **Conclusion:** Lung cancer screening program success is achievable with ongoing outcome reviews and program revisions as needed. The lung cancer screening patient population will benefit from shared program information and ongoing research.

Keywords: lung cancer screening, Tobacco Cessation

P2.11 SCREENING AND EARLY DETECTION
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.11-19 MICRORNAS AS LIQUID BIOPSY BIOMARKERS FOR EARLY DETECTION IN LUNG CANCER.

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Background: microRNAs (miRNAs) control the expression of key driver genes associated with tumorigenesis in several cancer types and can be detected as stable circulating molecules in body fluids. Deregulated miRNAs have been identified as potential biomarkers in plasma from cancer patients. In lung cancer, the most promising clinical application of circulating miRNAs is early disease detection, since late diagnosis is a major clinical problem associated with patient death. **Method:** 38 plasma samples from patients with lung adenocarcinoma and squamous cell carcinoma and 21 healthy controls from a screening population were profiled for an 800 miRNA set using the Nanostring nCounter® platform. Validation was performed in an independent sample set of 40 patients and 40 controls, paired by age and sex, using TaqMan® quantitative real-time PCR. Statistical analyses were performed using the Mann Whitney test, and miRNA signatures identified by Elastic net, improved Maximizing R Square Analysis (MARSA) and C-Statistics. Bioinformatic approaches were applied for external data validation against other miRNA expression datasets. **Result:** A subset of 149 miRNAs was significantly over-expressed in patient plasma compared to controls with fold change ≥ 2, $p \leq 0.01$ and FDR<0.05. In addition, three distinct miRNA signatures with 12 unique miRNAs were identified in the discovery set (hsa-miR-16-5p, hsa-miR-92a, hsa-miR-106b-5p, hsa-miR-148b-3p, hsa-miR-155-5p, hsa-miR-217, hsa-miR-378e, hsa-miR-451, hsa-miR-484, hsa-miR-1285-3p, hsa-miR-1285-5p and hsa-miR-664a-3p). All signatures were validated in the independent sample set, being able to distinguish patients from controls. Interestingly, miRNAs identified herein control the expression of tyrosine kinase, transcription factors and immune system related genes associated with lung tumorigenesis. **Conclusion:** By using a highly specific and sensitive assay and stringent criteria on sample selection and data analyses, we were able to identify known and novel miRNAs that are significantly deregulated exclusively in plasma from patients with a diagnosis of lung adenocarcinoma or squamous cell carcinoma. Our results contribute to the identification of circulating plasma miRNAs as potential biomarkers for early disease detection in lung cancer.

Keywords: microRNA, liquid biopsy, early disease detection

P2.11 SCREENING AND EARLY DETECTION
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.11-20 LUNG EPICHECK™ - RESULTS OF THE TRAINING AND TEST SETS OF A METHYLATION-BASED BLOOD TEST FOR EARLY DETECTION OF LUNG CANCER

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Background: Lung cancer is the leading cause of death from cancer worldwide. Screening with low-dose CT reduces mortality but is associated with substantial cost and harm[1]. Dying tumor cells release cell-free DNA (cfDNA) [2], where cancer-specific methylation changes can be detected[3]. [1] NLST. NEJM2011;365:395-409 [2] Rauch et al. ProcNatlAcadSciUSA2008;105:252–257 [3] Diehl et al. NatMed2008;14:985–990 **Method:** Plasma was collected from 23 centers and biobanks in Europe and Israel under IRB & informed consent. Inclusion criteria Cases Pathologically confirmed primary lung cancer Treatment naïve Controls Age 50-80 years Current/former smoker Exclusion criteria (*cases only*) Current diagnosis or history of cancer *(other than lung cancer)* Lung EpiCheck is a blood test that detects lung cancer-associated hypermethylation changes in 6 markers in cfDNA using real-time PCR. The algorithm for calculating EpiScore as well as the threshold for positivity were decided based on the training set and then tested on an independent test set. **Result:**

Table 1. Subject character-istics	Training set		test set	
	Cases	Controls	Cases	Control
Number	102	265	181	141
Age				
Range	51-83	50-82	23-90	51-88
Average	66	63	66	64
Gender # (%)				
Male	70 (69)	162 (61)	133 (73)	90 (63)
Female	32 (31)	103 (39)	48 (27)	51 (36)
Histology subtype # (%)				
Adenocarci-noma	44 (43)		77 (43)	
Squamous cell carci-noma	37 (36)		67 (37)	
Other NSCLC	8 (8)		18 (10)	
Small cell lung cancer	10 (10)		13 (7)	
Other	3 (3)		6 (3)	
Stage NSCLC # (%)				
I	26 (28)		39 (23)	
II	21 (23)		26 (15)	
III	23 (25)		62 (37)	
IV	19 (21)		36 (21)	
Unstaged	3 (3)		5 (3)	

Table 2. Lung EpiCheck performance	Training set	Test set
AUC	0.890	0.887
Specificity	94%	91%
Sensitivity		
Overall	74%	74%
Histological subtype*		
Adenocarcinoma	57%	71%
Squamous Cell Carcinoma	78%	73%
Other NSCLC	88%	50%
Small cell carcinoma	90%	92%
Unknown	50%	71%
NSCLC		
Stage I	50%	59%
Stage II	67%	77%
Stage III	82%	76%
Stage IV	94%	83%
Unstaged	100%	40%
Small cell lung cancer		
Limited	67%	100%
Extensive	100%	86%

Conclusion: Such promising results combined with the simplicity of the test, could offer added value in the fight against lung cancer.

Keywords: biomarker, methylation, Early Detection

P2.11 SCREENING AND EARLY DETECTION
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.11-21 FACTORS PREDICTING ATTRITION IN COMMUNITY-BASED HEALTHCARE NETWORK LUNG CANCER SCREENING PROGRAMS

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Background: Since publication of the National Lung Screening Trial, the national focus has been on implementation of Lung Cancer Screening Programs (LCSPs). However, lung cancer screening (LCS) is a continuum where the benefits are derived from long-term engagement and, to date, little is known about attrition in LCS. We aimed to identify the rate of attrition within two of our healthcare network, community-based LCSPs and identify the factors predictive of attrition. **Method:** We reviewed 2364 individuals who underwent LCS within two of our healthcare network LCSPs from 01/01/2012-03/31/2017. One LCSP is centralized (shared decision making/evaluation/management at a single site) and the other is decentralized (shared decision making/evaluation/management occur in geographically diverse community care settings with support from a central LCSP coordinator). Attrition was defined as declining further screening or lost to follow-up. Continuous data reported as median and 25th-75th interquartile range, and univariate/multivariable logistic regression analyses was performed to identify predictors of attrition. **Result:** We identified an attrition rate of 15% (351/2364) with median time to attrition of 15 (12-20) months. Patients who underwent attrition tended to be younger [62 (58-67) versus 65 (60-69) years, $p<0.001$], smoking on first visit (61% versus 55%, $p=0.05$), in the decentralized program (74% versus 67%, $p=0.01$), and less likely to have a nodule on first CT scan (48% versus 64%, $p<0.001$). Multivariable logistic regression demonstrated a younger age, decentralized program type, and the absence of a nodule on first CT scan to be significant predictors of attrition ($p<0.05$) [Table].

Predictors of Attrition				
UNIVARIATE ANALYSIS				
Characteristic	Odds Ratio	Lower 95% C. I.	Upper 95% C. I.	P Value
Age, years	0.95	0.93	0.97	<0.001
Gender				
Female				
Male	0.88	0.70	1.11	0.29
Race				
White				
Black	1.19	0.68	2.06	0.54
Native Hawaiian/Asian	1.74	1.03	2.95	0.04
American Indian	0.49	0.12	2.08	0.33
Declined/Other	0.97	0.58	1.62	0.90
Smoking Status on 1st Visit				
Former				
Current	1.28	1.01	1.61	0.04
Distance to CT scan, miles	1.00	1.00	1.00	0.70
Program				
Centralized				
Decentralized	1.41	1.09	1.82	0.01
Nodule on 1st CT scan				
No				
Yes	0.53	0.42	0.67	<0.001
Nodule Size on 1st CT scan	0.99	0.97	1.02	0.53
MULTIVARIABLE ANALYSIS				
Characteristic	Odds Ratio	Lower 95% C. I.	Upper 95% C. I.	P value
Age, years	0.96	0.94	0.98	<0.001
Program				
Centralized				
Decentralized	1.37	1.04	1.79	0.02
Nodule on 1st CT scan				
No				
Yes	0.58	0.46	0.73	<0.001

Conclusion: Overall attrition is low at 15%. Factors that correlated with failure to follow-up were young age, active smoking, being in a decentralized program, and lack of nodule on first scan. Ongoing efforts are necessary to ensure that screening is a continuum, particularly in populations of individuals at high-risk of attrition.

P2.11 SCREENING AND EARLY DETECTION
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.11-22 USE OF ELECTRONIC MEDICAL RECORDS FOR TOBACCO USE AND LUNG CANCER SCREENING DOCUMENTATION IN A LARGE URBAN ACADEMIC MEDICINE PRACTICE

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Background: There is sufficient evidence to support lung cancer screening with low-dose computed tomography (LDCT) in high-risk current and former adult smokers. However, guidelines have not been fully translated into clinical practice. Electronic Medical Records (EMRs) efficiently collect data that can identify high-risk patients (pts) and

monitor key metrics for lung cancer screening and smoking cessation efforts. In this study, we evaluated compliance with USPTF lung cancer screening guidelines and the use of EMRs for the documentation of tobacco use. **Method:** We retrospectively reviewed data from consults in a large urban, academic, outpatient clinic between January 2017 and June 2017. We evaluated documentation in the built-in functions in a well-established EMR system (Epic) and in medical visit notes for each pt. **Result:** A total of 1,124 pt charts were reviewed. 63% of pts were female and the median age was 61 years. 39% of pts were African American, 32% Hispanic, 5% Caucasian, 1% Asian, and 23% other. All charts had documentation of smoking status in the EMR social history flowsheet. 34% (379/1124) of pts had a history of tobacco use, out of which 39% (146/379) were current smokers. For current smokers, tobacco use disorder was documented as an active issue in the EMR medical problem flowsheet in only 37% (54/146) of cases. In 66% (96/146) of cases, smoking cessation was addressed in the physician's note and smoking cessation counseling or medications were offered during the consult. 18% of smokers (69/379) met USPTF criteria, of whom 44/69 (64%) were referred for LDCT. For pts that were not referred for LDCT, 92% (23/25) had a prior CT of the chest in the last year. 82% (36/44) of pts underwent the LDCT screening test and 100% had LDCT results documented in the EMR. 47% (17/36) of screened pts had pulmonary nodules and/or findings suspicious for lung malignancy. 76% (13/17) of pts had follow-up imaging studies and 11% (2/17) of pts subsequently underwent biopsy that yielded a diagnosis of lung cancer. **Conclusion:** Our data showed suboptimal compliance with the LDCT lung cancer screening guidelines in clinical practice. Current EMR-centered databases are being well implemented for the acquisition of critical information that is integrated with care delivery. However, there are instances of poor documentation and underutilization of existing built-in flowsheets in EMR systems that could help identify active smokers, better address smoking cessation efforts, and more efficiently monitor high-risk pts in need of future screening.

Keywords: Electronic Medical Record Utilization, Screening, Early Detection

P2.11 SCREENING AND EARLY DETECTION
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.11-23 RISK PERCEPTION AMONG A LUNG CANCER SCREENING POPULATION

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Background: To make lung cancer screening feasible, populations with the highest risk of developing cancer need to be targeted. Furthermore, factors which motivate individuals to participate in lung cancer screening programs should be integrated into recruitment strategies. Among these motivators, an individual's perception of their lung cancer risk is an important consideration. This paper analyzes factors associated with risk perception in subjects enrolled in the Pan-Canadian Early Detection of Lung Cancer Study (PanCan), and assesses the relationship between subjects' risk perception and actual calculated risk. **Method:** The PanCan low-dose screening CT study recruited individuals from the general population who were current or former smokers age 50-75 having at least a 2% risk of developing lung cancer over 6 years as calculated by the PanCan model. Risk perception was captured at baseline with a 5-point Likert scale question asking the subject to assess their personal chances of being diagnosed with lung cancer compared with other smokers of the same age. Multivariate linear regression analysis was used to assess the relationship between risk factors and risk perception. Baseline risk variables in the model include demographics, smoking history, symptoms, medications, occupation, previous chest imaging, history of COPD, medical comorbidities, and family history of cancer. **Result:** 2514 patients were included in the analysis. Median age was 62.3, 55.3% were male, median pack-year smoking history was 50 years (range 2.2-230), and median calculated lung cancer risk was 3.4% over 6 years (range 2-38.2). Calculated lung cancer risk increased by 0.08% (SE 0.02, p-value=0.001) for each increase in Likert risk perception category. On multivariable analysis, the following variables were associated with risk perception category: cigarettes smoked per day (+0.003 increase in category / cigarette, p=0.083), presence of dyspnea (+0.192), presence of wheeze (+0.272), known COPD (+0.110), no family history of cancer (-0.476) and no family history of lung cancer (-0.385) (all p<0.001). Increased perception of risk was associated with intent to quit smoking within 6 months (p<0.001). **Conclusion:** In this lung cancer screening study, risk perception was positively associated with calculated risk for lung cancer, despite a minimum 2% risk in the cohort. Individual factors and family history of cancer predicted risk perception. Risk perception was also associated with a willingness to quit smoking. Self-risk perception and associated factors could be used to tailor recruitment strategies to screening programs. The link between risk perception and willingness to quit smoking could aid integrated tobacco cessation programs.

Keywords: Screening, Risk, lung cancer

P2.11 SCREENING AND EARLY DETECTION
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.11-24 IMPACT OF SCREENING INTERVAL LENGTH ON NEW NODULES DETECTED IN INCIDENCE ROUNDS OF CT LUNG CANCER SCREENING: THE NELSON TRIAL

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Background: Low-dose computed tomography lung cancer screening is recommended by US guidelines. New solid nodules are regularly found in incidence screening rounds and have a higher lung cancer probability than baseline nodules. Contrary to baseline nodules, new nodules develop within a known screening interval (time between previous screen and new nodule detection). There is limited evidence concerning the impact of varying screening interval lengths on new solid nodules. **Method:** In the randomized Dutch-Belgian Lung Cancer Screening (NELSON) Trial, 7,557 participants underwent baseline screening. Three incidence rounds took place after intervals of 12months, 24months and 30months respectively and follow-up intervals ranged from 2-12months. We included solid non-calcified nodules registered after baseline as new and not visible in retrospect. Using logistic regression, screening interval length was assessed as predictor for lung cancer whilst adjusting for nodule size. The correlation of screening interval length and new nodule size was assessed with Spearman's rank correlation. Discriminative performance for lung cancer was quantified as area under the receiver operating characteristics curve (AUC). **Result:** Overall, 1,130 new solid nodules were included with 6% being lung cancer. Of the nodules, 13% were detected after a screening interval of <10months, 28% after 10-14months, 4% after 15-21months, 37% after 22-26months, and 20% after >26months. While the proportion of new solid nodules that subsequently resolved until first follow-up decreased with longer screening interval (76%, 70%, 59%, 57%, 41% respectively, p<0.001), the lung cancer proportion significantly increased (2%, 3%, 3%, 7%, 11% respectively, p=0.001). The screening interval length was a significant predictor for lung cancer when assessed in all nodules (p=0.018). However, there was no significant association when only assessed in nodules that persisted on first follow-up (p=0.223). Compared to benign nodules, lung cancer size at initial detection correlated stronger with screening interval length (spearman's rho 0.106 vs. 0.320) and the discriminative performance of volume for lung cancer increased with screening interval length (AUC: 0.71 at 10-14months vs. 0.84 at >26months). Comparing malignant nodules detected after 10-14months, 22-26months or >26months, the proportion of stage IA lung cancers decreased (73%, 63%, 39% respectively, p=0.139) and all IIIb/IV cancers were found after >22months. **Conclusion:** The longer the screening interval prior to new nodule detection, the lower the nodule's probability to resolve and the higher the nodule's lung cancer probability. While a longer screening interval might facilitate the discrimination between benign and malignant new solid nodules, there was a trend for less favorable staging.

Keywords: incidence screening rounds, new nodules, screening interval length

P2.11-25 LUNG CANCER SCREENING IMPLEMENTATION IN COMMUNITY PRACTICE: KAISER PERMANENTE WASHINGTON EXPERIENCE 2015-2018

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Background: We describe the implementation of lung cancer screening program at Kaiser Permanente Washington (KPWA), an integrated medical insurer and healthcare provider in Washington state. Since the US Preventive Services Task Force recommendation to screen for lung cancer, data is scarce on the implementation of community experience with lung cancer screening, and whether community experience is like the experience in clinical trials. **Method:** We purposefully employed a soft-launch of our lung cancer screening program with low-dose CT (LDCT) so we could rapidly evaluate our experience through audit and feedback. The program began in January 2015 and included several key implementation components: 1) guideline review supporting lung cancer screening; 2) continuing medical education to physicians regarding implementation; 3) Epic-registry build to account for eligible members, orders for LDCT, completion of LDCT, and radiologic results; 4) Nurse care coordinator to follow-up with screen positive members to return for imaging; 5) Development of a shared decision making tool for patient/provider discussions. LDCT is read by radiologists using American College of Radiology Lung-RADS™ grading system. We describe the uptake of LDCT in an age- and smoking-eligible population and alignment of Lung-RADS™ with expected population estimates overall among exams conducted from 2015-2018. Negative screen is defined as Lung-RADS™ 1 or 2. Positive screen includes Lung-RADS™ 3 and 4. **Result:** With an estimated 15,000 adults eligible for lung cancer screening, about 1,800 annual visits have a documented shared decision-making. While the majority of patients (89%) opt-in to screening, about 26% of those patients cancel or do not show up for their LDCT exam. As of March 2018, KPWA completed 3,092 LDCT exams: 2,104 initial screens and 988 subsequent screens. Among all initial LDCT performed, 84.6% screened negative; the proportion increased slightly to 88.6% on subsequent LDCT exams. On initial LDCT, the proportion of positive exams were as follows: Lung-RADS™ 3 (7.8%); Lung-RADS™ 4A (3.3%), and Lung-RADS™ 4B, C, X (2.4%). On subsequent LDCT exams, these proportion decreased slightly to 5.2% and 2.2% for Lung-RADS™ 3 and 4A, respectively. **Conclusion:** Overall implementation of KPWA lung cancer screening suggests an ability to identify eligible patients, engage in shared decision-making, appropriate referral and uptake of LDCT, appropriate use of Lung-RADS™ assessment, and patients who return for follow-up and subsequent annual screening. Opportunities remain for improvement in acceptance of LDCT based on patient needs and further adoption within our system.

Keywords: cancer screening, community practice

P2.11-26 FIRST OF ITS KIND MULTI-PRONGED TRAINING FOR PCPS IN AN EPICENTER OF LUNG CANCER – WHAT WAS ACHIEVED IN TWO YEARS?

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Background: Kentucky's lung cancer (LC) rates have been the highest in the U.S. and amongst the highest in the world. Primary care provider (PCP) understanding and adoption of the U.S. Preventive Services Task Force (USPSTF) recommendation for LCS with low-dose CT (LDCT) were very low over a year after its release. LDCT is the only recommended tool for early detection of LC; making PCP education crucial for impacting the leading cause of cancer death. **Method:** The Kentucky LEADS (Lung cancer Education Awareness Detection and Survivorship) Collaborative was initiated to reduce the LC burden through novel interventions to promote provider education (PE), survivorship care, and prevention/early detection. The PE component sought to improve referral of high-risk patients to LCS incorporating quality shared decision-making and tobacco cessation counseling through multi-pronged continuing education (CE) programs for PCPs statewide. Four unique interventions were developed, implemented, and evaluated: an interactive online course, didactic presentations with audience response system, academic detailing with a LEADS Primary Care Toolkit, and a webinar. **Result:** Participation in these CE programs was unprecedented including 1,400+ PCPs (more than 20% of the state's total) and 2,700+ health professionals total. Participation based on platform type, provider discipline, specialty, and years in practice will be shared, as well as self-reported changes in practice behaviors as a result of the training(s) and feedback on which elements were of most value. A remarkable increase in LDCT scans in accredited facilities statewide for eligible patients after the intervention period will be discussed, as well as potential for lower numbers needed to screen for the early detection of LC in higher risk geographic areas, as compared to those for the National Lung Screening Trial (NLST), upon which the USPSTF recommendation was based. **Conclusion:** Appropriate utilization of LCS must be an urgent and pervasive priority among referring providers. Limitations for screening such as LDCT availability, patient awareness and acceptance, and negative perceptions of treatment options are being diminished. However, PCP requirements for appropriate referral must be addressed for optimal utilization of this screening tool. These include provider understanding of recommendations, eligibility, and screening risks, benefits, and limitations, as well as knowledge of available screening facilities, reimbursement for shared decision making, screening coverage, and available resources. Adoption of new screening modalities by providers and patients alike always takes time, but education for referring providers is the "next big thing" in improving LC outcomes. It is imperative that it be comprehensive, appealing, innovative, and evidence-based.

Keywords: Continuing education, Provider training, Lung cancer screening referral

P2.11-27 A RAPID ACCESS LUNG CANCER CLINIC REDUCES VARIATION IN LUNG CANCER DIAGNOSTIC AND TREATMENT SERVICES.

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Background: The Western NSW Local Health District has one of the highest incident and mortality rates of lung cancer in Australia. Previous research revealed that there was a significant variation in timely access to lung cancer diagnostic and treatment services. In 2015, the Respiratory Clinic at Dubbo Base Hospital introduced a lung cancer fast track clinic which aimed to review all patients referred by GPs for lung cancer assessment within 14 days of referral. **Method:** A retrospective medical records audit of all patients diagnosed with primary lung cancer from July 2016 to August 2017 was conducted. Interval times from Referral to Diagnosis, Diagnosis to First Treatment and Referral to First Treatment were recorded. Diagnostic and treatment referral time intervals were compared for patients residing within a 100km radius of the referral hospital (Local patients) and those whose place of residence was beyond the 100km radius (Remote patients). We also compared overall survival rates between Fast track and non-fast track pathway patients. **Result:** 55 patients were included in the study. 82%, 37% and 50% of patients met our District recommended time intervals of 21, 21 and 42 days for Referral to Diagnosis, Diagnosis to First Treatment and Referral to First Treatment, respectively. Time taken to access diagnostic and treatment services was not statistically different for remote versus local patients. Patients referred through a lung cancer fast track clinic had a higher probability of surviving for at least 12 months following a diagnosis (51% versus 28%; CI 0.002 - 4.37) than non- fast track pathway patients. **Conclusion:** The lung cancer fast track clinic has resulted in equitable access to diagnostic and referral services at Dubbo Base Hospital in the Western NSW local Health District of Australia. We have now introduced a lung cancer rapid access system in all our facilities within the district and are extending that to cover lung cancer treatment services. Future studies looking at larger populations are needed to evaluate the possible improvements in lung cancer survival rates.

Keywords: Rapid, Lung, Clinic

P2.11-28 A FOCUS GROUP AND INTERVIEW STUDY TO EXPLORE THE INFORMATION-NEEDS OF LUNG CANCER SCREENING PARTICIPANTS

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Background: Lung cancer screening (LCS) by low-dose CT has been shown to improve mortality, but individuals must consider the potential benefits and harms before making an informed decision about taking part. In the US a shared decision-making process is mandated to qualify for LCS reimbursement. However, screening eligible individuals' (SEI) specific views of these harms, and their preferences for accessing this information, are not well described. **Method:** 16 semi-structured interviews were carried out with general practitioners, public health consultants, respiratory physicians and lung cancer nurse specialists. 35 SEI participated in seven focus groups, which were divided into current vs. former smokers and lower vs. higher educational backgrounds. Interviews and focus groups were audio-recorded and transcribed. Data were coded inductively and analysed using the framework method. **Result:** Lung cancer was generally perceived as an incurable condition, and smokers appeared to be particularly fatalistic. Despite this, a 'belief in screening' emerged from the interviews and focus groups. Participants' appetite for information varied; with many expressing a 'right' to be given all the information, while others cautioned against too much information, and HCPs also acknowledged this dichotomy. Of the harms of screening, false positives and false negatives generated the most concern, though for most participants, even these were unlikely to deter them from screening. Participants were aware of the harms of smoking though many current smokers perceived other factors as more detrimental to their health than smoking. Regarding smoking cessation advice at screening, most focus group and interview participants preferred an emphasis on the benefits of quitting, and for advice to be delivered in a positive and empowering manner. **Conclusion:** These findings can be used to directly inform the way in which information is presented to SEI in order to aid the shared decision-making process, motivate smoking cessation and minimise barriers to uptake of LCS.

Keywords: shared decision making, Qualitative research, lung cancer screening

P2.11-29 IMPACT OF AN INFORMATION-FILM TO PROMOTE INFORMED DECISION-MAKING IN INDIVIDUALS TAKING PART IN A LUNG CANCER SCREENING DEMONSTRATION PILOT

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Background: Lung cancer screening by Low Dose CT (LDCT) is underway in the United States, where a shared decision-making process is mandated for insurer funding. The potential harms of screening are complex and difficult to communicate. Participants do not always read written materials and audio-visual aids have been shown to improve informed decision-making in other areas of medicine. There are limited studies on the use of decision aids in lung cancer screening. **Method:** A five-minute information-film was made to explain the benefits and risks of lung cancer screening. Qualitative research informed the content and format to make it accessible for individuals of varying demographic and educational backgrounds. A sub-sample of participants (n=229) from a lung cancer screening pilot were randomised to watch the film and read a written information booklet (Group A) or read the booklet alone (Group B). Objective and subjective knowledge of the risks and benefits of screening were assessed before and after the intervention, and again after discussion with a heath care professional, when decisional conflict and satisfaction were also assessed. **Result:** 120 and 109 participants were randomised to groups A and B respectively. There was a statistically significant improvement in subjective and objective knowledge scores post-administration of the intervention in both groups (p<0.001). In a multivariate analysis adjusted for educational level and baseline knowledge score, post interventional scores were independently associated with film group (p=0.036). There were no group differences in decisional conflict or satisfaction, or in subsequent attendance for LDCT. Participants' views on the acceptability of the film are presented in table 1. **Table 1: Feedback and acceptability of information film**

	All of it	Most of it	Some of it	A little
How much of the film did you understand?	66.4%	30.9%	3.5%	0%
How much of the film do you think you can remember?	8.9%	60.2%	28.3%	2.7%
	A lot	A little	It didn't help	
How much do you think it helped you to make your decision about whether or not to be screened?	44.3%	0.4%	34.5%	
	Yes	No		
If the film had been available to you before the appointment, do you think you would have watched it?	79.6%	20.4%		
Overall, did you find the film:				
- Useful?	96.5%	3.5%		
- Difficult to understand?	1.8%	98.2%		
- Informative?	97.3%	2.7%		
- Too complicated?	0.9%	99.1%		
- Too little information?	8.4%	91.6%		

Conclusion: The information-film was well-accepted and increased knowledge scores more than a written booklet alone, without raising decisional conflict or reducing attendance for LDCT.

Keywords: lung cancer screening, shared decision making, informed decision making

P2.12-01 EFFICACY OF BELOTECAN AS SECOND-LINE TREATMENT FOR RECURRENT SMALL CELL LUNG CANCER: A PHASE IIB RANDOMIZED MULTICENTER STUDY

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Background: *Topotecan is recommended as second-line treatment for patients with progressive/recurrent extensive-stage small cell lung cancer (ES-SCLC) after platinum-based combination chemotherapy. Although some topotecan-treated patients may have at least an objective response (OR), response duration is often short. Belotecan, a camptothecin derivative topoisomerase I inhibitor, has shown promising antitumor activity and modest toxicities against advanced SCLC and ovarian cancers. We report efficacy data from a phase IIb randomized multicenter study of belotecan as second-line treatment for progressive/recurrent limited-disease (LD)- or ES-SCLC.* **Method:** *This study, conducted from March 2010 to March 2018, was designed to prove the non-inferiority of belotecan to topotecan. Patients were randomized (1:1) to belotecan 0.5 mg/m² or topotecan 1.5 mg/m² intravenously for 5 consecutive days every 3 weeks for 6 cycles or until disease progression. The primary endpoint was objective response rate (ORR; complete response [CR] or partial response [PR]) based on RECIST criteria; secondary endpoints were progression-free survival (PFS), overall survival (OS).* **Result:** Overall, 148 patients (belotecan, n=72; topotecan, n=76) were eligible in the full analysis set (FAS; patients who received at least one dose); 113 patients (belotecan, n=62; topotecan; n=51) were evaluable in the per-protocol set (PPS; patients who completed the study protocol). Clinical characteristics were well balanced between the two treatment arms. In the FAS, ORR was 33.33% (belotecan) and 21.05% (topotecan), respectively (95% CI: −0.0195 to 0.2651, p=0.0927). One belotecan recipient had a CR. Median OS was 396 days (belotecan) and 247 days (topotecan), respectively (p=0.0178); median PFS was 144 and 115 days, respectively (p=0.9608). Similar efficacy outcomes were observed in the PPS.

(See next page)

Primary Endpoint; Objective Response Rate (FAS)

Variable	Total (N=148)		Belotecan (n=72)		Topotecan (n=76)		p-value[a]	95% CI
	n	%	n	%	n	%		
Objective Response CR+PR	40	27.03	24	33.33	16	21.05	0.0927[a]	-0.0195, 0.2651
CR	1	0.68	1	1.39	-	-	0.0689[b]	-
PR	39	26.35	23	31.94	16	21.05		
SD	74	50.00	37	51.39	37	48.68		
PD	34	22.97	11	15.28	23	30.26		

a: Results of Chi-square test for comparison of treatment groups; b: Results of Fisher's exact test for comparison of treatment groups

Conclusion: *Our data met the hypothesis that the antitumor efficacy of belotecan is non-inferior to that of topotecan as second-line treatment for patients with progressive/recurrent LD- or ES-SCLC. Belotecan was also associated with significantly longer OS. (ClinicalTrials.gov. ID: NCT01497873; https://clinicaltrials.gov/ct2/show/NCT01497873)*

P2.12 SMALL CELL LUNG CANCER/NET
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P2.12-02 PHASE II STUDY OF COMBINATION OF NAB-PACLITAXEL AND GEMCITABINE FOR RELAPSED SMALL CELL LUNG CANCER (SCLC)

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Background: Almost all patients with extensive stage and two-thirds of limited stage small cell lung cancer develop disease recurrence or relapse after initial therapy. Most of these patients receive Topotecan as their subsequent therapy, which across multiple studies have shown response rates of approximately 15%. Though some of the newer agents have shown promising efficacy in biomarker selected patient-population;populations, ,in non-selected patients with relapsed SCLC, however, response rates with Nivolumab, Nivolumab in combination with Ipilimumab and Rovalpituzumab were only 10%, 23% and 18%, respectively. Among the conventional chemotherapies, both Gemcitabine and Paclitaxel have shown single agent activity in relapsed-refractory SCLC. Therefore, we hypothesized that combination of Gemcitabine and Nab-Paclitaxel will have additive effect, which will lead to improvement in therapeutic response compared to current standard of care. Based on the toxicity profile of this regimen in patients with advanced pancreatic cancer, we believe it will be better tolerated than Topotecan. **Method:** s: This is a single-arm phase II study. Primary end-point of the study is response rate as defined per RECIST 1.1 criteria. Eligible subjects will receive gemcitabine 1000 mg/m^2 and nab-paclitaxel 100 mg/m^2 on days 1 & 8 of every 21-day cycle. Response assessment will occur every 6 weeks. Target accrual is 32 with 28 evaluable subjects. This would achieve 82% power to detect a difference of 20% to current standard of care therapy, using a one-sided binomial exact test. The results assume that the current standard of care (Topotecan) has a response rate of 15%. Secondary end-points include overall survival, time to progression and treatment-related toxicity **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Gemcitabine, nab-paclitaxel, small cell lung cancer

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P2.12-03 PHASE I/II TRIAL OF 177LU-DOTA0-TYR3-OCTREOTATE (LUTATHERA) AND NIVOLUMAB FOR PATIENTS WITH EXTENSIVE-STAGE SMALL CELL LUNG CANCER (ES-SCLC)

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Background: Despite initial sensitivity to chemotherapy, most patients with ES-SCLC relapse quickly. Studies have shown that somatostatin receptors are expressed in SCLC. Lutathera is a ^{177}Lutetium-labeled somatostatin analog that targets somatostatin receptor positive cancer cells, which is approved for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors. Lutathera and nivolumab, an anti-PD-1 antibody, may have synergistic effects on the generation of anticancer immunity and this combination given as maintenance treatment may delay progression in patients with ES-SCLC. **Method:** This is a multicenter phase I/II trial of Lutathera and nivolumab in patients with ES-SCLC (NCT03325816). The phase I portion includes patients with either relapsed/refractory ES-SCLC or non-progressing ES-SCLC after first-line platinum-based chemotherapy, or advanced grade I-II pulmonary neuroendocrine tumors. The primary objective is to determine the recommended phase 2 dose (RP2D) of Lutathera when given with nivolumab. The phase I portion follows the standard 3+3 design, assessing two dose levels (dose level 1: Lutathera 3.7 GBq Q8W for 4 doses with nivolumab 240 mg Q2W; dose level 2: Lutathera 7.4 GBq Q8W for 4 doses with nivolumab 240 mg Q2W). In the phase II portion, patients with ES-SCLC not progressing after completion of first-line platinum-based chemotherapy are randomly assigned to either maintenance combination with Lutathera and nivolumab or observation. The primary endpoint for the phase II part is progression-free survival. Crossover is allowed at progression for those assigned to the observation group. **Result:** Three patients were enrolled at dose level 1. All patients had ES-SCLC at study entry with 2 patients with progressive disease and 1 patient with stable disease after platinum-based chemotherapy. No dose-limiting toxicities (DLTs) were observed at dose level 1. Treatment-related adverse events include anemia (n=1), arthralgia (n=1), and non-cardiac chest pain (n=1), all of which were grade 1 events per CTCAE 4.03. At first tumor assessment performed 8 weeks after starting treatment, one patient achieved a partial response and two patients had progressive disease per RECIST. Assessment of dose level 2 is underway. Updated safety and efficacy results will be presented. **Conclusion:** Early evidence from the phase I/II trial of Lutathera and nivolumab suggests that the combination is safe, well tolerated and showed initial signs of antitumor activity. The safety and efficacy of the combination will be further explored.

Keywords: Nivolumab, lutathera, small-cell lung cancer

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P2.12-04 LIPOSOMAL IRINOTECAN VS TOPOTECAN IN PATIENTS WITH SMALL CELL LUNG CANCER WHO HAVE PROGRESSED ON/ AFTER PLATINUM-BASED THERAPY

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Background: Small Cell Lung Cancer (SCLC) accounts for ~15% of all lung cancers; it is an aggressive disease marked by rapid growth and early metastasis. Patients typically demonstrate initial sensitivity to chemotherapy and radiotherapy, followed by rapid relapse and development of drug resistance. Topotecan, a topoisomerase I (TOP1) inhibitor, is the only agent approved for second-line treatment in the United States and Europe. Liposomal irinotecan (nal-IRI) has demonstrated sustained TOP1 inhibition, with liposomal deposition in tumor tissue through leaky vasculature, followed by irinotecan release and subsequent conversion to the active metabolite SN-38. Pre-clinical data suggests that nal-IRI has improved anti-tumor activity compared to topotecan. The current trial (NCT03088813) is being undertaken to investigate the safety and efficacy of nal-IRI versus intravenous topotecan in patients with SCLC who have progressed on or after platinum-based first-line therapy. **Method:** There are two parts of this study: Part 1 is an open-label, single-arm, safety run-in phase and Part 2 is a randomized, controlled, efficacy assessment phase. Key inclusion criteria include ECOG performance status of 0–1, adequate organ function, histopathologically/ cytologically confirmed SCLC, evaluable disease (RECIST v1.1), and life expectancy ≥12 weeks. Prior exposure of immuno-oncology therapies is allowed. Key exclusion criteria include a diagnosis of large cell neuroendocrine lung carcinoma, prior treatment regimens with TOP1 inhibitors, and retreatment with the same platinum-based regimen after relapse of first-line therapy. In Part 1, patients will be treated with different doses of nal-IRI to identify a tolerable dose level; this dose level will be expanded to include a total of 24 patients. The primary endpoint is safety and tolerability, with secondary endpoints including objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). In Part 2, ~450 patients will be randomized in a 1:1 ratio between nal-IRI and IV topotecan. The primary endpoint is OS, followed by PFS, ORR, patient-reported outcomes, and exploratory analyses.

Patients will be treated for a minimum of 3 cycles (1 cycle = 6 weeks) or until progressive disease or unacceptable toxicity. Safety analyses will be performed using the safety population, defined as all patients receiving any study drug. **Result:** Section not applicable - Trial in progress **Conclusion:** Section not applicable - Trial in progress

Keywords: small cell lung cancer, nal-IRI, Second-line treatment

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TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.12-05 SUKSES (SMALL CELL LUNG CANCER UMBRELLA KOREA STUDIES): A PHASE II BIOMARKER-DRIVEN UMBRELLA STUDY IN RELAPSED OR REFRACTORY SCLC

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Background: Although initial platinum-based treatment demonstrated high response rate (RR) in extensive stage SCLC, limited options are available for subsequent systemic therapy. Recent studies with comprehensive genomic profiling identified cell cycle-related gene alteration, such as *TP53* and *RB1* inactivation, and *RICTOR* amp as a major characteristic of SCLC. Based on this observation, we designed umbrella clinical trial based on the hypothesis that controlling cell cycle checkpoint, DNA damage repair mechanism, and mTOR pathway with small molecules and monoclonal antibodies targeting these pathways might be an effective approach for the later line SCLC treatment. **Method:** SUKSES trial (NCT02688894) is a phase 2 study with seven treatment arms. Four arms for the biomarker-positive population. Arm A (*AKT1* mt); Arm B (*BRCA1* or *BRCA2* mt, *ATM* deficiency, *MRE11A* mt or other HR pathway gene mt); Arm C (*MYC* family protein amplification or *CDKN2A* mt either of which combined with *TP53* mt); Arm D (*RICTOR* amp). Three arms for the biomarker-negative population. Arm-N1, N2, and N3. Pathologically confirmed SCLC patients are eligible for the molecular screening. For study participation, patients must have at least one measurable lesion after progression from first-line platinum-based therapy. Patients are enrolled in either second or third line based on their initial treatment response. Following treatment is applied after allocation: Arm-A (AZD5363); arm-B (Olaparib); arm-C (AZD1775); arm-D (AZD2014); arm-N1 (AZD1775); arm-N2 (Olaparib and AZD6738); arm-N3 (AZD2811). Primary endpoint for this study is objective RR. Duration of treatment, disease control rate at eight weeks, progression-free survival, exploratory biomarker will be evaluated as secondary endpoint. As of May 2018, 157 patients have been screened for the molecular profiling. Arm A was closed due to low discovery rate of *AKT1* mutation. Of the planned 28 patients for each biomarker positive arm, 9 for arm B, 7 for arm C and 4 for arm D have enrolled. For the negative-biomarker arms, 24 out of 45 patients are recruited for arm N1 and 9 patients for Arm N3. Arm N2 is under review by Institutional Review Board. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: small cell lung cancer

P2.12 SMALL CELL LUNG CANCER/NET
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P2.12-06 THE EFFICACY OF APATINIB PLUS TOPOTECAN AS LATERLINE THERAPY FOR ADVANCED SMALL CELL LUNG CANCER

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Background: Small cell lung cancer(SCLC) is a malignant, aggressive and rapidly progressing cancer. There is no standard treatment strategy for patients with advanced SCLC who experienced progression with first line of chemotherapy. Apatinib, an oral tyrosine kinaese inhibitor targeting vascular endothelial growth receptor 2 (VEGFR 2), has shown well anti-tumor activity and manageable toxicities in SCLC. Some previous cases showed that apatinib plus topotecan for laterline therapy for advanced SCLC patients is safe and effective, but there is no similar studies at home and abroad.Small cell lung cancer(SCLC) is a malignant, aggressive and rapidly progressing cancer. There is no standard treatment strategy for patients with advanced SCLC who experienced progression with first line of chemotherapy. Apatinib, an oral tyrosine kinaese inhibitor targeting vascular endothelial growth receptor 2 (VEGFR 2), has shown well anti-tumor activity and manageable toxicities in SCLC. Some previous cases showed that apatinib plus topotecan for laterline therapy for advanced SCLC patients is safe and effective, but there is no similar studies at home and abroad. **Method:** Our study retrospectively assessed the efficacy and safety of apatinib plus topotecan in patients with advanced SCLC after the first line of chemotherapy. The primary endpoint was progression free survival (PFS). The study was expected to enroll 25 patients who received apatinib (250mg QD) plus topotecan (2mg QD; day1-5, every four weeks). Treatment was continued until disease progression and the tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. **Result:** The main results are showed as follows.

From January 10, 2017 to March 20, 2018, 14 patients were enrolled

Baseline Patient Characteristics	Num.(%)
Patients	14
Age	
median	54
range	28-67
Sex	
male	12(86%)
female	2(14%)
ECOG score	
0	0
1	13(93%)
2	1(7%)
No. Of previous CT lines	
2	5(36%)
≥3	9(64%)

Table 1. Baseline Patient Characteristics

All the patients were evaluable. There were 2 patients showed partial response (PR), 11 patients showed stable disease (SD), and 1 patient showed progressive disease (PD) when make efficacy evaluation at the first time. Although only 2 patients showed PR, most the target lesions were reduced as Figure 1.

Figure 1. Change of target lesions

The toxicities associated with Apatinib plus topotecan were generally manageable. Only 1 patient was with 3-grade Hypertension and 1 patient was with 3-grade Proteinuria.

Adverse event N=14	Grade 1	Grade 2	Grade 3	All grades
Hypertension	3	2	1	6
Proteinuria	1	2	1	4
Hand-foot syndrome	6	1	0	7
Oral mucositis	3	1	0	4
Diarrhea	1	1	0	2
Inappetence	3	1	0	4
Leukopenia	5	2	0	7
Thrombocytopenia	1	1	0	2

Table 2. Adverse event related with the treatment
Table 1. Baseline Patient Characteristics

Up to March 20, 2018, 5 patients were off treatment. Another 9 patients were still on treatment as Figure 2.

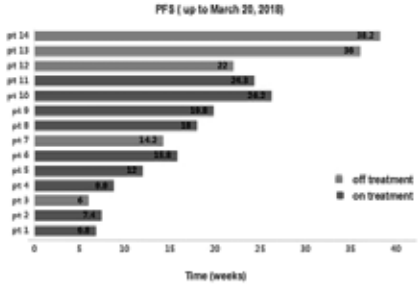

Figure 2. The PFS of 14 patients up to March 20, 2018)

Conclusion: Apatinib plus topotecan exhibits superior activity and generally manageable toxicities for the pretreated patients with advanced small cell lung cancer. It may provide a new therapy strategy for them, but large sample and additional clinical trials are also needed.

Keywords: Apatinib, Advanced Small Cell Lung Cancer, topotecan

P2.12 SMALL CELL LUNG CANCER/NET
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P2.12-07 UTILITY OF STEREOTACTIC BODY RADIOTHERAPY IN PULMONARY CARCINOID TUMORS

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Background: Pulmonary carcinoid (PC) tumors are rare malignant neoplasms, accounting for approximately 2% of all lung cancers. While most patients with PC undergo surgical resection, some patients either decline surgery or are not surgical candidates. Stereotactic body radiotherapy (SBRT) is primarily used in patients with early stage, inoperable non-small cell lung cancer or patients who refuse surgery. We sought to determine the role of SBRT in patients with PC. **Method:** The records of all patients with PC seen at our clinic were retrospectively reviewed. Demographics, pathologic characteristics, and treatment data were collected. Only patients meeting the World Health Organization criteria for typical and atypical carcinoids were included. Radiographic evaluation of all patients was performed at 3-month intervals. **Result:** Of the 251 patients with PC who were retrospectively reviewed, 3 patients were identified who underwent SBRT at our institution. All patients were female with a median age of 72 years. All patients received SBRT consisting of 50 Gy over 5 fractions. Median follow up time was 7 months. Median decrease in tumor size following SBRT was 29%. No adverse events from SBRT were reported.

Patient ID	1	2	3
Tumor Locality	LLL	RUL	RML
T-stage	T1b	T1b	T1b
N-stage	N0	N0	N0
M-stage	M1b	M1b	M1b
AJCC Stage Group	IV	IV	IV
Histology	Atypical	Typical	Typical
Ki-67 Index	5%	<1%	12% (liver)
Decrease in Tumor Size (cm)	0.9 (32%)	0.5 (22%)	0.7 (29%)
Duration of response (months)	7	3	5
Length of Follow up (months)	8	7	6

Conclusion: Our study demonstrates that SBRT is safe and feasible in patients with PC tumors. SBRT may represent a treatment option in patients with PC who are deemed inoperable due to comorbid conditions or decline surgery. Larger studies are needed to further determine the role of SBRT in PC.

Keywords: Atypical carcinoids, pulmonary carcinoids, typical carcinoids

P2.12 SMALL CELL LUNG CANCER/NET
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P2.12-08 NETWORK META-ANALYSIS OF ANGIOGENESIS INHIBITORS ON SURVIVAL OF PATIENTS WITH SMALL CELL LUNG CANCER

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Background: This network meta-analysis aimed at providing a comprehensive evaluation of the effects of angiogenic inhibitors on small cell lung cancer by using network meta-analysis. **Method:** The relative efficacy of angiogenesis inhibitors vandetanib (Van), bevacizumab (Bev), Rh-endostatin (End), sunitinib (Sun) and thalidomide (Tha) was evaluated by conducting a network meta-analysis of progression-free survival and overall survival. **Result:** Nine phase II-III RCTs involving 1599 participants that investigated angiogenesis inhibitors on the treatment of SCLC were included. Sun and Bev achieved better PFS than Tha (Bev VS. Tha, HR=0.88, 95%CI: 0.79-0.98, Sun VS. Tha, HR=0.80, 95%CI: 0.65-1.00). Moreover, Sun and Bev were superior to placebo in terms of PFS (Bev VS. Placebo, HR=0.89, 95%CI: 0.81-0.97, Sun VS. Placebo, HR=0.81, 95% CI: 0.66-1.00). No significant difference of OS was found.

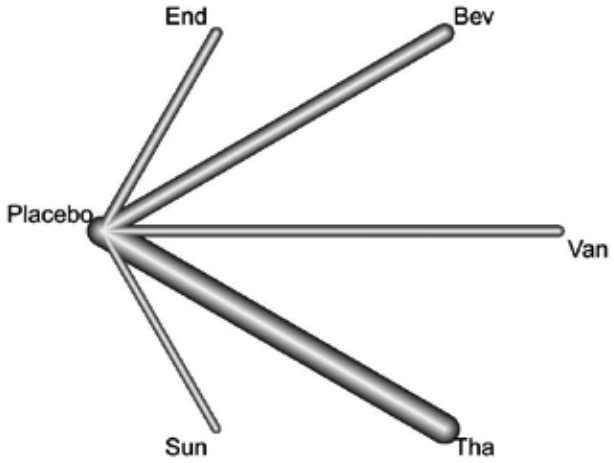

Figure 1 Networks of angiogenic inhibitors for the treatment of small-cell lung cancer. **Conclusion:** In this network meta-analysis, the effect of sunitinib and bevacizumab may be superior to that of thalidomide for small cell lung cancer.

Keywords: small cell lung cancer, survival, Angiogenesis Inhibitors

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P2.12-09 EFFICACY AND SAFETY OF CARBOPLATIN AND PACLITAXEL FOR PATIENTS PREEXISTING INTERSTITIAL LUNG DISEASE WITH SMALL CELL LUNG CANCER

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Background: The small cell lung cancer (SCLC) is chemosensitive. However, in patients with interstitial lung disease (ILD) , chemotherapy-related acute exacerbation (AE) of ILD is one of the most lethal complications. Results of some reports suggest that patients with ILD and SCLC might benefit from chemotherapy, but the efficacy and safety are unclear. **Method:** Retrospective study of patients preexisting ILD with SCLC who treated with carboplatin and paclitxel after second-line chemotherapy. Between January 2012 and July 2017, 17patients preexisting ILD with SCLCwho treated carboplatin and paclitaxel. **Result:** Among 17 patients the overall response rate (ORR) was 35%. The median progression free survival (PFS) was 3.5 months(95% C.I. 1.9-4.0 months), whereas he median survival time was 11.8 months(95%C.I. 8.6-15.5 months). The most common grade 3-4 toxicity was neutropenia (71 %), one patient (6%) suffered from febrile neutropenia. Two patients (12%) experienced chemotherapy-related exacerbation of ILD. There were no treatment-related deaths.

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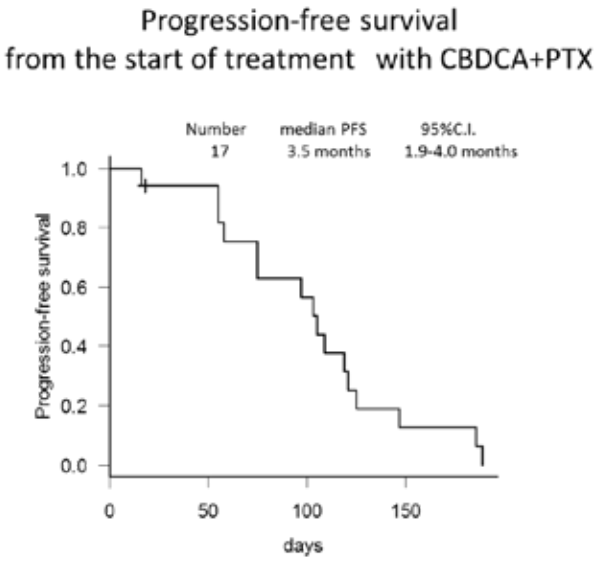

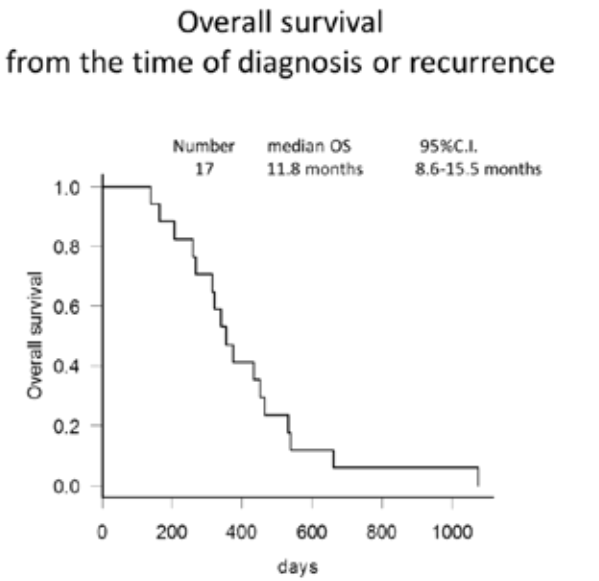

Conclusion: Carboplatin and Paclitxel for patients preexisting Interstitial Lung Disease with small cell lung cancer are tolerable and can be a treatment option.

Keywords: small cell lung cancer, interstitial lung disease, carboplatin and paclitaxel

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P2.12-10 NOVEL PROGNOSTIC MODEL FOR LIMITED-STAGE SMALL-CELL LUNG CANCER

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Background: There is currently no prognostic model designed specifically for patients with limited-stage small cell lung cancer (SCLC). The objective of this study was to construct a novel prognostic model for this patient population using baseline characteristics readily available in clinic. **Method:** An institutional retrospective consecutive patient database was constructed by reviewing the charts of patients diagnosed with limited-stage SCLC between January 2000 and December 2013. Baseline patient characteristics, treatment details and outcomes were extracted. The primary endpoint for the prognostic model was overall survival (OS) and the secondary endpoint was progression-free survival (PFS). Univariable and multivariable Cox regression analyses were performed to identify variables associated with OS and PFS. Prognostic models were generated using recursive partitioning analysis (RPA). **Result:** A total of 398 patients were eligible for analysis. Median follow-up was 8.2 years. The median age was 67 (range: 40-87). Overall, 94% of patients received chemotherapy, 82% received radiotherapy and 65% received both concurrently. Both hypofractionated (40 Gy in 15 fractions) and conventionally-fractionated (50-66 Gy in 25-33 fractions) radiotherapy were used. Prophylactic cranial irradiation was used in 45% of patients. The median OS for the entire cohort was 15.4 months, with a 5-year OS of 19.7%. Overall median PFS was 9.3 months, with a 5-year PFS of 14.1%. On multivariable Cox regression, age, Eastern Cooperative Oncology Group (ECOG) performance status, tumor location and baseline presence of any pleural effusion (non-malignant or unknown status) were prognostic of OS, while performance status and T-stage were prognostic of PFS. RPA model of OS divided patients into favorable (ECOG 0-2, no pleural effusion, middle/upper lobe location: 5-year OS 31%), intermediate (ECOG 0-2, no pleural effusion, non-middle/upper lobe location: 5-year OS 21%) and unfavorable (ECOG 3-4 or any pleural effusion: 5-year OS 5-8%) groups (log-rank $p < 0.001$). RPA for PFS divided patients into favorable (ECOG 0-2, <=T3: 5-year PFS 21%) and unfavorable (ECOG 3-4 or T4: 5-year PFS 5-9%) groups (log-rank $p < 0.001$). **Conclusion:** Novel prognostic factors for OS and PFS based on baseline patient characteristics were successfully identified for patients with limited-stage SCLC. RPA prognostic models were able to separate patients into distinct risk groups for OS and PFS. Our results will benefit from further external validation and can be useful in stratifying patients in future prospective studies.

Keywords: small cell lung cancer, Prognosis, recursive partitioning analysis

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P2.12-11 A PROGNOSTIC MODEL INTEGRATING IMMUNOHISTOCHEMISTRY MARKERS FOR EXTENSIVE-DISEASE SMALL-CELL LUNG CANCER

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Background: Extensive-disease small-cell lung cancer (ED-SCLC) is a subtype of high-grade neuroendocrine carcinoma (HGNEC) with poor prognosis. We tend to build a prognostic nomogram and illustrate the failure pattern of first line etoposide/Irinotecan with paclitaxel (EP/IP) treatment. **Method:** 250 ED-SCLC patients received first line EP/IP treatment were enrolled. Cox regression analysis was used to identify the prognostic factors to establish nomogram. The predictive accuracy of nomogram was evaluated by concordance index (C-index). Further stratification based on Ki67 and brain metastasis was performed through X-tile plot and Kaplan Meier. **Result:** Cox regression analysis indicated brain metastasis as the prognostic factor and we further selected NSE, gender, TTF-1, Syn, tumor size and smoking status under clinical consideration for nomogram. C-index of nomogram suggested 0.65 with moderate predictive effect. Subgroup analysis showed patients with Ki67 lower than 85% had poorer prognosis than those over 90% (HR 0.59, 95%CI 0.39-0.92, p=0.02). Those without brain metastasis at baseline achieving partial response (PR)/complete response (CR) suggested no prognostic significance in brain progression compared to other progression group.

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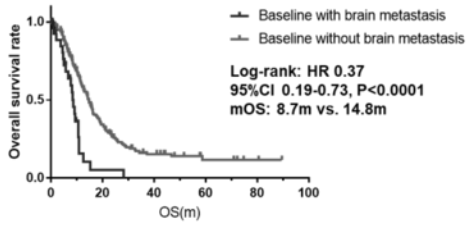

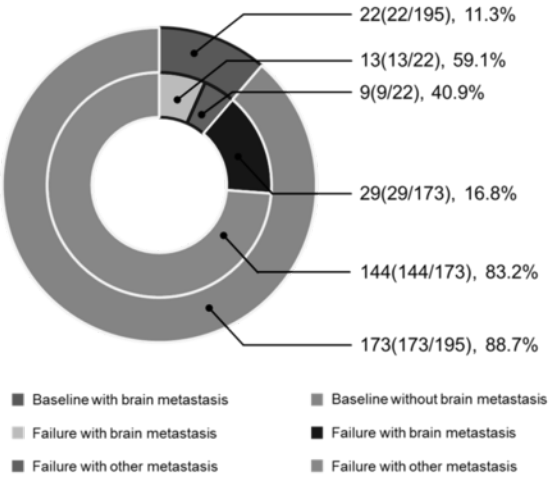

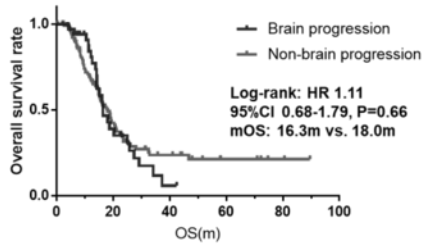

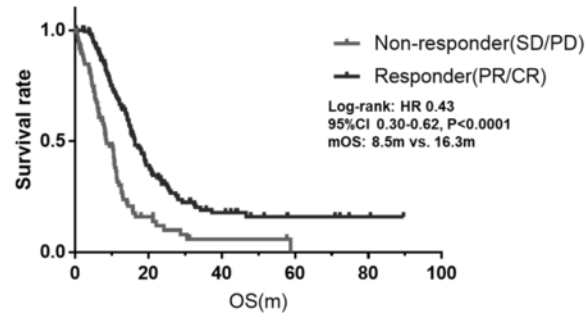

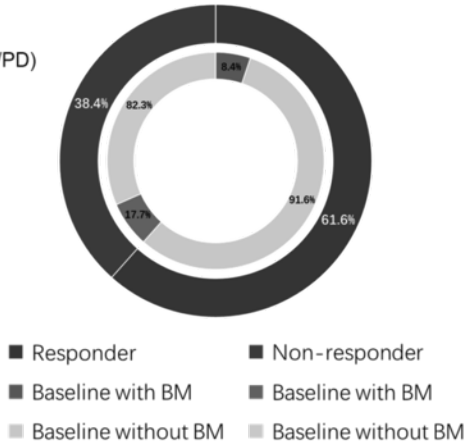

Stratification	Baseline		Post-treatment	
	BM	Non-BM	BM	Non-BM
Responder	13/154(8.4%)	141/154(91.6%)	34/154(22.1%)	120/154(77.9%)
Non-responder	17/96(17.7%)	79/96(82.3%)	4/96(4.2%)	92/96(95.8%)

Conclusion: Established nomogram could well predict prognosis in ED-SCLC. Ki67 might play a potential role in prognosis of SCLC. Application of preventive cranial irradiation might be challenged in ED-SCLC patients without brain metastasis.

Keywords: extensive-disease small-cell lung cancer, Nomogram, Brain metastasis

P2.12 SMALL CELL LUNG CANCER/NET
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.12-12 PLASMA VITAMIN D LEVEL IS AN INDEPENDENT PROGNOSIS FACTOR IN SCLC PATIENTS TREATED WITH PLATINUM PLUS ETOPOSIDE AS FIRST-LINE CHEMOTHERAPY

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Background: Small cell lung cancer accounts for approximately 13.6% of all lung cancer cases, which is a very aggressive form of lung cancer and associated with a very poor prognosis.Investigations into the prognostic factors of SCLC may help in the development of new biotherapeutic regimens.VD deficiency has been well documented to be unfavorable for the prognosis of patients with several types of cancer.However,there is no study focus on the relationship between the plasma VD level and the prognosis of SCLC patients. The primary objective of this study was to examine the prognostic role of the plasma 25-hydroxyvitamin D (25(OH) D) level in SCLC patients treated with platinum plus etoposide as first-line chemotherapy. **Method:** A total of 178 SCLC patients were consecutively and prospectively hospitalized to receive platinum plus etoposide as first-line chemotherapy. The baseline 25(OH)D level was measured at the time of diagnosis. Main outcome measures included overall survival (OS) and progression-free survival (PFS). **Result:** The median OS values of patients with 25(OH)D < 10ng/mL and ≥10ng/mL were 12.5 months (95% confidence interval[CI], 9.4–18.0 months) and 21.3 months (95%CI,12.8–29.1months),respectively; the median PFS values were 6.6 months(95%CI,5.1–7.6months) and 12.7months (95%CI,9.1–17.7months), respectively. Both univariate and multivariate analyses showed that having a plasma 25(OH)D level < 10 ng/mL was associated with a significantly shorter OS(*P* = 0.000; *P* =0.000) and PFS(*P* = 0.000; *P* =0.000).The median OS values of patients with 25(OH)D < *20*ng/mL and ≥20ng/mL were 14.7 months (95% confidence interval[CI], 10.7–22.1 months) and 29.1 months (95%CI, 26.9–38.9 months), respectively; the median PFS values were 8.2months(95%CI, 6.5–10.7 months) and 22.4 months (95%CI, 21.2–24.2 months), respectively. Both univariate and multivariate analyses showed that having a plasma 25(OH)D level <*20* ng/mL was associated with a significantly shorter OS (*P* = 0.000), while the baseline plasma 25(OH)D level was not significantly associated with PFS. **Conclusion:** Plasma vitamin D level is an independent prognosis factor in small cell lung cancer patients treated with platinum plus etoposide as first-line chemotherapy.

P2.12 SMALL CELL LUNG CANCER/NET
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P2.12-13 EFFECTIVENESS OF HYPOFRACTIONATED THORACIC RADIOTHERAPY IN LIMITED-STAGE SMALL-CELL LUNG CANCER: A PROPENSITY SCORE ANALYSIS

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Background: Hypofractionated thoracic radiotherapy may be advantageous in limited-stage small-cell lung cancer (LS-SCLC) due to shorter overall treatment times, decreased resource utilization, and patient convenience. However, there are no randomized data comparing hypofractionated radiotherapy (HFRT; defined as 40-45 Gy in 15-20 fractions) and high dose conventionally-fractionated radiotherapy (CFRT; defined as >= 60 Gy in 2 Gy fractions) in LS-SCLC patients. The objective of this study was to compare the survival outcomes and toxicities of HFRT and CFRT using propensity score-matched retrospective data to simulate the setting of a clinical trial. **Method:** This retrospective study examined institutional records of patients diagnosed with LS-SCLC between January 2000 and December 2013 who were treated with HFRT or CFRT. Propensity scores were estimated by logistic regression using age, performance status, concurrent chemoradiation usage and prophylactic cranial irradiation (PCI) usage. Nearest neighbor-matching was performed on a 1:1 basis using a caliper distance of 0.1, without

replacement. Overall survival (OS) and progression-free survival (PFS) endpoints were estimated by the Kaplan-Meier method and compared with log-rank tests. Cumulative incidences of normal tissue toxicity were compared with Fisher's exact tests. A two-sided significance level of 0.05 was used. **Result:** Among 398 LS-SCLC patients reviewed, 57 patients treated with HFRT and 61 patients treated with CFRT were included in the unmatched analysis. Five-year OS was 26% for the HFRT cohort and 24% for the CFRT cohort (p = 0.82). Five-year PFS was 22% for both cohorts (p = 0.79). Significant differences in age, performance status, concurrent chemoradiation usage and PCI usage were noted in the unmatched cohorts. After propensity score-matching, the balanced cohorts each contained 37 patients. Five-year OS was 25% and 27% (p = 0.72) and 5-year PFS was 25% and 24% (p = 0.63), respectively for the HFRT and CFRT cohorts. Incidence of any esophageal toxicity was not significantly different between the cohorts (92% HFRT vs. 84% CFRT, p = 0.60), though there was a trend towards a higher incidence of any pulmonary toxicity in the CFRT cohort (59% vs. 38%, p = 0.06). Skin toxicity was significantly higher for CFRT (39% vs. 14%, p = 0.01). **Conclusion:** OS and PFS were similar between HFRT and CFRT in balanced cohorts. HFRT was associated with a potentially reduced incidence of pulmonary and skin toxicity. As such, HFRT could result in an improved therapeutic ratio in patients with LS-SCLC. A randomized controlled trial would provide level 1 evidence in this comparison.

Keywords: small cell lung cancer, radiation therapy, Propensity score

P2.12 SMALL CELL LUNG CANCER/NET
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P2.12-14 STEREOTACTIC RADIOSURGERY FOR BRAIN METASTASES IN SMALL CELL LUNG CANCER.

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Background: Prophylactic cranial irradiation (PCI) omission in favor of brain magnetic resonance imaging (MRI) staging and surveillance in the management of small cell lung cancer (SCLC) is controversial yet accepted by some centers policy. The latter strategy implies stereotactic radiosurgery (SRS) treatment (Tx) for limited brain metastases (BM). Data regarding SRS efficacy in this setting is limited. **Method:** Ten consecutive SCLC patients (pts) with BM treated with SRS at Davidoff Cancer center between Aug 2012 and July 2017 were identified through the institutional database; pts receiving PCI or whole brain radiotherapy (WBRT) as a primary intervention were excluded. Brain MRI images were reviewed by neuro-radiology specialist. Intracranial objective response rate (IORR), progression-free survival (IPFS), intracranial failure patterns, overall survival (OS) and time-to-WBRT/death whichever occurred first (TTWD) were analyzed. **Result:** Baseline pt characteristics are presented in the Table. SRS dose ranged from 16 Gy to 22.5 Gy. IORR comprised 57% by RECIST 1.1 and 60% by mRECIST 1.1. Intracranial progression developed in 8 pts; median IPFS was 3.9 mo (95% CI, 1.7-7.2). In-site, off-site and combined pattern of intracranial failure was seen in 0, 6, and 2 pts, respectively; median number of new BM per disease course was 2 (range, 1-11). Nine additional rounds of SRS were delivered in 6 pts (median number of lesion irradiated per round-1, range, 1-5). WBRT was ultimately administered in 3 pts; 4 pts died. Median TTWD comprised 23.2 mo (95% CI, 1.9-26.8). Median OS since SRS administration was 23.2 mo (95% CI, 4.2-26.8).

Table.

Total, n	10
Age, y (median, range)	60 (43-83)
Gender, n	
Female	6
Male	4
Smokers, n	10
Stage, n	
Limited	5
Extensive	5
Platinum-based chemotherapy, n	9
Chest radiation, n	7
Time to BM diagnosis, mo (median, range)	5.1 (0-17.2)
BM at presentation, n	3
BM	
N (median, range)	1 (1-11)
Size, mm (median, range)	15 (3-22)
Supra-/infratentorial/both, n	6/1/3
GPA score (median, range)	1.5 (0.5-4)

Conclusion: MRI surveillance combined with multiple rounds of SRS in case of limited BM development might provide reasonable alternative to PCI or therapeutic WBRT in SCLC. SRS in SCLC warrants prospective evaluation.

Keywords: Stereotactic Radiosurgery, small cell lung cancer, brain MRI surveillance

P2.12 SMALL CELL LUNG CANCER/NET
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P2.12-15 PROGNOSTIC AND PREDICTIVE COVARIATES IN LIMITED-STAGE SMALL-CELL LUNG CANCER: ANALYSIS OF THE PHASE 3 CONVERT TRIAL

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Background: The majority of patients with limited-stage small cell lung cancer (LS-SCLC) progress after concurrent chemo-radiotherapy (cCTRT). Data from the CONVERT trial was analysed to investigate prognostic and predictive covariates in LS-SCLC patients. **Method:** CONVERT is an international multi-centre phase III trial that randomly assigned fit patients to receive either twice-daily (45Gy in 30 fractions) or once-daily (66Gy in 33 fractions) radiotherapy starting on day 22 of chemotherapy cycle 1 (ClinicalTrials.gov NCT00433563). Chemotherapy consisted of 4 or 6 cycles (centres choice) of cisplatin and etoposide. Prophylactic cranial irradiation was offered, if indicated. The following covariates were investigated for prognostic and predictive significance (benefit from twice-daily radiotherapy and completion of cCTRT): clinical (age, performance score, TNM staging, smoking status, weight loss >10% and lung function), laboratory (alkaline phosphatase, sodium and lactate dehydrogenase) and dosimetric (gross tumour volume (GTV), heart and lung dose). Completion of chemotherapy was defined as delivery of all planned cycles while completion of radiotherapy was defined as delivery of all fractions. Results of the multivariate regression analysis of overall survival (OS) and progression-free survival (PFS) were reported after correcting for multiple comparisons. **Result:** Of 547 patients recruited to CONVERT, 449 with complete covariate and outcome data were eligible for this analysis. GTV was the strongest prognostic covariate of OS (hazard ratio (HR) 1.37 (95% confidence interval (CI) 1.21-1.56); p<0.001). The addition of weight loss and performance score modestly improved the concordance probability (0.59 to 0.61) of this model. The HR for OS between high and low risk groups using this model was 2.72 (95% CI 1.94-3.81), median OS: 21 months (95% CI 19-26) *vs* 44 months (95% CI 36-not reached), respectively. For PFS, the HR between high and low risk groups was 2.55 (95% CI 1.86-3.5), median PFS: 13 months (95% CI 12-15) *vs* 26 months (95% CI 18-48), respectively. None of the tested covariates predicted patient benefit from twice-daily radiotherapy. Increase in patient age (continuous variable) predicted non-completion of planned chemotherapy (p=0.002). Due to the high completion of radiotherapy (86% in twice-daily and 80% in once-daily group), a multivariate analysis to predict radiotherapy completion was not performed. **Conclusion:** We report a clinical prognostic model in LS-SCLC, providing information that clinicians can relay to their patients to aid clinical decisions. The addition of biological covariates could help refine these prognostic models in the future.

Keywords: CONVERT, prognostic & predictive, SCLC

P2.12-16 SIGNIFICANT TUMOR REGRESSION AND TOXICITY WITH NIVOLUMAB PLUS IPILIMUMAB IN SMALL CELL LUNG CANCER PATIENTS FOLLOWING RADIATION

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Background: Nivolumab plus ipilimumab demonstrated an approximately 20 percent response rate in patients with Small Cell Lung Cancer (SCLC) who had received 1 or more previous regimen (Antonia et al., 2016). The study did not include data on the clinical response and toxicity in patients who had received previous radiotherapy. However, there is pre-clinical (Deng et al., 2015; Dovedi et al., 2017) and clinical evidence (Antonia et al., 2017) that radiation may potentiate effectiveness of anti - PD-1/PDL-1 immune checkpoint inhibitors. Tumor responses and toxicities in six patients with progressive SCLC treated with second line nivolumab plus ipilimumab after chest radiotherapy and/or radiotherapy to a metastatic site are described. **Method:** This is a retrospective study of 6 patients who had received radiotherapy within 90 days to at least 1 site of gross disease. Response to immunotherapy was assessed by CT scans approximately 8 weeks after beginning treatment. RECIST criteria was utilized in determining responses. Patients were followed for at least 120 days after initiation of immunotherapy. **Result:** Three patients with extensive stage SCLC progressed after chemotherapy at 79, 98, and 125 days prior to starting immunotherapy. Three patients with limited stage SCLC progressed after chemotherapy/radiation at 23, 99, 304 days prior to starting immunotherapy. All six patients had grade 3 or 4 toxicities that required discontinuation or delay of immunotherapy. Toxicities included two patients with myasthenia gravis, two patients with grade 3 rashes, one patient with grade 3 fatigue and one patient with grade 3 stomatitis. At time of initial re-assessment CT scan, four patients had partial response and two patients had stable disease. At 120 days, all six patients had tumor responses. Currently, four patients continue with durable responses. One patient has remained progression free at 182 days after receiving one dose of nivolumab plus ipilimumab. One patient has remained progression free at 197 days after two doses of nivolumab plus ipilimumab. Two patients have remained progression free at 183 and 209 days after two doses of nivolumab plus ipilimumab followed by nivolumab maintenance. In two patients, progression occurred at 132 and 192 days after receiving two doses of nivolumab plus ipilimumab without maintenance nivolumab. **Conclusion:** These observations support that combined immune checkpoint inhibitors following radiation are associated with severe immune mediated toxicity in SCLC patients. The rapid tumor responses and relatively long disease control in these patients with aggressive disease suggest that modified versions of this treatment strategy should be considered.

Keywords: small cell lung cancer, Immune Mediated Toxicity, Radiotherapy

P2.12-17 PROPHYLACTIC CRANIAL IRRADIATION CAN NOT PROVIDE SURVIVAL BENEFITS FOR RESECTED SMALL CELL LUNG CANCER WITHOUT LYMPH NODE INVOLVEMENT

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Background: Currently, prophylactic cranial irradiation (PCI) was recommended for all patients after resection small-cell lung cancers, even those without lymph node metastasis. However, there is no directly evidence supporting this recommendation. The purpose of the present study is to assess the role of PCI for this subset of patients. **Method:** We retrospectively identified completely resected SCLC without lymph node involvement (N0M0) at the Shanghai Chest Hospital between January 2006 and May 2017. **Result:** A total of 146 patients (44 patients received PCI, 102 patients did not) were identified in the study. During the observation period, 8.8 % (9/102) patients in the non-PCI-treated cohort and 11.4 % (5/44) patients in the PCI-treated cohort developed brain metastases. There was no significant difference in the risk of cerebral recurrence between the two cohorts with regard to the time to recurrence (P = 0.677). What is more, neither overall survival benefit (HR = 0.88, 95% CI: 0.47–1.65, P = 0.700) nor disease-free survival (HR = 0.95, 95% CI: 0.55–1.62, P = 0.835) was significant between the PCI-treated and non-PCI-treated cohorts. **Conclusion:** The present study did not support using PCI in surgically resected small cell lung cancer without lymph node involvement. A relatively lower risk of brain metastasis in this particular subset might explain the inferior efficacy of PCI.

Keywords: resection, prophylactic cranial irradiation, small cell lung cancer

P2.12-18 INTERSTITIAL LUNG ABNORMALITIES ARE A RISK FACTOR FOR RADIATION PNEUMONITIS IN PATIENTS WITH LIMITED-STAGE SMALL-CELL LUNG CANCER

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Background: Previous studies reported that patients wth preexisting radiological interstitial lung abnormalities (ILAs) were more susceptible to developing radiation pneumonitis (RP) after thoracic radiation therapy (TRT). The present study aimed to evaluate the incidence and predictors of RP after TRT in patients with limited-stage small-cell lung cancer (LS-SCLC) with or without preexisting radiological ILAs. **Method:** A total of 183 consecutive patients with LS-SCLC between January 2015 and December 2016, who were treated with thoracic intensity-modulated radiation therapy at our institution, were analyzed. The diagnosis of ILAs was reviewed by two experienced thoracic radiologists based on the pretreatment high-resolution computed tomography(CT) imaging, such as honeycombing, subpleural reticular opacities, ground-glass opacity, and traction bronchiectasis. Univariate and multivariate analyses were used to assess the correlation of clinical factors, preexisting radiological ILAs, and dose-volume histogram-based dosimetric parameters with RP. The correlation between the preexisting ILAs score on CT findings and the grade of RP was analyzed by Pearson Correlation. **Result:** Twenty (10.9%) patients had preexisting radiological ILAs. The median follow-up time was 10.9 months. RP was observed in 75 (41.0%), 35 (19.1%), 11 (6.0%), and 0 (0%) patients with grades 1, 2, 3, and ≥4 RP, respectively. The incidence of ≥ grade 2 and 3 RP at 1 year was 26.3% and 6.2% in the entire cohort, respectively. Preexisting radiological ILAs were associated with an increased risk of ≥grade 2 RP (84.1% in ILAs + vs 18.7% in ILAs-, P <0.001) and ≥ grade 3 RP (27.7% in ILAs + vs 3.8% in ILAs-, P <0.001) at 1 year. Preexisting radiological ILAs was a significant predictors of ≥grade 2 RP and ≥grade 3 RP in multivariate analysis (P <0.001, P = 0.004, respectively). Lower forced expiratory volume in 1 second was a significant predictor of ≥grade 2 RP in multivariate analysis (P = 0.043). The ratio of CD4 and CD8 cells has a tendency to predict ≥grade 3 RP in multivariate analysis (P = 0.053).There was a moderate correlation between the preexisting ILAs score on CT findings and the grade of RP (Pearson Correlation Coefficient = 0.364, P <0.001). **Conclusion:** Preexisting radiological ILAs is associated with an increased risk of ≥grade 2 RP and ≥grade 3 RP after TRT in patients with LS-SCLC.

Keywords: small-cell lung cancer, Interstitial lung abnormalities, Radiation pneumonitis

P2.12-19 PROPHYLACTIC CRANIAL IRRADIATION IN EXTENSIVE SMALL CELL LUNG CANCER: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Previous studies have demonstrated that prophylactic cranial irradiation (PCI) can reduce the risk of brain metastases and prolong overall survival in patients with small cell lung cancer (SCLC). However, whether different characteristics of patients with extensive SCLC effects the efficacy and safety of PCI remains controversial. This meta-analysis aims to test the efficacy and safety of PCI in patients with extensive SCLC. **Method:** PubMed, EmBase, and the Cochrane Library were searched for relevant studies published through 12 September 2017. Hazard ratios (HRs) were used to measure overall survival (OS) and progression free survival (PFS), and relative risks (RRs) were employed to

calculate brain metastases, survival rate, and adverse events. Summary results were pooled using the random-effect model. **Result:** Of 1,124 identified citations, we included 13 trials reporting on 1,286 patients with extensive SCLC. PCI did not associate with significantly improved OS (HR: 0.82; 95%CI: 0.60-1.11; P=0.192) or PFS (HR: 0.82; 95%CI: 0.68-1.00; P=0.052) compared with patients not receiving PCI, while PCI did associate with significantly decreased brain metastases (RR: 0.54; 95%CI: 0.41-0.72; P<0.001). We noted further that PCI significantly increased the 1-year survival rate (RR: 1.50; 95%CI: 1.05-2.14; P=0.027) while it had no significant effect on 2- (RR: 0.85; P=0.387), 3- (RR: 0.74; P=0.294), 4- (RR: 0.49; P=0.053), or 5-year survival rates (RR: 0.59; P=0.522) compared with the non-PCI group. Finally, increased adverse events including fatigue, dermatitis, anorexia, nausea, vomiting, malaise, and cognitive functioning were found in the PCI group. **Conclusion:** The findings of this meta-analysis suggest that patients with extensive SCLC who receive PCI can reduce the risk of brain metastases and increase their 1-year survival rate. However, PCI is associated with a significantly increased risk of adverse events.

Keywords: prophylactic cranial irradiation, small cell lung cancer, overall survival

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-01 BRIGATINIB USE IN ENGLAND – WHERE NEXT?

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Background: ALK positive NSCLC is estimated to account for 1,600 cases per year in England. Brigatinib is a next generation ALK inhibitor with proven efficacy after crizotinib but its role in 1st line is still under investigation. If licensed in Europe it may further extend survival for this rare group of patients. **Method:** We conducted a multicentre retrospective study across hospitals from the National Health System (NHS) in England on ALK positive patients who were offered treatment with the newer generations of ALK inhibitors. For this analysis, patients who received treatment with brigatinib through Compassionate use program or clinical trials between 2012 and 2018 were selected. The primary aims were time of exposure to brigatinib (as a surrogate of clinical benefit) and the objective response rate (ORR). The secondary aim was the incidence of grade 3-4 toxicity. And an exploratory aim analysed the value of ALK inhibitors treatment sequence. **Result:** A total of 30 patients with an ALK positive lung adenocarcinoma were included with a median age of 50 years. 53% of patients were female and 77% never smoked. 90% presented at diagnosis with metastatic disease and 63% developed brain metastasis. The median follow-up time since the start of brigatinib was 9.7 months and 53% of patients were on brigatinib at the time of analysis. In 57% of cases brigatinib was only used after a 2nd line of treatment. Only 6 patients were treated in the first line setting. The overall median time of exposure was 12.1 months (95% CI, 4.7 to 19.6) with a maximum exposure of 30 months. The ORR was 50% within the 28 evaluable patients. Median overall survival was not reached. Only 1 patient had grade 3-4 toxicity with increased AST. The use of brigatinib in 1st and 2nd lines (13 patients) did not reach a median exposure time and the ORR was 69%. Brigatinib post-crizotinib (9 patients) had a higher exposure time compared with post-ceritinib (13 patients), respectively, 9.1 (95% CI, 0.5 to 25.7) and 6.6 months (95% CI, 2.6 to 10.6). However the first sequence was more often used in 1st/2nd lines (50% vs 15%). **Conclusion:** Brigatinib is an active and very well tolerated drug. Despite being used mainly in heavily pre-treated patients, our data confirm a meaningful clinical benefit in this population. Its efficacy may be higher in earlier lines and we found no clear signal favouring a specific sequence of treatment.

Keywords: brigatinib, NSCLC, ALK

P2.13 TARGETED THERAPY
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P2.13-02 ALK-TRANSLOCATION AND BRAIN METASTASES: A RETROSPECTIVE STUDY. CORRELATION BETWEEN CLINICAL OUTCOME, DISEASE BURDEN AND MANAGEMENT.

O. Grundberg, S. Friesland, S. Abdel-Halim, S. Gagatek, R. Karimi, A. Öjdahl-Boden, G. Tsakonas, M. Bradic-Lindh, K. Kölbeck, G. Wagenius, S. Ekman, K. Lindberg, L. De Petris

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Background: Brain metastases from non-small cell lung cancer is often regarded as the ominous sign of disease progression . In the ALK-translocated population, brain metastases are seen in a higher incidence, either at diagnosis or as a common site of progression for patients receiving tyrosine kinase inhibitors (TKI). The management of brain metastases in this population remains a challenge since several methods of treatment are available. TKI-treatment, especially with second or third generation drugs can be effective but the role of radiation therapy, with either whole brain radiotherapy (wbrt) or stereotactic radiosurgery (srs), has not been fully elucidated. A retrospective study was conducted at ou Institution in order to evaluate the frequency of brain metastases in this subggroup of patients and in order to explore clinical features associated with survival.

Method: 88 consecutive patients with advanced ALK+ adenocarcinoma were treated at our institution. during the perod 2011-2018. Data on CNS imaging modality, treatment strategy and outcome was collected by chart review. **Result:** Cns-imaging with either MRI or CT (in 38% and 62% of the cases respectively) was performed in 73 cases. 44 patients (61%) were found to have CNS metastases (Male/female ratio 48/52%; median age 60y). 23% were found at the time of primary cancer diagnosis, 36% on time of PD on chemotherapy, 34% on PD on crizotinib and 7% at PD on 2nd gen ALKinh . 27% of the patients had 1-3 metastases, 34% 4-10 met and 39 % >10. Pharmacological treatments in the group as a whole: chemotherapy (n=38); crizotinib (n=35); alectinib (n=10); ceritinib (n=20); brigatinib (n=3), lorlatinib (n=1). Radiotherapy was administered in 57% as either SRS or WBRT (52/48%) . Treatment strategies upon discover of CNS-metastes: Radiotherapy solely 27%, combination of radiotherapy and pharmacological treatment in 25%, switch to crizotinib and to 2nd gen ALKi in 18 and13 % respectively. **Median OS from the diagnosis of CNS metastasis was 29months (95% CI 11-59). 1- and 2-year survival was 61% and 51%, respectively. Neither gender, age, timing for diagnosis of CNS metastases nor the use of radiotherapy were significant prognostic factors for OS (Cox proportional hazard analysis).** Use of 2nd gen ALKin as treatment strategy seemed to be superior to crizotinib and radiotherapy alone even if median OS not yet was reached. **Conclusion:** The high incidence of CNS metastases in this subpopulation of patients (Caucasian with advanced ALK+ NSCLC) was confirmed in this study. The wider implementation of 2nd generation ALKi in clinical practice will probably change the prognosis of these subjects.

Keywords: ALK, brain metastases

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-03 REAL-LIFE EXPERIENCE WITH BRIGATINIB IN PRETREATED EML4-ALK TRANSLOCATED NSCLC PATIENTS

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Background: Patients with lung cancer, who show *EML4-ALK* translocation are routinely treated with ALK inhibitors (ALKi) as Alectinib, Ceritinib or Crizotinib, but develop resistance over time in the majority of cases. Brigatinib, a new next-generation ALKi, is FDA approved in crizotinib-refractory ALK-positive NSCLC. The role of Brigatinib after Ceritinib or Alectinib failure is unknown in clinical practice. We report about our experience with Brigatinib in *EML4-ALK* translocated NSCLC patients, who became resistant to Alectinib, Ceritinib or Crizotinib. **Method:** We treated 35 *EML4-ALK* translocated NSCLC patients with Brigatinib. Patient characteristics including sex, age, race, presence/absence of brain metastases and smoking history of ALK+ NSCLC patients were collected. All data were obtained from Otto-Wagner hospital from August 2015 until April 2018. Before receiving Brigatinib, the patients were either only treated with Crizotinib (n = 15), with Crizotinib and then

Ceritinib (n = 12), with Alectinib (n=1), with Crizotinib and then Alectinib (n=3), with Crizotinib, then Ceritinib and then Alectinib (n=1) or with Ceritinib and Alectinib (n=3). All patients were treated with daily dose of 180 mg oral Brigatinib after a 7- day lead- in at 90 mg. **Result:** 27 patients were women and 8 men. 3 patients were smokers (8,5%), 9 were former smokers (25,7 %) and 23 were never smokers (65,7%). 13 patients had initial brain metastases (31%). 34 of the treated patients are Caucasians and 1 is Asian. 3 of the 35 showed a complete response (9%), 25 a partial response (76%) and 5 a disease progression (15%), 2 were not evaluable. 7 of the 13 patients with brain metastases responded to Brigatinib (54%). The median PFS (progression free survival) was 7.5 months (range 1-21) and treatment of 21 patients is still ongoing. Of the 15 patients, who received only Crizotinib before Brigatinib, 2 patients were complete responders, 12 were partial responders and 1 had disease progression. Of the 12 patients, who received Crizotinib followed by Ceritinib, 1 patient had a complete response, 9 partial response and 2 disease progression. All other patients demonstrated a partial response except two, who had disease progression with Brigatinib following Ceritinib/ Alectinib treatment. Brigatinib was well tolerated overall. **Conclusion:** Brigatinib was highly effective in these pretreated *EML4-ALK* translocated NSCLC patients in clinical practice.

Keywords: NSCLC, EML4-ALK, brigatinib

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-04 OUTCOMES OF ALK-POSITIVE NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH CRIZOTINIB: A MULTICENTER COHORT RETROSPECTIVE STUDY.

P. Xing[1], Q. Wang[2], D. Ma[1], X. Hao[1], M. Wang[3], Y. Wang[1], L. Shan[4], T. Xin[5], L. Liang[6], H. Liang[7], Y. Du[5], Z. Zhang[6], J. Li[1]

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Background: Crizotinib has demonstrated promising efficacy in patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) in clinical trials. However, there is lack of multicenter real-world data summary with large cohort of patients, especially in China. We conducted this multicenter and retrospective study to assess the outcomes of crizotinib in, to our knowledge, the largest cohort of patients with ALK-positive advanced NSCLC. **Method:** We reviewed medical records of 484 unselected ALK-positive NSCLC patients treated with crizotinib at five cancer centers in China from January 2013 to November 2017. Clinical data were collected from crizotinib initiation to RECIST-defined progressive disease (PD), and post-PD systemic treatment outcomes were also analyzed. **Result:** A total of 428 eligible ALK-positive NSCLC patients were enrolled. Among them, 273 (63.8%) patients received crizotinib as first-line treatment. The median progression-free survival (PFS) and overall survival (OS) from crizotinib initiation were 14.4 months (95%CI: 12.4-16.4) and 53.4 months (95% CI: 33.7-73.1) respectively. In the subgroup analysis, patients received crizotinib as first-line treatment showed a higher disease control rate (DCR) and longer median OS with statistical significance compared with second-/ further line crizotinib treatment (94.8%, not estimated *vs.* 89.0%, 40.5 months, respectively). For 261 patients with RECIST-defined PD, multivariate COX analysis revealed that patients who received first-line crizotinib (P=0.013), continued crizotinib beyond progressive disease (CBPD) (P=0.011) and received next-generation ALKis after crizotinib failure (P<0.001) were associated with improved survival both from crizotinib progression and from the first crizotinib dose. **Conclusion:** This study demonstrated the clinically meaningful benefit of crizotinib treatment in the largest cohort of Chinese ALK positive NSCLC patients. CBPD and next-generation ALK TKI treatment may provide survival improvement after RECIST-defined progression on crizotinib.

Keywords: crizotinib, Anaplastic lymphoma kinase, Non-small-cell lung cancer

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-05 REAL-WORLD CLINICAL BENEFIT OF CONTINUING CRIZOTINIB BEYOND PROGRESSION DISEASE (CBPD) IN PATIENTS WITH ADVANCED ALK-POSITIVE NSCLC.

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Background: Most ALK-positive NSCLC patients treated with crizotinib would ultimately develop progressive disease (PD), and continuing crizotinib beyond initial PD (CBPD) may be potentially beneficial. We aim to evaluate the survival outcomes of patients with crizotinib resistance in real-world setting and to explore the clinical efficacy of continuing CBPD treatment. **Method:** A total of 261 ALK-positive NSCLC patients treated with crizotinib experienced RECIST-defined PD and were included in this multi-center retrospective analysis. Clinicopathologic characteristics, progressive pattern, post-PD treatment and overall survival (OS) were compared between patients continuing CBPD and those not. **Result:** 140 patients who continued crizotinib after disease progression were allocated to CBPD group and others were non-CBPD group. Two-sided Chi-square test showed that patients who never smoked (P=0.047), with ECOG 0-1(P=0.001), isolated intracranial progression (P<0.001) and <median PFS of initial crizotinib (P=0.002) were more likely in the CBPD group. At the analysis, 84 patients had re-PD and the median duration of crizotinib treatment post-PD was 6.8 months (95%CI: 3.639-9.869). The median OS for the overall population from the time of PD (post-PD OS) was 15.3 months (95%CI: 11.376-19.181), and was significantly longer in CBPD patients than non-CBPDs (24.1 months *vs.* 8.5 months, 95% CI: 0.326-0.669, HR 0.467, P<0.001). Furthermore, next-generation ALK inhibitors (ALKis) following crizotinib failure was associated with improved post-PD OS (24.9 months *vs.* 10.7 months, 95% CI: 0.307-0.686, HR 0.459, P<0.001). **Conclusion:** Continuing CBPD treatment after crizotinib resistance favorably impact survival outcomes of advanced ALK-positive NSCLC patients in the real-world. Next-generation ALKis may provide survival improvement, but comparative studies between different subsequent treatment options after PD on crizotinib are still needed.

Keywords: crizotinib, Anaplastic lymphoma kinase, Treatment beyond disease progression

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-06 TP53 STATUS IN RELATION TO RESPONSE TO ANTI-ALK AGENTS IN PATIENTS WITH EML4-ALK-TRANSLOCATED NSCLC

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Background: Patients with non-small-cell lung cancer (NSCLC) carrying the *EML4-ALK* translocation are responsive to anti-ALK agents, such as crizotinib. However, about 30%-40% of patients show primary resistance to treatment. We previously demonstrated that *TP53* mutations are associated with poorer prognosis in *EGFR*-mutated patients treated with tyrosine-kinase inhibitors. In the present study we analyzed the impact of *TP53* mutations on response to anti-ALK treatment in *EML4-ALK*-translocated NSCLC **Method:** Eighty-three patients with *EML4-ALK*-translocated NSCLC identified in the Wide Catchment Area of Romagna between 2012 and 2016 were considered. *TP53* status was evaluated in 61 patients on the basis of DNA availability. Of these, 28 patients received an anti-ALK agent as second-or-more-line treatment and follow-up data were available. *TP53* status was analyzed in relation to disease control rate (DCR): complete response (CR), partial response (PR) or stable disease (SD). **Result:** Overall, *TP53* mutations were observed in 14 (23%) patients, 6 (43%) showing a mutation in exon 5, 1 (7%) in exon 6, 3 (21%) in exon 7 and 4 (28%) in exon 8. We found one insertion (7%), one deletion (7%) and 12 point mutations (86%). Of the 28 patients treated with an anti-ALK agent, 5 (20%) showed *TP53* mutations, 2 (40%) in exon 5, 1 (20%) in exon

5 and 2 (40%) in exon 8. Clinical response was not evaluable in 3 patients due to rapid disease progression (2 had a stop mutation in exon 5 of *TP53*). DCR for the remaining 25 patients was 60% in those with *TP53*-mutated tumors and 92% in those with *TP53* wild-type disease. **Conclusion:** *TP53* mutations were associated with a poorer DCR in *EML4-ALK*-translocated NSCLC patients treated with an anti-ALK agent. These results highlight the potential role of *TP53* in determining primary resistance to anti-ALK agents, and should be confirmed in a wider case series.

Keywords: EML4-ALK, TP53, Resistance

P2.13 TARGETED THERAPY
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P2.13-07 CUX1-ALK: A NOVEL ALK REARRANGEMENT THAT RESPONDS TO CRIZOTINIB IN NON-SMALL-CELL LUNG CANCER

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Background: Lung cancer is the leading cause of cancer-related deaths worldwide. *ALK* rearrangement has been identified in 3% to 5% non-small-cell lung cancer (NSCLC) patients. The most common *ALK* rearrangement is *EML4-ALK*. Other rare *ALK* arrangements, such as *KIF5IB-ALK* and *KLC-ALK*, have also been identified that might be potential therapeutic targets, although the efficacy of ALK inhibitors on the majority of these rare *ALK* rearrangements has not been assessed in clinic. **Method:** In this study, using comprehensive next-generation sequencing targeting 416 pan-cancer genes and introns of 16 genes frequently rearranged in cancer, we identified a novel *CUX1-ALK* fusion gene in a lung adenocarcinoma patient. The exact *CUX1-ALK* fusion transcript was determined via RNA-seq, and confirmed by RT-PCR. The oncogenic ability of *CUX1-ALK* fusion gene was further validated in 293T cells for the activation of ALK self-phosphorylation and downstream signaling pathways. **Result:** After the detection of *CUX1-ALK* fusion gene, RNA-seq analysis of FFPE sections from the primary tumor specimen was applied to reveal a 97 nt fragment from *CUX1* intron 8 inserted before the 53 nt position in *ALK* exon 20. Expression of the CUX1-ALK fusion protein in 293T cells confirmed the self-phosphorylation of the fusion protein and the activation of ALK downstream signaling pathways, including MAPK, JAK-STAT, and PI3K/AKT signaling pathways, which all could be inhibited by the addition of crizotinib. Furthermore, the patient showed a superior response to crizotinib with a progression-free survival of 20 months. **Conclusion:** This study provides the novel finding of *CUX1-ALK* fusion gene from NSCLC patient which could provide personalized treatment solutions for the maximum benefit to NSCLC patients.

Keywords: next generation sequencing, crizotinib, CUX1-ALK fusion

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-08 PHASE 1 STUDY OF THE AXL INHIBITOR DS-1205C IN COMBINATION WITH OSIMERTINIB IN SUBJECTS WITH METASTATIC OR UNRESECTABLE EGFR-MUTANT NSCLC.

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Background: In patients with metastatic EGFR-mutant (EGFRm) non-small cell lung cancer (NSCLC), resistance to EGFR tyrosine kinase inhibitors (TKIs) arises from the T790M EGFR mutation in over half of cases; up-regulation of "bypass track" activity in non-EGFR signaling pathways is observed in other cases. Up-regulation of expression of the AXL tyrosine kinase has been observed in EGFRm NSCLC patients experiencing disease progression on erlotinib, and xenograft studies have supported the role of AXL inhibition in combination with EGFR TKI treatment in overcoming such resistance. DS-1205c is a novel, orally administered, specific small molecule inhibitor of AXL. **Method:** This is a multicenter, open-label, Phase 1, dose escalation and dose expansion study of DS-1205c in combination with osimertinib in metastatic or unresectable EGFR-mutant NSCLC subjects experiencing disease progression during treatment with erlotinib, gefitinib, or afatinib, and without T790M resistance mutation; or during treatment with osimertinib. Eligible subjects are at least 18 years of age, have ECOG PS 0 or 1, have radiological documentation of disease progression while receiving continuous treatment with erlotinib, gefitinib, afatinib, or osimertinib, have at least one measurable lesion per RECIST v1.1, and do not have any factors that increase the risk of QTc prolongation. This study includes two parts: Dose Escalation and Dose Expansion. In Dose Escalation, subjects receive DS-1205c during a run-in period, followed by continuous combination treatment with DS-1205c and 80 mg daily of osimertinib. Escalation of DS-1205c dosing is guided by the modified Continuous Reassessment Method (mCRM) using a Bayesian logistic regression model (BLRM) following the escalation with overdose control (EWOC) principle. In Dose Expansion, subjects receive DS-1205c at the recommended dose for expansion (RDE) determined in Dose Escalation, in combination with 80 mg daily of osimertinib. Primary objectives are to determine the safety, tolerability, and RDE of DS-1205c in combination with osimertinib. Secondary objectives are to assess the pharmacokinetic parameters of DS-1205a (free form of DS-1205c), osimertinib, and osimertinib active metabolites, and to assess antitumor activity (RECIST v1.1). Retrospective analysis of AXL expression by immunohistochemistry will be conducted using tumor tissue collected prior to study treatment. Enrollment opened in December 2017. Clinicaltrials.gov identifier: NCT03255083 **Result:** Section not applicable - Clinical trial in Progress **Conclusion:** Section not applicable - clinical trial in progress

Keywords: EGFR, drug resistance, AXL

P2.13 TARGETED THERAPY
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P2.13-09 EFFICACY AND SAFETY OF OSIMERTINIB AFTER PRIOR EGFR TKI: ANALYSIS OF PATIENTS UNDERREPRESENTED IN RANDOMIZED CLINICAL TRIALS

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Background: Osimertinib is a new standard of care in non-small cell lung cancer (NSCLC) after progression to an EGFR TKI in the presence of T790M mutation. Following results of the phase III study AURA 3, which led to the approval of osimertinib worldwide, we have conducted ASTRIS in Brazil. **Method:** This is a phase IV, international, multicentric, open trial, with the aim of confirming the efficacy and safety of osimertinib at a dose of 80 mg daily, orally. Eligible patients presented with diagnosis of T790M-positive NSCLC on progression after prior EGFR TKI. Herein, we present the Brazilian experience at ASTRIS, including subsets that were underrepresented in the phase III trial. **Result:** Eighty-eight patients were enrolled in Brazil between August 2015 and March 2017. The median age was 64 years (34-89), and most were females (66%). Fifty-four patients (61%) had received prior therapy with erlotinib, forty-two (48%) with gefitinib, and 3 (3%) with afatinib. Nineteen patients (22%) were exposed to a EGFR TKI more than 6 months before enrolment. Importantly, 11 patients (12.5%) presented with a PS of 2, 23 (26%) presented with brain metastases, and 3 with leptomeningeal disease. Exon 19 deletions were the most common primary mutation in *EGFR*, present in 55 cases (62.5%), followed by L858R in 24 cases (27%). Tumor samples were acquired from the primary tumor in 14 cases (45%) and in a metastatic site in 16 (52%); all other cases had T790M detected at plasma. After a median follow-up of 9.3 months, 26 progression events and 23 deaths were documented. The response rate was 58.2% (95%CI 46.6-69.2), and median progression-free survival was 9.4 months (95%CI 8.2-not reached). The 12-month overall survival was 69.7% (95%CI 56.5-79.6). Thirty patients (34%) presented an adverse event, 14 of which led to dose modification and 5 to treatment discontinuation. The most common adverse events were infection in 14 cases (15%), gastrointestinal and hematologic (4 cases each). Nineteen patients (22%) had a serious adverse event, mostly infections (14 cases). **Conclusion:** The profile of patients enrolled in Brazilian institutions highlights the presence of cases with poor PS, which was excluded in the AURA 3 trial. Despite these features, the efficacy and safety of osimertinib was confirmed, suggesting that results could be extrapolated to a broad range of subsets. This study also underscores the role of liquid biopsy in the detection of T790M, in detriment to tumor re-biopsy.

Keywords: osimertinib, T790M, NSCLC

P2.13 TARGETED THERAPY
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P2.13-10 PH I/II STUDY OF ORAL SELECTIVE AXL INHIBITOR BEMCENTINIB (BGB324) IN COMBINATION WITH ERLOTINIB IN PTS WITH EGFRM NSCLC

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Background: Bemcentinib is a first-in-class, oral, selective AXL TKI which is being evaluated as a combination therapy across several phII clinical trials. Increased AXL expression is associated with innate immune suppression and the appearance of resistance to targeted therapies in models of NSCLC and pt samples. AXL inhibition via bemcentinib prevents the appearance of such resistance *in vivo* and has shown immunomodulatory effect in AML patients. **Method:** This study was designed to confirm the safety and tolerability of bemcentinib as a monotherapy and when administered in combination with erlotinib (arm A). Pts with activating EGFR mutation driven NSCLC who had progressed on an approved EGFR inhibitor (arm B) or were receiving erlotinib in the first line setting (arm C) were treated with bemcentinib at RP2D in combination with full dose erlotinib to evaluate the potential of bemcentinib to reverse or prevent resistance to EGFR targeted therapy, respectively. Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM) at C1D1 and C2D1. **Result:** 2 out of 8 pts (25%) with stage IV disease who received bemcentinib monotherapy achieved SD for close to 1 year including evidence of tumour shrinkage of 19% in 1 pt. 1 pt who had progressed on previous erlotinib monotherapy (12.5%) achieved a PR receiving bemcentinib in combination with erlotinib and remains on treatment well beyond 2 years later (arm A). A further 3 pts had SD at 6 wks. 11 patients (4 female, median age 58; 38-67) were enrolled in arm B and had received a median of 2 (1 - 4) previous lines of cytotoxic chemotherapy and a median of 2 previous EGFR inhibitors. 2 of these 11 pts (18%) including 1 pt who was refractory to erlotinib therapy at the onset of combination therapy remain on treatment more than 6 months into therapy at the time of writing with best responses of PR and SD, respectively. 1 further pt had SD at 6 weeks. The most common treatment-related AEs have been gastrointestinal and rash.There was no evidence of any impact of bemcentinib on erlotinib pharmacokinetics. Protein biomarkers predictive of pt benefit following bemcentinib treatment were identified. **Conclusion:** Bemcentinib can be safely administered in combination with erlotinib to pts with NSCLC and achieves additional benefit in a proportion of patients who do not have T790M and have progressed on EGFR inhibition or are maintained on erlotinib alone. Clinical trial information: NCT02424617.

Keywords: EGFR, Axl, bemcentinib

P2.13 TARGETED THERAPY
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P2.13-11 EGFR AMPLIFICATION AND SENSITIZING MUTATIONS CORRELATES WITH SURVIVAL FROM ERLOTINIB IN LUNG ADENOCARCINOMA PATIENTS (MUTP-CLICAP¶)

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Background: Tumor heterogeneity causes different *EGFR* mutation abundances, and is believed to be responsible for varied progression-free survival (PFS) in lung adenocarcinoma (ADC) patients receiving EGFR-TKI treatment. *EGFR* amplification and its common presence in *EGFR* mutant allele might be determined by the *EGFR* copy number variation. Examination of *EGFR* amplification status in *EGFR* mutant patients could predict the efficacy of EGFR-TKI treatment **Method:** 72 lung ADC patients, who harbored *EGFR* activating mutations and received erlotinib as first line treatment, were examined for *EGFR* amplification by FISH. We analyzed the relationship between the *EGFR* mutational status and copy number profile with clinical outcomes including response rate, overall-survival (OS), and PFS. **Result:** Median age was 62-yo (r, 20-87 years), 53 patients were females (73%), and 89% had common mutations. Twenty-two (30.6%) samples with *EGFR* activating mutations were identified as having *EGFR* amplification. *EGFR* amplification was more frequent in patients with exon 19 deletion (p=0.05) and in those with better performance status (p=0.01). Patients with *EGFR* gene amplification had a significantly longer PFS than those without [(25.2 months, 95%CI 22.0-38.5) vs. (12.4 months, 95%CI 5.3-19.5); p=0.002] as well as better OS [(*EGFR* amplified 37.8 months, 95%CI 30.9-44.7) vs. (*EGFR* non-amplified 27.1 months, 95%CI 12.8-41.3); p=0.009]. *EGFR* amplification significantly influenced the response to erlotinib (p=0.0001). **Conclusion:** *EGFR* amplification occurs in one third of patients with lung ADC harboring *EGFR* activating mutations, and could serve as an indicator for better response and survival from EGFR-TKI treatment.

Keywords: EGFR mutations, EGFR amplification, Adenocarcinoma

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-12 THE DENOVO T790M MUTATION RECOVERED BY DDPCR IS ASSOCIATED WITH A POOR RESPONSE TO 1ST AND 2ND GENERATION EGFR-TKI IN LUNG ADENOCARCINOMA.

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Background: The discovery of the EGFR-tyrosine kinase inhibitor (TKI) sensitizing mutation and the customized application of the 1st generation EGFR-TKI dramatically improved the clinical outcome of patients with lung adenocarcinoma. However, EGFR-mutation positive lung adenocarcinoma has ultimately acquired drug resistance against EGFR-TKI, resulting in treatment failure. The EGFR T790M mutation is found in approximately half of patients with resistance during 1st and 2nd generation EGFR-TKI therapy and is also a therapeutic biomarker of indications for EMSI treatment. In this study, authors aimed to investigate the effect of presence of T790M mutation in the treatment naïve lung adenocarcinoma tissues on the response to 1st and 2nd generation EGFR-TKI using droplet digital PCR (ddPCR). **Method:** 113 specimens from the patients who visited Severance Hospital from 2009 to 2017 were recruited from the institutional tissue bank. Detailed inclusion criteria for the cases are as follows; (1) pathologically proven lung adenocarcinoma; (2) pStage IIIB ~ IV (3) 1st line treatment with 1st or 2nd generation EGFR-TKI (4) sufficient FFPE tissue blocks for gDNA extraction (5) provided informed consent for the use of tissues. gDNA was extracted with QIAamp DNA FFPE tissue kit and T790M mutation was identified using BioRad Droplet Digital PCR (ddPCR) QX200 according to the manufacturer's manual. **Result:** To date, 46 cases have been tested for T790M mutations, with 69.2% cases with ≥10 copies, 42.3% with 20 copies, and 30.7% with ≥30 copies. When 30 copies or more were defined as positive, the cases with higher de novo T790M mutations showed shorter progression free survival for 1st and 2nd generation EGFR-TKI. In 31 cases, EGFR mutation was measured at re-biopsy. There was no significant relationship between pre-treatment T790M mutation status and re-biopsy T790M mutation, and there was no significant relationship between pre-treatment and overall survival. *Depending on the results of additional experiments, the above information will be updated at the time of presentation. **Conclusion:** In treatment naïve lung adenocarcinoma, a de novo T790M mutation is frequently observed and may related to the poor response to 1st and 2nd generation EGFR-TKI. The further studies on the applicability of EMSI to these subgroups and its clinical usefulness are required.

Keywords: lung adenocarcinoma, ddPCR, de novo T790M mutation

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-13 REAL-WORLD STUDY OF OSIMERTINIB IN EGFR T790M-MUTATED NON-SMALL CELL LUNG CANCER (NSCLC): ASTRIS CANADIAN COHORT ANALYSIS

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Background: ASTRIS is an open-label, single-arm, multinational, real world study of osimertinib for patients with advanced/metastatic epidermal growth factor receptor-mutated (EGFRm) T790M-positive non-small cell lung cancer (NSCLC) who previously received therapy with an EGFR tyrosine kinase inhibitor (EGFR-TKI) (NCT02474355). Data cut-off (DCO) for the second interim analysis was 20 October 2017, with 3014 patients enrolled (full analysis set), including 99 patients in Canada. **Method:** Adult patients with locally advanced/metastatic EGFRm NSCLC, not amenable to curative surgery/radiotherapy, with confirmation of T790M and prior EGFR-TKI therapy were enrolled. Patients were included with World Health Organization performance status of 0 to 2, as well as those with asymptomatic stable central nervous system (CNS) metastases. Patients received osimertinib 80 mg once daily until loss of clinical benefit. The primary efficacy outcome was overall survival (OS), with secondary outcomes of investigator-assessed response rate (RR), progression-free survival (PFS), and time to treatment discontinuation (TTD). **Result:** From study start (14 January 2016) to DCO (20 October 2017), 99 patients were enrolled at 12 Canadian centres. Median age was 64 years (30-89 years). Patients were 68% female, 57% Asian, and had ECOG 0/1/2 of 22%/65%/13%. Twenty-five patients had CNS metastases at screening. Gefitinib was the most commonly used previous EGFR-TKI (gefitinib, erlotinib and afatinib were 80%, 14%, and 14%, respectively). Thirty-nine percent had previous chemotherapy; 6% previous immunotherapy; 46% previous radiotherapy. All patients had T790M: 75% tissue, 7% blood and 18% cytology. Biomarker testing methods varied, with the majority (61%) identified by Entrogen EGFR kit. At DCO, 45 patients had discontinued treatment. OS data were immature. Median PFS was 11.0 months (95% CI, 8.9-13.3). Median TTD was 14.9 months (95% CI, 11.2-not calculated). RR was 67.0% (95% CI, 56.7-76.2); sub-analyses showed RR of 69.9% (58.0-80.1), 66.7% (22.3, 95.7) and 55.6% (30.8, 78.5) for patients with T790M by tissue, blood and cytology, respectively. Serious adverse events (AEs) were reported for 18% of patients. AEs leading to dose modifications and discontinuations were reported for 12% and 5% of patients, respectively. **Conclusion:** The Canadian results from this real world study of osimertinib in advanced/metastatic EGFRm T790M-positive NSCLC, which includes heavily pretreated patients and various approaches to biomarker testing, were comparable to outcomes reported in the phase III study AURA3 (NCT02151981). These findings provide further support for osimertinib as standard of care for EGFRm T790M-positive NSCLC.

Keywords: advanced NSCLC, EGFR mutated NSCLC, Osimertinib

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-14 THE CLINICAL USEFULNESS OF LIQUID BIOPSY FOR DETECTION AND DYNAMIC MONITORING OF EGFR T790M IN NSCLC PATIENTS ON EGFR-TKI THERAPY

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Background: The greatest limitation of the I & II generation EGFR TKIs' efficacy is the resistance acquired by most treated patients through the T790M mutation present in exon 20 of EGFR gene. Non-invasive access to the tumor DNA circulating in the blood of NSCLC patients, so called liquid biopsy, enables the real-time monitoring of status and level of mutated EGFR gene DNA (mEGFR) during EGFR TKI treatment instead of retrospective evaluation of tumor tissue specimens. In the present study we evaluated the feasibility and the diagnostic usefulness of quantitative EGFR mutations analysis in liquid biopsy collected from NSCLC patients during EGFR TKI treatment. **Method:** The study group consists of 40 patients with advanced NSCLC treated with EGFR TKI (erlotinib, gefitinib or afatinib) in the first line. Peripheral blood is prospectively collected at the time of diagnosis (baseline) and then every month during treatment. In 10 patients (7 patients with deletion in exon 19 and 3 patients with L858R mutation in exon 21 of EGFR gene) sampling was followed until clinical progression. The mutated EGFR DNA was analyzed quantitively in plasma using cobas EGFR Mutation Test v2 (Roche, Germany). **Result:** The mEGFR in plasma of NSCLC patients demonstrated notable dynamics during EGFR TKI treatment. In 8 out of 10 (80%) patients followed until progression, who responded well to EGFR TKIs, the complete clearence of mEGFR in plasma in first 2 months of treatment was observed, regardless the type of activating EGFR mutation. The levels of mEGFR remained undetectable in plasma for several months of treatment in those patients. In 6 (60%) patients a rapid raise to or above mEGFR baseline preceded clinical progression in time, in 4 patients by at least four weeks. In 4 patients, the raising level of mEGFR in plasma was accompanied by the increasing T790M mutation level. In 2 patients, the plasma level of mEGFR was undetectable at diagnosis and during treatment. **Conclusion:** The dynamic changes in levels of mutated EGFR gene DNA in plasma of NSCLC patients reflect their response to EGFR TKI treatment. The monitoring of T790M mutation levels in plasma by allele-specific qPCR assay allows to observe disease progression on EGFR TKIs much earlier than conventional imaging techniques. The study is ongoing: at least 80 patients are to be recruited and clinical data correlated with results of molecular tests. This study is financed by the investigator initiated research grant from AstraZeneca.

Keywords: liquid biopsy, monitoring of EGFR TKI treatment, EGFR T790M mutation

P2.13 TARGETED THERAPY
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P2.13-15 SHORT-TERM RESPONDERS OF NSCLC TO EGFR-TKIS DISPLAY HIGH PREVALENCE OF TP53 MUTATIONS AND PRIMARY RESISTANCE MECHANISMS

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Background: Non-small cell lung cancer (NSCLC) with activating *EGFR* mutations in exon 19 and 21 usually responds to EGFR tyrosine kinase inhibitors (TKI), but sometimes the responses can only be maintained for a few months. The underlying mechanisms of such short responses have not been fully elucidated. **Method:** The genomic profiles of sixteen short-term responders (SR) that had progression free survival (PFS) of less than 6 months on the first-generation EGFR TKI were interrogated, in comparison to twelve long-term responders (LR) that had more than 24 months of PFS. All patients were diagnosed with advanced lung adenocarcinoma and harbored *EGFR* 19del or L855R mutation before treatment. Paired tumor samples collected before treatment and after relapse (or at the last follow-up) were subjected to next-generation sequencing of 416 cancer-relevant genes. **Result:** SR patients were significantly younger than LR patients (p<0.001). 88% of SR patients have *TP53* variations compared to 13% in LR patients (p<0.001), and 37.5% SR patients carry *EGFR* amplification, which is much higher than LR patients (8%). In addition, 12 SR patients (75%) were identified with other potential primary resistance mechanisms in pre-treatment samples, including *PTEN* loss, *BIM* deletion polymorphism, amplifications of *EGFR, ERBB2, MET, HRAS and AKT2*. Comparatively, only 3 LR patients (25%) were detected with *EGFR* or *AKT1* amplification that could possibly exert resistance. **Conclusion:** The diversified pre-existing resistance mechanisms in SR patients revealed the complexity of defining treatment strategies even for EGFR sensitive mutations.

Keywords: Resistance, TP53, EGFR amplification

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-16 PREFERENCE OF ADJUVANT TREATMENTS FOR EGFR-MUTANT RESECTED NSCLC PATIENTS: RESULTS OF A NATIONAL-WIDE SURVEY IN CHINA

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Background: EGFR mutated patients represent half of NSCLC cases in China. ADJUVANT study (NCT01405079), a published multicenter RCT, showed that EGFR-TKIs were associated with significant longer DFS than chemotherapy in stage II to IIIA resected NSCLC patients. We sought to investigate the preference on adjuvant EGFR-TKI of the surgeons specializing on NSCLC in China by conducting an online national-wide

survey. **Method:** The question 'would you recommend EGFR-TKIs as adjuvant therapy in postoperative patients with EGFR mutation? -Yes; No' was included on an online survey system. Interviewee personal information was also collected. Logistic regression model was conducted to explore factors associated with the choices. **Result:** We received 732 responses from lung cancer surgeons from 30 provinces of China, 618 (84.43%) doctors were from department of general thoracic surgery and 114 (15.57%) surgeons from department of thoracic oncology surgery, 660 (90.16%) were from tertiary hospitals and 65 (8.88%) from the secondary ones. The interviewees consisted of 93 (12.70%) master candidates, 15 (2.05%) doctoral candidates, 98 (13.39%) residents, 217 (29.64%) attending doctors, 174 (23.77%) associate chiefs of surgeon and 135 (18.44%) chiefs of surgeon. As a result, 572 (78.1%) surgeons selected "Yes", 143 (19.5%) selected "No", and the rest abstained. Logistic regression analysis revealed that the result was not influenced by different career duration, location, economic status of living, hospital grade, department type, etc. **Conclusion:** This national-wide large sample survey showed that recommending EGFR-TKIs as adjuvant therapy for postoperative EGFR-mutant NSCLC patients was widely supported by specialists in lung cancer in China.

Keywords: nationwide survey, adjuvant EGFR-TKIs, China

P2.13 TARGETED THERAPY
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P2.13-17 NON-SMALL LUNG CANCER IN THE VERY YOUNG: MORE EGFR/ALK MUTATION RATE THAN THE ELDER

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Background: Lung cancer was the leading cause of cancer in worldwise1. Although it remains a disease of older patients, there is a subset of patients who are diagnosed at younger age, such as blow 40 year old. Several studies had shown that the younger group had more females, more non-smokers, more advanced stages of disease, and better survive rate. However, most of these studies didn't include tumor EGFR/ALK mutation data, especially for the younger group. We retrospectively studied the clinical difference between the younger and the older in patients, including pathologic type, treatment characteristics, and EGFR/ALK mutation status. **Method:** We retrospective reviewed data of NSCLC patients diagnosed during Jun. 2007 to Dec. 2014, and whose age was less than 90 year-old. at Taipei Veterans General Hospital(TPEVGH). **Result:** There were 5,051 cases of NSCLC, including 168 patients who were <40 years old (younger group) and 4,883 patients aged 40 years or older (older group). It was found younger group had significantly higher *EGFR* mutation rate than older group (22.6% VS 16.2%, p=0.026), and *ALK* mutation (4.2% VS 0.5%, p<0.001). Although the younger group had more stage IV patients (60.1% VS 49.6%, p=0.002), they had better (one year:73.7% VS 66.2%, five year:44.4% VS 33.7%) overall survival rate(OS) (median survival time: 55 VS 26 months ,p=0.002). Regarding histologic subtype, younger group had less squamous cell carcinoma (4.2% VS 16.1% , p<0.001), while adenocarcinoma subtype was similar between two groups (76.8% VS 76.5%, p=0.924).

Figure 1A

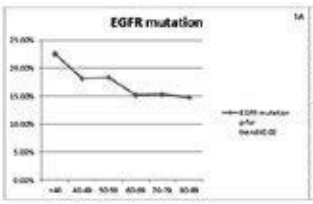


Figure 1B

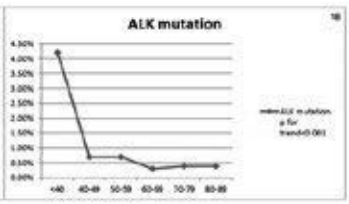
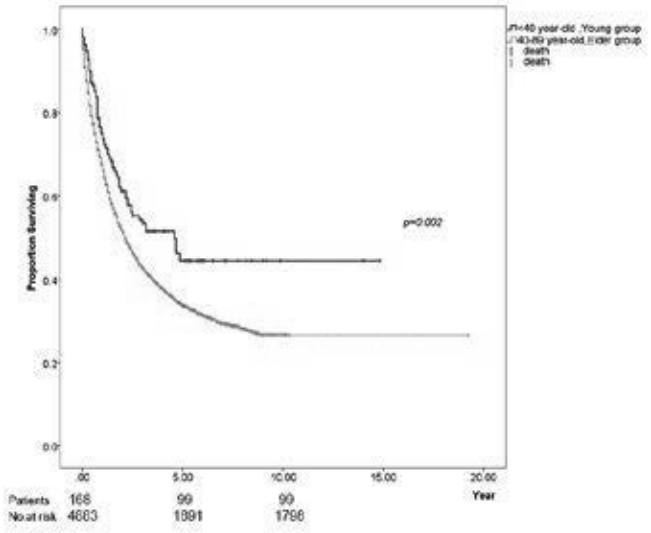


Figure 2



Conclusion: Overall survival rate in younger NSCLC patients were better than the older ones. This survival benefit most likely due to higher *EGFR* mutation and *ALK* mutation rate and corresponding TKI treatment. Although more advanced-stage NSCLC patients were seen in the younger group at the same time.

Keywords: EGFR mutation, young, ALK mutation

P2.13 TARGETED THERAPY
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P2.13-18 A MULTICENTER PROSPECTIVE BIOMARKER STUDY TO EXPLORE MECHANISMS OF AFATINIB RESISTANCE BASED ON DIGITA PCR AND NEXT-GENERATION SEQUENCING

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Background: Afatinib is an oral irreversible blocker of ErbB-family kinases and shows a pronounced anti-tumor efficacy for advanced non–small cell lung cancer (NSCLC) positive for activating mutations of *EGFR*. We applied digital polymerase chain reaction (dPCR) and next-generation sequencing (NGS) to explore mechanisms of afatinib resistance. **Method:** Eligible patients had advanced lung adenocarcinoma with *EGFR* activating mutations. Tumor and plasma samples were collected before afatinib treatment and after treatment failure with disease progression (systemic progressive disease, SPD). DNA from the samples was analyzed by dPCR and NGS. **Result:** Thirty-five patients were enrolled, with a median follow-up time of 15.8 months. Among 25 patients with SPD, tumor, plasma, or both samples were available for 18, 23, and 16 individuals, respectively. dPCR and NGS detected *EGFR* T790M mutation in 13 (56.5%) and 11 (47.8%) of 23 plasma samples at SPD, with sensitivity and specificity compared with tumor samples being 83.3% and 70.0% (dPCR) and 50.0% and 70.0% (NGS), respectively. Applying the ratio of the number of T790M alleles to that of activating mutations (T/A) for determination of the T790M positivity improved the sensitivity and specificity of plasma analysis compared with tumor analysis to 83.3% and 100% (dPCR) and 57.1% and 100% (NGS), respectively. Among 25 patients with SPD, the T790M mutation of *EGFR* alone (n = 11), copy number gain (CNG) of *NRAS* (n = 1), CNG of *MET* (n = 1), CNG of *EGFR* plus T790M (n = 1), and

CNG and E545K of *PIK3CA* plus T790M of *EGFR* (n = 1) were identified by NGS as putative resistance mechanisms against afatinib. No tumor showed transformation to small cell carcinoma. Median progression-free survival was longer in patients with than in those without T790M at SPD (15.1 versus 10.9 months, P =0.25). Median time to SPD was much longer in patients with than in those without T790M at SPD (17.9 versus 10.9 months, P =0.18). **Conclusion:** Assessment of T/A ratio with dPCR or NGS improved specificity of plasma analysis for determination of T790M positivity compared with tumor analysis. dPCR and NGS analysis in tumor and plasma samples shed light on exploring mechanisms of afatinib resistance.

Keywords: afatinib, Resistance, liquid biopsy

P2.13 TARGETED THERAPY
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P2.13-19 PROGNOSTIC VALUE INFERRED FROM THE QUANTITATIVE MEASUREMENT OF EGFR MUTATION USING PNA-CLAMPING METHOD IN ADVANCED EGFR MUTANT NSCLC PATIENTS

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Background: Lung cancer is the leading cause of cancer death worldwide, with non-small cell lung cancer (NSCLC) accounting for the majority of cases. Recent advances in the understanding of the biology of tumors and in highly sensitive detection technologies for molecular analysis offer targeted therapies, such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). However, not all EGFR mutation positive NSCLC patients are equally responsive to EGFR-TKIs. Although many factors have been introduced to predict EGFR TKIs response, there seems to be no factor that can clearly explain the mechanism. The aim of this study was to evaluate whether the quantification of EGFR mutation predicts clinical outcomes of EGFR-TKI therapy. **Method:** This study is retrospective analysis of prospectively collected data about all patients who underwent EGFR mutation test using peptide nucleic acid (PNA)-mediated clamping polymerase chain reaction (PCR) at the Pusan National University Hospital between October 2015 and December 2017. The efficiency of PCR clamping was determined by measuring the Ct value. The delta (Δ) Ct-1 value (standard Ct value minus sample Ct value) was calculated to measure the quantification of EGFR mutation. **Result:** Among the total 552 patients tested for EGFR mutations and 142 (25.7%) were positive for EGFR mutations. Seventy-one patients received EGFR-TKIs. The patient population was subdivided using a mean ΔCt-1 value of 5.28. There was no clinically significant difference between the two groups. Patients with high ΔCt-1 value had significantly longer median overall survival (OS) than did patients with low ΔCt-1 value (24.5 vs 16.7 months, p=0.002). Patients with common EGFR mutation (exon 19 deletion or L858R) and high ΔCt-1 value showed a significantly longer median OS than did patients with common mutation and low ΔCt-1 value (24.1 vs 18.0 months, p=0.014). Multivariate analysis revealed only high ΔCt-1 value was significant prognostic factor of survival in advanced advanced EGFR mutant NSCLC. **Conclusion:** The ΔCt-1 value, which refers to EGFR quantification by PNA-clamping method, is a significant good prognostic factor of survival to EGFR-TKI therapy.

Keywords: PNA clamping method, EGFR mutation, Prognosis

P2.13 TARGETED THERAPY
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P2.13-20 THE COMPARATIVE EFFECTIVENESS OF GEFITINIB VERSUS ERLOTINIB ON THE INTRACRANIAL PROGRESSION-FREE SURVIVAL IN PATIENTS WITH BRAIN METASTASIS

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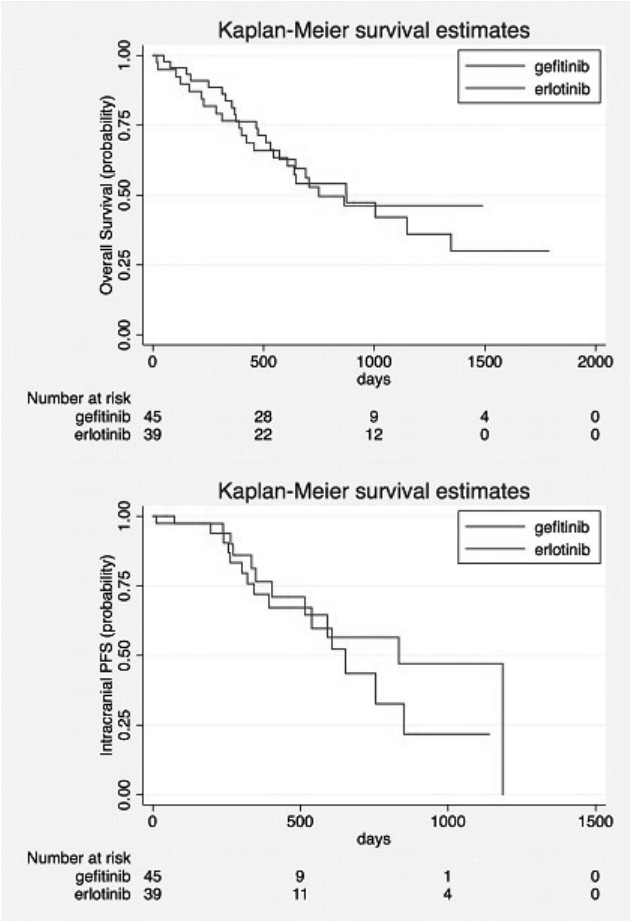
Background: The high peak plasma concentrations and better blood-brain barrier permeability of erlotinib compared with gefitinib was reported. However, there were few researches comparing their treatment effect for brain metastasis. This study aimed to investigate the comparative effectiveness of gefitinib versus erlotinib on the survival in patients with brain metastasis from lung adenocarcinoma. **Method:** Incident lung adenocarcinoma patients at National Taiwan University Hospital between Jan 2013 and May 2015 were reviewed and analyzed. The inclusion criteria were: (1) tumor harboring either EGFR exon 19 deletion or L858R mutation (2) patient taking gefitinib or erlotinib as their first-line treatment (3) patients with brain metastasis. Kaplan-Meier analyses with long-rank testing were used to estimate the intracranial progression-free survival (PFS) and overall survival between the gefitinib and erlotinib group. A Cox proportional hazard model was used to calculate the hazard ratio (HR) and 95% confidence intervals (CI) for age, gender, gefitinib vs. erlotinib, Eastern Cooperative Oncology Group performance status(ECOG), and pre-treatment for brain metastasis. Cumulative incidence of intracranial progression using competing risks regression model was also conducted. **Result:** A total of 84 patients were included; 61 patients were female. 37 patients harbored EGFR exon 19 deletion. 39 patients received erlotinib as their first-line treatment.73 patients had Eastern Cooperative Oncology Group performance status scores of 0-1. 48 patients had multiple brain metastases (number >5) and 14 patients had brain metastasis ≥ 3 cm in size. 25 patients received whole brain radiation therapy and 7 patients received stereotactic radiosurgery before taking the tyrosine kinase inhibitors. The median overall survival for the gefitinib group and the erlotinib group was 874 vs. 750 days (p=0.86, Fig 1), and the median intracranial PFS 652 vs. 833 days (p=0.38, Fig 2). **Multivariable analysis indicated that erlotinib was associated with a better intracranial PFS. (HR: 0.34, 95% CI: 0.12-0.97).** The competing risks regression model showed erlotinib was associated with a trend toward lower probability of intracranial progression, with adjusted subdistribution hazard ratio of 0.40 (95% CI, 0.16-1.03; p=0.06, Fig 3).



Conclusion: In patients with brain metastasis from lung adenocarcinoma, this study showed the beneficial effectiveness of erlotinib on the intracranial progression-free survival compared with gefitinib.

Keywords: Tyrosine kinase inhibitors, Brain metastasis, intracranial progression-free survival

P2.13 TARGETED THERAPY
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P2.13-21 MET ADDICTION CAN BE CIRCUMVENTED THROUGH EGFR INHIBITION VIA AXL IN MET-AMPLIFIED PRIMARY RESISTANT EGFR-MUTANT NSCLC

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Background: Primary resistance to EGFR-TKI is observed in approximately 10% of patients with activating EGFR mutations. In a patient harboring L858R mutation and high cMET amplification (MET copy number 7.3, CEP7 ratio 3.4) who progressed after just 4 weeks of erlotinib (ERL), significant tumor regression was achieved with MET inhibition alone (Crizotinib, CRZ). We confirmed this phenotype in the corresponding patient-derived cell line model (A482) and identified EGFR-AXL interaction as a mechanism that can circumvent clonal cMET addiction. **Method:** We generated patient-derived cell lines from the patient's baseline neck excision biopsy (A482) and evaluated the effect of mono and combination therapy (ERL, CRZ, ERL-CRZ) on A482, including viability (CellTiter-Glo Luminescent Assay, Promega), colony forming (Crystal Violet Assay), downstream signaling (Western blots) and adaptive pathways (Human Phosho-Receptor Tyrosine Kinase Array Kit, R&D systems). AXL was identified as a key mediator of resistance and subsequently subjected to further functional validation. Finally, we examined the prevalence of this clinical phenomenon in a retrospective series of MET amplified EGFR-mutant NSCLC. **Result:** Cell viability assays confirmed the patient-derived cell line to be more sensitive to CRZ as compared to ERL alone or with combination CRZ-ERL. Upregulation of AXL, RET and FGFR3 expression were identified as adaptive changes 24 hours upon ERL exposure. A targeted pharmacologic screen revealed A482 to be exquisitely sensitive to combination EGFR and AXL inhibition. Immunoprecipitation revealed a direct interaction between EGFR and AXL, which upon treatment with ERL resulted in attenuation of cMET addiction. Co-existing cMET amplification with demonstrated suboptimal response to EGFR TKI was found in 3% of EGFR-mutant NSCLC in a retrospective series of patients. **Conclusion:** Targeting the EGFR-AXL axis through EGFR inhibition alone can lead to paradoxical MET pathway activation, while the combination of EGFR and AXL inhibition can circumvent downstream signaling in MET amplified EGFR-mutant NSCLC. AXL expression levels can potentially identify patients in whom combination or monotherapy with MET inhibitors may be most beneficial. Our data highlights the challenge in interpreting genomic alterations alone; and how cellular context can lead to differential sensitivities to EGFR and MET inhibitors alone and/or in combination in MET amplified EGFR-mutant NSCLC.

Keywords: TKI-resistance, cMET, Axl

P2.13 TARGETED THERAPY
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P2.13-22 RESISTANT PATTERNS TO OSIMERTINIB IN NON-SMALL CELL LUNG CANCER PATIENTS WITH BOTH T790M AND SENSITIZING EGFR MUTATION

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Background: Osimertinib is a 3rd generation, EGFR-TKI which is active for both sensitizing mutations and T790M of EGFR. Although it has proven its efficacy, the acquired resistance eventually occurs requiring the investigation for resistant mechanisms to provide overcoming strategies. **Method:** We retrospectively reviewed the medical records of T790M+ lung cancer patients treated with osimertinib after acquiring resistance to 1st- or 2nd generation EGFR-TKI between February 2016 and June 2017 to evaluate the efficacy and safety of the drug. In addition, the moleculo-pathologic data of re-biopsy samples after the development of resistance to osimertinib were analyzed. **Result:** In 23 patients included, the median age was 59.0 years and thirteen (56.5%) were female. The median duration of follow-up was 11.9 months. 17 patients achieved an objective response (73.9%) and the disease was controlled in 22 patients (95.7%). Median progression-free survival was 7.4 months (95% CI 3.6-11.0) and median overall survival was not reached. The adverse effects were minimal except one case of severe pneumonitis. Among 14 patients who finally experienced the disease progression during osimertinib, the re-biopsy was performed in 10 patients. T790M disappeared in 7 patients (70%) and one of them showed the wild-type conversion. Transformation to small cell carcinoma was observed in 2 patients who responded to chemotherapy with etoposide and cisplatin. A newly developed C797S mutation was detected in one patient. Interestingly, C797S disappeared after 6 cycles of pembrolizumab following osimertinib-resistance and the patient responded well to osimertinib again. **Conclusion:** Osimertinib showed the clinical activity and the favorable toxicity profile comparable to those of clinical trials in real world practice in Korea. The evaluation with repeated biopsy sample after osimertinib-resistance is needed to guide the following treatment strategy.

Keywords: T790M, Resistance, Osimertinib

P2.13 TARGETED THERAPY
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P2.13-23 OSIMERTINIB TREATMENT RESULT OF PLASMA T790M POSITIVE IN DIFFERENT CLINICAL FAILURE MODES AFTER FIRST-LINE EGFR TKI FOR EGFR MUTANT NSCLC

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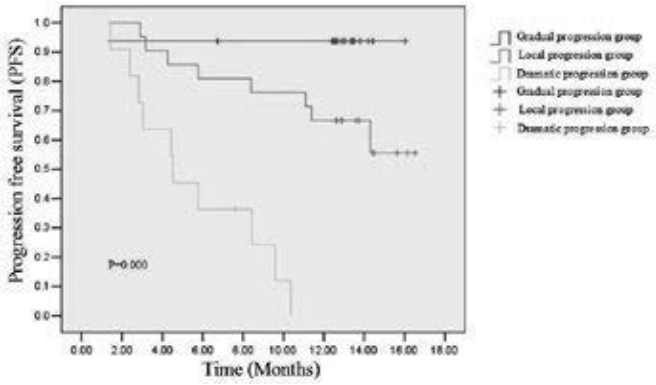
Background: Acquired resistance is inevitable after epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment in advanced NSCLC with EGFR mutation. Clinical modes of EGFR-TKI failure has been reported to be associated with the efficacy of subsequent treatment. More than 50% patients treated with first-line EGFR-TKI acquired resistance had a secondary EGFR Thr790Met (T790M) mutation. Osimertinib is a potent, irreversible EGFR-TKI targeting EGFR T790M mutation. This study aimed to investigate the difference of disease control rate (DCR) and progression free survival (PFS) after Osimertinib treatment and exam their association with clinical failure modes after first line EGFR-TKI. **Method:** This is a secondary analysis of a prospective randomized study from two clinical centers. The eligibility criteria of the trial included: NSCLC Stage IIIB/IV; EGFR mutation positive; Failed after first-line EGFR-TKI treatment; Plasma T790M Positive; Second-line Osimertinib. According to Yang et el 2013, the clinical modes of EGFR-TKI failure were classified to dramatic progression, gradual progression, local progression. The primary endpoints were DCR and PFS. **Result:** From December 2016 to April 2017, a total of 48 patients enrolled: 11 patients dramatic progression,16 gradual progression, and 21 local progression. After a median follow-up of 12.6 (range 1.3-16.5) months, the DCR rate was 10 of 11(90.9%), 15 of 16 (93.8%), and 21 of 21 (100.0%), for the dramatic progression, gradual progression, and local progression groups, respectively. The mean PFS for the dramatic progression, gradual progression, local progression groups were 5.7, 13.0, 15.1 months, respectively. The median PFS for the gradual progression and local progression groups have not reached. The median PFS for the dramatic progression was 4.5 months. There was a significant difference in PFS between the three groups (p<0.0001).(Figure 1)



Conclusion: Osimertinib has a significant better PFS in gradual progression and local progression groups than dramatic progression group with plasma EGFR T790M mutations acquired resistance in NSCLC.

Keywords: osimertinib, Clinical failure modes, plasma T790M

P2.13-24 PROSPECTIVE EFFICACY OF OSIMERTINIB IN CIRCULATING TUMOUR DNA (CTDNA) T790M-MUTANT NSCLC PATIENTS

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Background: Liquid biopsy circulating tumor DNA (ctDNA) analysis in advanced EGFR-mutant NSCLC patients is an approved tool for molecular profiling and disease surveillance when tissue is not available. Long-term efficacy of osimertinib in patients with the T790M resistance mutation positive detected only by ctDNA (without tissue information) has not been fully validated. **Method:** In a prospective study, EGFR-mutant advanced NSCLC patients with acquired resistance to EGFR TKI, in whom a repeat tissue biopsy was not feasible, were assessed for ctDNA T790M mutational status using InVisionSeqTM. T790M-positive NSCLC patients received osimertinib (80 mg daily; extended access program or approval) at RECIST progression. The objectives were to assess: proportion of patients with acquired ctDNA-T790M positive; overall survival (OS) of the overall EGFR-mutant population as well as OS comparison for T790M +ve/-ve. Also, for those T790M-positive NSCLC patients who received osimertinib in a real world data we assessed: response rate (RR) according to RECIST 1.1 by investigator and progression free survival (PFS), calculated from the date of osimertinib initiation until the date of progression or death (whichever came first), or the date of last follow-up are also reported. **Result:** We recruited 82 patients (71% female, median age 64 years, 72% Del19 EGFR mutation, 71% never-smokers). The ctDNA T790M mutation was detected in 55% (N=45) of NSCLC patients. Median OS of EGFR-mutant population was 38.2 months (mo.). According to T790M status, median OS was 41.2 months and 30.4 mo. for T790M-positive and T790M-negative NSCLC patients, respectively. Both cohorts had already received a median of 3 previous treatment lines. In 40 T790M-positive NSCLC patients who receive osimertinib, RR was 55% (PR: 55%, SD 27.5% and PD: 12.5%) and median PFS of 8.5 mo. Median OS on osimertinib among 10 patients with brain and/or leptomeningeal metastases at baseline was of 13.4 months. **Conclusion:** In patients with acquired resistance to first- or second-generation EGFR TKIs, ctDNA T790M detection by InVisionSeq™ is equivalent to what has been reported in tissue biopsy. Osimertinib has clinical benefit in patients for which the T790M resistance mutation is detected only through a liquid biopsy procedure.

Keywords: ctDNA T790M, advanced NSCLC, osimertinib

P2.13-25 ANALYSIS OF EGFR MUTATIONS USING CIRCULATING TUMOUR DNA (CTDNA) IN NON-SMALL CELL LUNG CANCER PATIENTS IN NORTH EAST SCOTLAND

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Background: Treatment with 1st or 2nd generation *EGFR* tyrosine kinase inhibitors (EGFR-TKIs) can benefit patients with EGFR-TKI sensitising mutations but eventually patients develop resistance. The main cause of resistance - *EGFR* c.2369C>T (T790M) mutation - can now be targeted using 3rd generation EGFR-TKIs. *EGFR* testing using ctDNA provides a minimally invasive method of mutation detection. This study aimed to: 1) Validate the Roche CE-IVD cfDNA workflow for *EGFR* mutation detection. 2) Assess the usefulness of monitoring patients using ctDNA *EGFR* testing throughout EGFR-TKI treatment, particularly to determine whether *EGFR* c.2369C>T resistance mutation could be detected prior to clinical progression **Method:** Control samples with known allele frequencies and 86 blood samples, collected from 17 patients throughout EGFR-TKI treatment, were analysed. The ctDNA was extracted using the cobas® cfDNA sample preparation kit and mutation analysis conducted by the cobas® EGFR mutation test v2. The semi-quantitative index (SQI) was used to indicate intra-patient fluctuations in mutation level between sequential samples. Mutation results were correlated with clinical status. **Result:** Control samples proved the method was highly sensitive, with the ability to detect a range of *EGFR* mutations present at 1% allele frequency, with 100% specificity. A valid result was obtained for all patient samples tested. Radiological/clinical assessment of 11/17 patients indicated progression; 6/11 (55%) displayed T790M in ctDNA which was detectable prior to clinical progression in 4 patients. Other well documented resistance mechanisms were not sought in this study. The original *EGFR* mutation was not detected in sequential ctDNA samples during treatment in 7 patients. Within this group, 3/7 patients continued to respond well to treatment. However, 4/7 displayed signs of clinical progression including brain metastasis only progression. The lack of mutation detection in these patients may be due to false negative results relating to inadequate ctDNA level, in particular due to the blood-brain barrier. **Conclusion:** Analysis of controls and sequential samples obtained from patients undergoing EGFR-TKI treatment showed the technique to be sensitive and specific with the ability to detect original sensitising mutations and emergence of T790M. There is evidence that this technique can be useful in identifying the T790M mutation prior to signs of clinical progression, and that results from ctDNA generally correlate well with clinical status.

Keywords: lung cancer, ctDNA, T790M

P2.13-26 IMPACT OF CONCURRENT TUMOR SUPPRESSOR GENE MUTATION ON CLINICAL OUTCOMES IN EGFR MUTATED NSCLC TREATED WITH FIRST-LINE TKI

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Background: Epidermal growth factor receptor (EGFR) mutations confer good prognosis in non-small cell lung cancer (NSCLC) and a multitude of tyrosine kinase inhibitors (TKI) are currently available for treatment of these tumors. However, development of resistance to these drugs is imminent and remains a challenging clinical conundrum. Few studies have demonstrated the presence of concurrent tumor protein 53 (TP53) mutation to result in earlier resistance to TKI. We conducted a retrospective study to determine whether or not TP53 or other tumor suppressive gene mutations impacted clinical outcomes in EGFR mutated NSCLC. Progression free survival (PFS) and disease control rate (DCR) as defined by complete response (CR), partial response (PR) or stable disease (SD) were assessed. **Method:** Patients with EGFR mutated NSCLC treated with first-line TKI at our institution from January 2014 to June 2017 were included. Patients were dichotomized based on presence or absence of TP53 mutation. Comparisons were also made between patients with and without any tumor suppressor gene mutations. Descriptive statistics was used to summarize the data. Two sample t-test assuming unequal variance was used to compare mean PFS between groups and chi-square test to compare proportions. **Result:** Of 44 patients, 72.7% had exon 19 deletions and 27.3% had exon 21 L858R point mutation. 54.5% patients had a concomitant tumor suppressor gene mutation with TP53 being the most common gene mutated (47.7%). 45.4% patients had no concurrent mutations. Comparative results is shown in Table 1

(See next page)

	TP53	NO TP53	Any tumor suppressor gene mutation	No tumor suppressor gene mutations
Total patients (n=44)	21 (47.7%)	23 (52.3%)	24 (54.5%)	20 (45.4%)
Type of EGFR Mutation				
Exon 19 deletion (n=32)	15/21 (71.4%)	17/23 (73.9%)	17/24 (70.1%)	15/20 (75%)
Exon 21 L858R point mutation (n=12)	6/21 (19%)	6/23 (13%)	7/24 (16.7%)	5/20 (15%)
Type of EGFR Inhibitor				
Afatinib (n=7)	4/21 (19%)	3/23 (13%)	4/24 (16.7%)	3/20 (15%)
Erlotinib(n=37)	17/21 (81%)	20/23 (87%)	20/24 83.3%)	17/20 (85%)
Results				
Mean PFS	13.6 months	20.9 months	16.1 months	18.9 months
Median PFS	9.7 months	16.7 months	10.9 months	16.7months
Geomean PFS	10.3 months	17.3 months	11.9 months	15.7 months
P (T<=t) two tail	0.172		0.611	
DCR (CR+PR+SD)	10/21(47.6%)	10/23 (43.5%)	12/24 (50%)	8/20 (40%)

Table 1: Descriptive data and statistical value of patients with TP53, no TP53, any tumor suppressor gene mutation and no tumor suppressor gene mutations

Conclusion: Mean and median PFS were longer in patients without concomitant tumor suppressive gene mutations. Though statistically not significant likely due to lack of power, these results are provocative. This should be explored further in a larger patient population and future clinical trials with EGFR TKI stratifying patients based on concomitant tumor suppressor gene mutations.

Keywords: EGFR, TKI, tumor suppressor gene mutation

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P2.13-27 DEVELOPMENT, INTERNAL VALIDATION, AND CALIBRATION OF A RISK SCORE TO PREDICT SURVIVAL IN PATIENTS WITH EGFR MUTANT NSCLC

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Background: The emergence of molecularly targeted therapy has transformed the clinical landscape of metastatic non-small cell lung cancer (NSCLC). We profiled a local cohort of *EGFR* mutation-positive, advanced NSCLC patients who were treated with first-line *EGFR* tyrosine kinase inhibitors (TKIs) and sought to develop a nomogram-based prognostic model for predicting clinical outcomes in this patient subgroup. **Method:** A cohort of 199 *EGFR* mutation-positive, advanced NSCLC patients was retrospectively analyzed, with the inclusion criteria as follows: at least one sensitizing *EGFR* mutation, diagnosed with metastatic disease at diagnosis or incurable disease recurrence, and subsequently treated with first-line *EGFR* TKI for at least one-month duration. The Mnet machine learning algorithm was used to select variables for inclusion into the Cox model, with an alpha of 0.06 and gamma of 3. Internal validation was performed by plotting the bootstrapped (*n = 200* bootstrap samples) time-dependent AUC according to the method described in Uno *et* al. (2007), and the predictive power of the model was assessed by computing Harrell's C and Somers' D concordance statistics. Internal calibration was evaluated using a plotted graph of observed vs predicted mortality risks of five risk groups ("low risk", "medium-low risk", "medium risk", "medium-high risk", and "high risk" quintiles), as well as the Kaplan-Meier survival estimates for each quintile. **Result:** The resultant prognostic nomogram included the following variables - total white blood cell (WBC) count, hemoglobin levels, serum LDH levels, Neutrophil/Lymphocyte Ratio (NLR), ethnicity (Chinese *vs* non-Chinese), Karnofsky-Performance Status (score of '90-100' or '70-80' *vs* '0-60'), Charlson Comorbidity Index (≥3, 2, or 1 *vs* 0), neurological symptoms, brain, lung/pleural and adrenal metastases. The time-dependent AUC at 6, 12 and 18 months were 62.8%, 65.5%, and 67.4% respectively and the Harrell's C and Somers' D concordances were 0.6342 and 0.2684 respectively. The 12-month observed *vs* predicted overall survival (OS) probabilities were 0.56 *vs* 0.61, 0.64 *vs* 0.66, 0.55 *vs* 0.69, 0.77 *vs* 0.71, and 0.87 *vs* 0.73 respectively for each of the five risk groups described earlier, suggesting good calibration. Survival curves for the five risk groups also segregated well on visual inspection, and was corroborated by log-rank P < 0.001. **Conclusion:** We herein report a novel nomogram-based risk scoring system that incorporates biochemical, immune and clinical variables to provide fairly robust OS estimation in *EGFR* mutation-positive, advanced NSCLC patients treated with first-line *EGFR* TKIs.

Keywords: Risk prediction, EGFR, Nomogram

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P2.13-28 COMPARISON OF DDPCR AND NGS IN LIQUID BIOPSY TO PATHOLOGY RESULTS IN EGFR-MUTATED NSCLC

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Background: In the blood of EGFR-mutated NSCLC patients, primary activating mutations as well as the resistance mutation T790M can be detected in ctDNA (liquid biopsy). Several methods have been developed for this purpose but techniques are still evolving. We compared two tests (BioRad digital droplet PCR (ddPCR) and IonTorrent/Oncomine next generation sequencing (NGS)) for ctDNA primary activating EGFR mutations and T790M to results of pathological investigation of a tissue biopsies or pleural fluid. **Method:** We collected the data on liquid biopsies performed on EGFRm+ NSCLC patients from November 2016 untill February 2018 at the Erasmus MC. In this study we analyzed all liquid biopsies from patients with EGFR mutations at baseline or after progression from whom also pathology results in the same time frame of treatment were available. Liquid biopsy results obtained from the two methods were compared to each other as well as to the pathology results. Cohen's kappa was calculated as measure of agreement. **Result:** In total, 29 out of 123 patients (24%) did meet the criteria and were included in our study. Concordance for the detection of the primary activating mutation between pathology results and blood was 66% for the BioRad ddPCR and 83% for the IonTorrent/Oncomine NGS (n=29). Concordance for the detection of p.T790M between pathology results and blood was 76% for both ddPCR and NGS (κ=0.51, n=29). In 5 patients (17%), p.T790M was detected by pathology results but not in cfDNA. In 2 patients (7%), p.T790M was detected in blood but not in the pathology specimen. Concordance between ddPCR and NGS on blood for the primary activating EGFR mutation was 83% (κ=0.57, n=29) and for p.T790M detection 93% (κ=0.86, n=29). **Conclusion:** Detection of mutations in plasma show reasonable to high concordance with tissue biopsy. The method of testing defines the extent of the number of tested mutations and therefore the height of concordance. NGS seems to upscale the concordance of detection of the primary mutation due to examination of a broader panel of available mutations (in ddPCR only exon 19 deletions and exon 21 p.L858R are tested), but is comparable to ddPCR on the level of a specific mutation in the panel (p.T790M). Discrepant results between pathology specimens and liquid biopsy remain a difficult issue for clinical practice.

Keywords: EGFR, liquid biopsy, NSCLC

P2.13 TARGETED THERAPY
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P2.13-29 IL-22 CONFERS RESISTANCE TO EGFR-TKIS IN NON-SMALL CELL LUNG CANCER BEARING EGFR GENE MUTATION AND AMPLIFICATION

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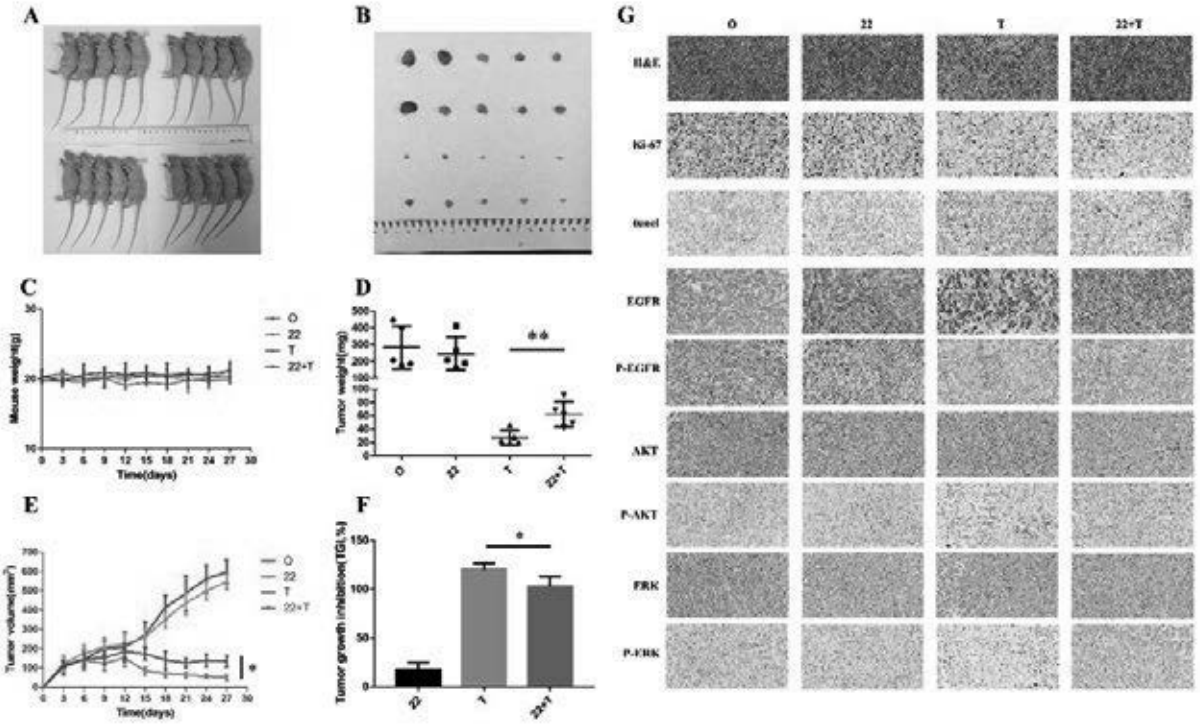
Background: The effect of epidermal growth factor receptor(EGFR)-targeted strategy is hindered by drug resistance. IL-22 can promote tumor growth and induce resistance to chemotherapy in human lung cancer cells. The aim of our study was to investigate the mechanism of IL-22-induced resistance to EGFR-tyrosine kinase inhibitors(EGFR-TKIs)in the NSCLC. **Method:** The tissues and plasma of patients taking EGFR-TKIs

were used to examine the correlation between the drug's efficacy and IL-22 level. We identified IL-22-induced EGFR-TKIs resistance and the effect of IL-22 on EGFR/AKT/ERK pathways in NSCLC PC-9 and HCC827 cells by CCK-8 assay, flow cytometric analysis, and western blotting. Then, we established the PC-9 xenograft model with IL-22 exposure and used gefitinib combined with vehicle or IL-22 to treat mice. **Result:** We confirmed that IL-22 can inhibit the effect of gefitinib on NSCLC cells and determined the effects of IL-22 on EGFR/AKT/ERK pathways. Then, we showed that IL-22 exposures could promote tumor growth and induce resistance to gefitinib in the PC-9 xenograft model. **Conclusion:** These results suggest that IL-22 contributes to tumor progression and EGFR-TKIs resistance in NSCLC. Therefore, IL-22 is a potential therapeutic target for EGFR-TKIs resistance.

Keywords: IL-22, EGFR, Resistance



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P2.13-30 HIGH-DOSE ICOTINIB IN ADVANCED NON-SMALL CELL LUNG CANCER WITH EGFR 21 L858R MUTATION: THE RANDOMIZED, OPEN-LABEL INCREASE STUDY

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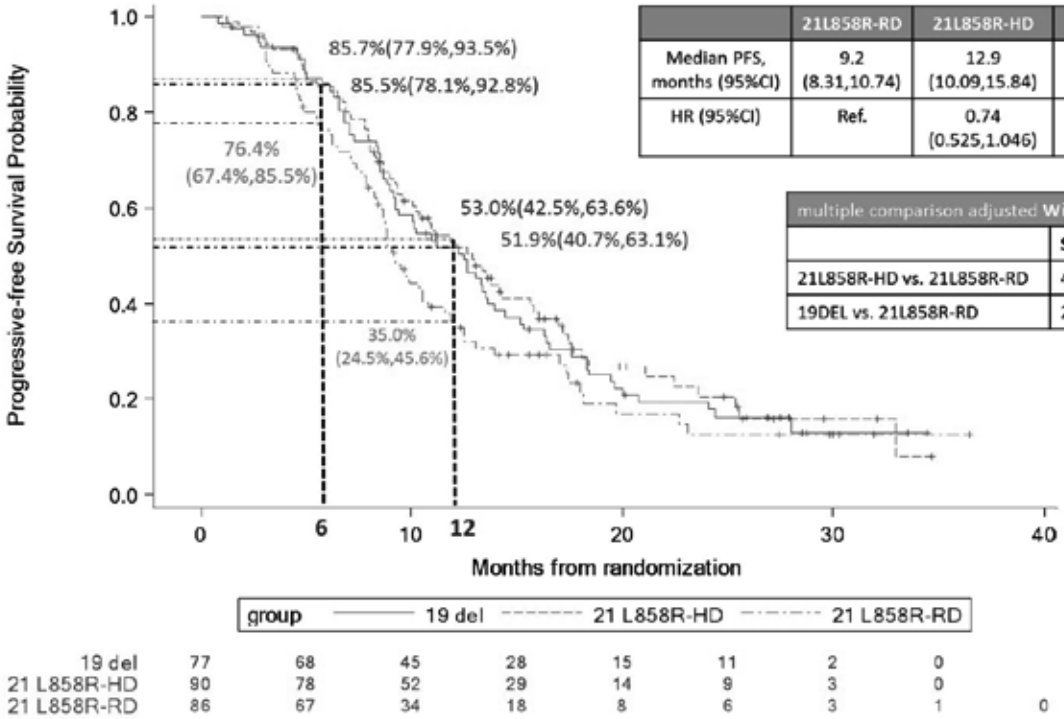
Background: NSCLC patients with 21 L858R mutation are less responsive to EGFR TKI treatment. This study aims to determine if high-dose icotinib can improve tumor response and progression-free survival (PFS) in this patient population. **Method:** In this randomized, open-label, multicenter phase II trial (INCREASE), patients with treatment-naïve, EGFR-mutant (19 deletion or 21 L858R at 1:2 ratio) lung adenocarcinoma were enrolled. Patients with 21 L858R were randomized to receive either routine-dose (125mg tid, 21 L858R-RD) or high-dose icotinib (250mg tid, 21 L858R-HD), whereas patients with 19 del receive icotinib 125mg tid until progression. The primary endpoint is PFS. **Result:** Between May 22, 2015 and November 15, 2017, 253 patients were enrolled (21 L858R-RD group, n=86; 21 L858R-HD group, n=90; 19 del group, n=77). Baseline characteristics were similar among groups with the exception of age. The median PFS (by IRC) were 9.20 months (95%CI 8.31, 10.74), 12.85 (10.09, 15.84), and 12.48 (9.23, 13.93) for 21 L858R-RD, 21 L858R-HD, and 19 del group, respectively, for modified intent-to-treat population (p=0.0848); and 8.84 months (8.21, 10.55), 12.62 (9.59, 14.26), and 12.22 (9.17, 13.60) for per-protocol set (p=0.0445). The ORR were 47.7%, 73.3%, and 75.3% for 21 L858R-RD, 21 L858R-HD, and 19 del group, respectively (p=0.0007). Patients in high-dose group experienced significantly higher incidence of AEs than routine-dose groups (21 L858R-RD vs 21 L858R-HD vs 19 del: 54.7% vs 81.1% vs 66.2%, p=0.0007), but the incidences of grade 3/4 AE were similar among the groups (4.7% vs 5.6% vs 5.2%, p=0.9632).

(See next page)

Figure1. PFS in 21 L858R-RD,21 L858R-HD,and 19del group (mITT ,by IRC)



	21L858R-RD	21L858R-HD	19DEL
Median PFS, months (95%CI)	9.2 (8.31,10.74)	12.9 (10.09,15.84)	12.5 (9.23,13.93)
HR (95%CI)	Ref.	0.74 (0.525,1.046)	0.80 (0.562,1.124)

multiple comparison adjusted Wilcoxon test（vs 21L858R-RD）		
	Statistic	P-value
21L858R-HD vs. 21L858R-RD	4.3408	0.0744
19DEL vs. 21L858R-RD	2.7454	0.1951

Conclusion: A prolonged PFS and improved ORR were observed in patients treated with high-dose icotinib in NSCLC patients harboring 21 L858R mutation with tolerable toxicity.

Keywords: EFGR 21 L858R mutation, non-small-cell lung cancer (NSCLC), icotinib

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-31 P.(LEU747PRO) MUTATION LEADS TO MISDIAGNOSIS IN EGFR MUTATION ASSESSMENT – ANALYSIS IN A COHORT OF 1841 POLISH NSCLC PATIENTS

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Background: Epidermal growth factor receptor (EGFR) mutation assessment is essential for targeted therapy of non-small cell lung cancer (NSCLC) as predictive biomarker of the response to EGFR tyrosine kinase inhibitors (EGFR-TKI). There is a number of well-known actionable mutations in EGFR gene such as a deletions in exon 19 or p.(Leu858Arg), still some others, infrequent or complex are also observed. Missense substitution p.(Leu747Pro) (c.2239_2240TT>CC) is one of the rare mutations that might be misdiagnosed if EGFR mutation analysis is performed with commercial real-time PCR based kits. The eventual clinical consequences are considerable. While p.(Leu747Pro) substitution is reported as an most likely inhibiting mutation, it might be confused with an activating deletion in exon 19 of EGFR gene. Up to date, majority of published reports providing data on p.(Leu747Pro) role in resistance towards EGFR-TKI came from Asia. The frequency of p.(Leu747Pro) in the European population has not been evaluated yet. It was detected accidentally in large NSCLC patients cohorts using varied molecular methods. The aim of the study was to assess the frequency of p.(Leu747Pro) in a group of 1841 NSCLC patients referred for EGFR mutation analysis between 2015 and 2017 to the National Institute of Tuberculosis and Lung Diseases. **Method:** EGFR mutation analysis was performed with CE-IVD real-time PCR kit using complementary primer pairs and oligonucleotide probes. The frequency of EGFR gene mutations was 8,4% (n=155), including deletions in exon 19 (n=84), p.Leu858Arg (n=56), insertions in exon 20 (n=9), p.Glu719X (n=1), p.Glu719X and p.Ser768Ile(n=5). All samples with a deletion in exon 19 were reanalyzed by PNA-LNA PCR clamp to confirm the test result. In case of a discrepancy between the outcomes, direct Sanger sequencing was performed. **Result:** Upon reanalysis, 4 (4,8%) lung adenocarcinoma patients (3 female, 1 male) with initially identified deletion in exon 19 proved to be misdiagnosed. Instead, in all p.(Leu747Pro) substitution was decisively confirmed with direct sequencing. One patient with p.(Leu747Pro) mutation in EGFR gene gained clinical benefit from EGFR-TKI therapy. She achieved partial response according to RECIST while treated with erlotynib for 7 months. **Conclusion:** Diagnostic laboratories as well as clinicians should be aware of the commercial real-time PCR based test limitations, despite their IVD certification. New methods such as next generation sequencing may solve misdiagnosis problem with the exon 19 deletion of EGFR gene. Data concerning rare variants in EGFR gene are limited and results are varied, the mechanism of the p.(Leu747Pro) variant response to EGFR-TKIs needs further investigation.

Keywords: EGFR mutation assessment, NSCLC, misdiagnosis

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-32 TAK-788 IS A NOVEL AND POTENT TYROSINE KINASE INHIBITOR WITH SELECTIVE ACTIVITY AGAINST EGFR/HER2

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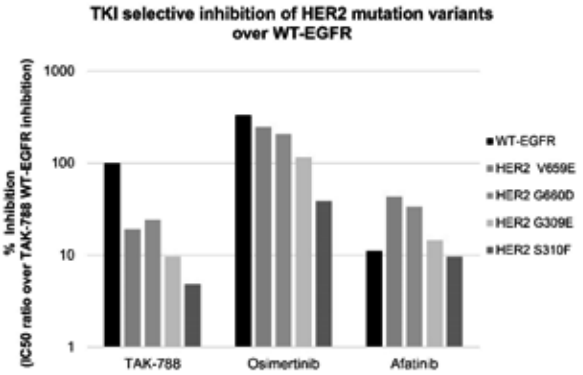
Background: Dysregulation of the EGFR family member HER2 (human epidermal growth factor receptor 2) plays an important role in many cancers. HER2 exon 20 in-frame insertion mutations occur in 2–4% of non-small cell lung carcinomas (NSCLC). Despite current HER2-directed treatments, no approved therapies exist for patients with cancers harboring HER2 mutations. Unlike other activating mutations, exon 20 insertions induce a conformational change leading to significant homology to the ATP-binding pocket of WT proteins. As such, clinical development of tyrosine kinase inhibitors (TKIs) against these insertions has been challenging, as inhibition of WT-EGFR is associated with clinical dose-limiting toxicities, such as diarrhea and skin rash. TAK-788 was designed to potently inhibit oncogenic variants with desirable selectivity over WT-EGFR. TAK-788 inhibits mutant EGFR and HER2 via covalent modification of EGFR-Cys797 and HER2-Cys805. Here, we characterized the non-clinical activity of TAK-788 in HER2 exon 20 insertion and substitution mutants and contrasted it with other TKIs. **Method:** *In vitro* activity was assessed by measuring viability in engineered Ba/F3 lines expressing different HER2 mutation variants (substitutions and insertions). Inhibition of WT-EGFR was assessed by measuring EGFR phosphorylation in A431 cells that overexpress WT-EGFR. *In vivo* activity was assessed by monitoring tumor volume. **Result:** TAK-788 inhibited all HER2 mutations tested, including exon 20 insertions and point mutations, more potently than it inhibits WT-EGFR (**Figure**), suggesting an acceptable therapeutic window compared with other TKIs. TAK-788 *in vitro* potency in these mutations has also been confirmed *in vivo* with tumor xenograft models and in a phase 1 clinical trial.



Conclusion: The favorable selectivity and potency observed in these *in vitro* experiments for HER2 exon 20 insertions/point mutations supports the ongoing exploration of TAK-788 in NSCLC patients with HER2 mutations (NCT02716116) as well as in other HER2 mutant–driven cancer patients.

Keywords: tyrosine kinase inhibitor, HER2, exon 20

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-33 A CASE REPORT OF EXCEPTIONAL CLINICAL RESPONSE TO MEK INHIBITION IN A PATIENT WITH NRAS MUTATION POSITIVE NSCLC

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Background: NRAS mutation occurs in <1% patients with non-small cell lung cancer (NSCLC). Pre-clinical lung cancer models with NRAS mutation have demonstrated response to single agent MEK inhibition with activation of the PI3K-AKT-mTOR pathway as a putative resistance mechanism. There are a paucity of data for MEK inhibition in the clinical setting for NRAS positive disease. To our knowledge, this is the first report of an NRAS positive NSCLC patient to be treated with a MEK inhibitor. **Method:** A 51 year old female with advanced NSCLC was identified to have an NRAS Q61K mutation in both archival tumour and circulating tumour DNA (ctDNA) within the TARGET study. Tumour was analysed for a panel of 24 genes using an amplicon based NGS assay and circulating tumour DNA using a hybridisation capture technique of 650 genes. The patient was allocated in the Molecular Tumour Board to participate in the Phase I study of LNP3794, a first-in-human dose escalation study of a MEK inhibitor with primary endpoint of safety and tolerability. Serial plasma samples were acquired during treatment for ctDNA analysis and fresh tissue was acquired pre-treatment and on disease progression. A PDX model was implanted from the disease progression sample to explore functional mechanisms of resistance **Result:** The patient was commenced on LNP3794 in Jun 2015 having previously progressed on first line chemotherapy with extensive lung metastases. Initially she exhibited G3 toxicity with LNP3794, managed by dose reduction and subsequently was well tolerated. Within 6 weeks the patient demonstrated an exceptional response with 44% reduction in tumour by RECIST 1.1, resolution of a number of lesions and with clear symptomatic benefit. She remained on study for 12 months with maintained PR. The NRAS mutant allele fraction in blood fell from 20% to not detectable within 6 months and subsequently started to rise 3 months prior to radiological progression. A PIK3CA Q546K mutation was identified by Foundation Medicine at progression. The PDX is currently growing at a slow rate and the hypothesis of re-sensitisation with a combination of an mTOR inhibitor with MEK inhibition will be explored. **Conclusion:** These data support further evaluation of MEK inhibitors in patients with NRAS positive NSCLC. As a rare population a multi-site study would be required. Combination with inhibitors of the PI3k-AKT-mTOR pathway, if tolerated, may further prolong response and clinical benefit and should also be explored.

Keywords: NRAS, MEK, NSCLC

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-34 LONG INTERGENIC NON-CODING RNA 00665 INDUCES ACQUIRED RESISTANCE TO GEFITINIB IN NON-SMALL-CELL LUNG CANCER

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Background: Gefitinib, a tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR-TKI), has been used as the first choice of treatment for advanced non-small cell lung cancer (NSCLC). However, during the course of treatment cancer cells often develop resistance to gefitinib without fully understood mechanisms. In recent years, numerous studies have shown that long non-coding RNAs (lncRNAs) play vital roles in modulating various biological processes, such as cell apoptosis, proliferation, migration, and invasion. Nevertheless cancer drug resistance mechanisms related to LncRNAs and their important roles in cancer development are still poorly understood. In this study, we aimed to elucidate an important role of long intergenic non-coding RNA 00665 (LINC00665) in developing resistance to gefitinib in NSCLC. **Method:** Quantitative reverse transcription PCR (qRT-PCR) was performed to examine the expression levels of LINC00665 in 10 pairs of LUAD tissues from patients who had never been treated with gefitinib (NG) and those who were treated with gefitinib but developed resistance (GR). The effect of LINC00665 on proliferation and apoptosis in gefitinib-resistant cells was evaluated by CCK8, colony formation, flow-cytometric analysis and in vivo tumor formation assays. Western-blot and immunohistochemistry were used to evaluate the expression of EGFR and its downstream event. **Result:** LINC00665 expression levels were significantly increased in NSCLC patients who developed acquired resistance to gefitinib compared to the NG group.Furthermore, LINC00665 inhibition reversed gefitinib sensitivity both in vitro and in vivo by suppressing cell growth and induced cell apoptosis. Importantly, knockdown of LINC00665 marked decreased activation of EGFR and its downstream event Akt and ERK1/2. **Conclusion:** Taken together,our study demonstrates that LINC00665 may be a potential biomarker of response to gefitinib as well as a novel therapeutic target for future treatment of NSCLC.

Keywords: lncRNA, Acquired resistance, EGFR-TKIs

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-35 INHIBITION OF H3K27 DEMETHYLATION IS TOXIC IN POORLY DIFFERENTIATED SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) is a solid tumor with a 5% 5-year survival rate, and often contain major alterations within the epigenetic landscape. In a high throughput drug screen by the Genomics of Drug Sensitivity in Cancer (GDSC), SCLC cell lines were found exquisitely sensitive to GSK-J4, a selective H3K27 demethylase inhibitor. Given that increases in H3K27me3 are associated with cell differentiation, GSK-J4 offers a potential therapeutic strategy in the treatment of SCLC. Our goals here were to validate the screen data, determine the mechanism of GSK-J4 action, and identify putative biomarkers that impart sensitivity to this epigenetic therapeutic strategy. **Method:** Using a combination of bioinformatics and western blotting, we identified biomarkers for the effectiveness of GSK-J4 in SCLC. RNA-seq, western blotting, cell viability and apoptosis assays were used to determine the mechanism for GSK-J4 action. Multiple mouse patient derived xenograft (PDX) models were used to determine the effectiveness of GSK-J4 *in vivo*. **Result:** We found that several markers of neuroendocrine differentiation were markedly decreased in GSK-J4 sensitive SCLCs when compared to resistant SCLC cell lines, suggesting that a lack of differentiation imparts SCLC sensitivity to GSK-J4. As expected, GSK-J4 induced a global accumulation of H3K27me3 in SCLC cell lines, and induced cell death through an ER stress mediated pathway. This cell-death response was blocked by knockdown of the ER stress pathway. Further, mouse SCLC PDX models demonstrated that GSK-J4 is effective in poorly differentiated SCLC *in vivo*. **Conclusion:** These findings offer a novel epigenetic-based therapeutic strategy for the treatment of poorly differentiated SCLCs.

Keywords: ER stress, SCLC, epigenetics

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-36 ANALYSIS OF CDK4/6 PATHWAY ACTIVITY IN LUNG ADENOCARCINOMA PATIENTS WITH ONCOGENIC DRIVER MUTATIONS IN CHINA

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Background: Selective tyrosine kinase inhibitors (TKIs) targeting key driver mutations have significantly improved the outcomes of lung adenocarcinoma (ADC) patients. However, rapid emergence of drug resistance underlines the need for more sustainable treatment options, which mostly requires the combined use of multiple drugs. This study aims to establish the relationship between CDK4/6 pathway activity and oncogenic driver mutations in EGFR, ALK and KRAS in Chinese lung ADC patients. The results will provide a biomarker strategy for rational combination therapy involving TKIs and CDK4/6 inhibitors. **Method:** Total of 108 stage I-III NSCLC ADC patients who have completed resection in Shanghai Chest Hospital, and whose oncogenic driver mutations including EGFR, ALK and KRAS have been determined, were selected for the current study. Paraffin-embedded tissue samples from these patients were analyzed by Immunohistochemistry (IHC) for expression level of various CDK4/6 pathway markers. Stained sections were examined using Aperio eSlide manager, and H score was calculated for each marker and used for expression comparison between patients. **Result:** EGFR, ALK and KRAS mutations were examined in all the patients. EGFR L858R mutation was found in 30 patients (27.8%) and 27 patients (25%) showed EGFR Exon19 deletion. In addition, KRAS mutation was found in 5 patients (4.6%) and only one patient manifested EML4-ALK fusion positive. Preliminary IHC results show that EGFR L858R mutation seems to be associated with higher Rb and phospho-Rb levels. A trend of increased number of patients carrying EGFR L858R mutation was detected in Rb/ phospho-Rb positive samples (18/54, 33.3% & 17/50, 34%) compared with Rb/ phospho-Rb negative samples (12/54, 22.2% & 13/58, 22.4%), although the differences are not yet statistically significant (P= 0.28 & 0.2, Fisher's exact test). And EGFR Exon 19 deletion was just the opposite. Higher percentage of patients with EGFR 19 exon deletion was found in Rb/ phospho-Rb negative group (17/54, 31.5% & 19/58, 32.8%) compared with Rb/ phospho-Rb positive group (10/54, 18.5% & 8/50, 16%) with P value of 0.18 and 0.049, respectively. KRAS mutation also appeared to be linked with higher Rb and phospho-Rb levels in tumor tissue. **Conclusion:** The observed correlation between oncogenic driver mutations and Rb/phospho-Rb levels suggests that combined use of EGFR TKIs and CDK4/6 inhibitors may be beneficial to lung ADC patient with EGFR L858 mutation. Patients with KRAS mutations may also benefit from CDK4/6 inhibitors as a single therapeutic agent.

Keywords: lung adenocarcinoma, oncogenic driver mutation, CDK4/6 pathway

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-37 CHLOROQUINE OVERCOMES ACQUIRED RESISTANCE TO ICOTINIB IN VITRO AND IN VIVO THROUGH STAT3/STMN1 PATHWAY

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Background: Icotinib, an oral first-generation EGFR inhibitor, in non-small cell lung cancer (NSCLC) patients rarely results in complete tumor remission and frequently challenged by acquired resistance, eventually leading to tumor relapse. Recently, autophagy is considered as an important mechanism of resistance to TKI. Herein, we investigated the autophagy induction as well as the effects of its inhibitor chloroquine on anti-acquired resistant lung adenocarcinoma activity of icotinib in vitro and in vivo. **Method:** Apoptosis was measured with flow cytometry and tunel. Growth-inhibitory effects of icotinib were evaluated in vitro with MTT and colony formation assay as well as in vivo with mouse xenograft models. Autophagy was performed by transmission electron microscopy, immunochemistry and immunofluorescence. The inhibition of autophagy was achieved with siRNA or inhibitors. Gene expression was determined by western blot. **Result:** Icotinib potently induced apoptosis in PC-9 cell. Significant pro-apoptotic effects were noted in vitro and in vivo. In contrast, PC-9/GR and H1975 were found to be highly resistant to icotinib treatment. Autophagy was found in patients with acquired resistance to EGFR-TKIs and Icotinib was also detected to induce productive autophagy in PC-9/GR and H1975 cells. Mechanistically, icotinib triggers STAT3/ STMN1-dependent early protective autophagic response in PC-9/GR and H1975 cells. The crucial role of this pathway in icotinib-induced drug resistance was verified by silencing STAT3 and STMN1. Genetic and pharmacological autophagy blockade resulted in significant icotinib-induced apoptosis in cells defined as sensitive or resistant. Finally, chlororquine-based combinatorial therapy effectively blocked tumor growth in xenografts with TKI-resistant cancer cells. **Conclusion:** Our findings strongly support chloroquine, generally considered nontoxic and remarkably inexpensive, might be used in combination with TKIs in patients with non–small cell lung cancer, harboring EGFR mutations to overcome TKI resistance and prolong survival.

Keywords: Autophagy, acquired resistance to EGFR-TKI, icotinib

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-38 IMPACT OF TYROSINE KINASE INHIBITOR (TKI) DOSE ON OUTCOMES OF PATIENTS WITH LUNG CANCER

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Background: FDA approved starting doses of TKis are based on maximum tolerated dose (MTD) in clinical trials. In practice however, patients are started on lower doses due to tolerability concerns or dose-reduced subsequently for toxicity. Very few studies have addressed the impact of dose on clinical outcomes. **Method:** An IRB approved chart review of lung cancer patients receiving oral TKI therapy between 1/2014 and 6/2017 at our institution was conducted. Patients who were started on TKIs at the FDA dose (Group A) dose were compared to those started on a lower dose (Group B) for progression free survival (PFS), overall survival (OS), and time-to-discontinuation. Fisher's exact test was used to compare groups on categorical variables and the Mann-Whitney test was used for continuous variables. The Kaplan-Meier method was used to estimate time-to-event stratified by group, and Cox regression models were used to adjust for potential confounders. **Result:** Seventy-nine patients were treated with an EGFR inhibitor and 11 patients were treated an ALK inhibitor. The Kaplan-Meier estimates of the median time-to-progression for Group A (n = 67) and Group B (n = 23) were 13.4 months (95% CI: 8.88, 15.55) and 15.1 months (95% CI: 5.56, 21.5), respectively; and for time-to-discontinuation, the estimates were 13.5 months (95% CI: 11,

20.15) for Group A and 21.5 months (95% CI: 6.44,) for Group B. Median time to death was not estimable for OS. The predicted OS probability at approximately 15 months post treatment initiation for Group A was 81.8% (95% CI: 0.69, 0.90) vs. 80.5% (95% CI: 0.55, 0.92) for Group B. No statistically significant differences resulted from the Cox regression models. **Conclusion:** We found no evidence to support that patients who initiated therapy at full dose have different outcomes with respect to OS and PFS compared to those who initiated at a lower starting dose. Future prospective studies are needed to further evaluate this finding. Future clinical trials should report minimal effective dose in addition to MTD.

Keywords: tyrosine kinase inhibitor, starting dose, reduced dose

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-39 A PHASE IB TRIAL OF THE HSP90 INHIBITOR AUY922 IN COMBINATION WITH PEMETREXED IN METASTATIC NON-SQUAMOUS, NON-SMALL CELL LUNG CANCER PATIENTS

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Background: AUY922 demonstrates preclinical activity in non-small cell lung cancer (NSCLC) cell lines by potently inhibiting HSP90. As a single-agent, AUY922 showed clinical activity for NSCLC patients in a phase II trial, particularly in those with driver mutations in epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*), client proteins of HSP90. We previously demonstrated that AUY922 reliably decreases dihydrofolate reductase (DHFR) mRNA expression. Therefore, we conducted a phase Ib trial of the combination of AUY922 with pemetrexed, an antifolate inhibitor of DHFR. **Method:** In the dose-escalation portion, 9 patients with previously-treated metastatic non-squamous NSCLC were treated using a standard 3 + 3 design with pemetrexed at the standard 500 mg/m^2 dose, plus: AUY922 40 mg/m^2, 55 mg/m^2, or 70 mg/m^2 per week, respectively. After the maximum tolerated dose (MTD) was determined, an additional 4 patients were treated at the MTD. The primary endpoint was safety and tolerability. **Result:** Of 13 total patients, 9 (70%) harbored an *EGFR* mutation. Two grade 3 dose-limiting toxicities were observed in the 70 mg/m^2 cohort (thrombocytopenia and supraventricular tachycardia). Therefore, the MTD was determined to be 55 mg/m^2 with pemetrexed. At the MTD, 71% (n=5) required a dose reduction, with a median relative dose intensity (RDI) of 88%. Common drug-related adverse events (DRAE) included ocular toxicity or visual disturbances (n=9, 70%), fatigue (n=6, 46%), diarrhea (n=5, 38%), anemia (n=5, 38%), anorexia (n=4, 31%), and nausea (n=3, 23%). There were no grade 4-5 events. Maximum serum concentration (C_{max}) of AUY922 was associated with increased grade 2 DRAEs (r_s = 0.74, p < 0.01). The volume of distribution (VZ) was inversely associated with number of DRAEs (r_s = -0.81, p = 0.004) and number of ophthalmologic related DRAEs (r_s = -0.65, p = 0.04). The best response was partial response in one patient for 20 months, prior to expiration of all AUY922. Immunohistochemistry of available pre-treatment tumor tissue (n = 10) revealed that this responder was also the only patient with tumor DHFR cytoplasmic and membranous pattern staining (2 to 3+ intensity). **Conclusion:** In patients with previously treated metastatic non-squamous NSCLC, the MTD of AUY922 in combination with pemetrexed was determined to be 55 mg/m^2 per week. DHFR expression was seen only in the one long-term responder, but relevance is difficult to determine based on limited patient number based in part to closure of the study for lack of unexpired drug. Tolerability of AUY922 with pemetrexed is limited by ocular toxicity.

Keywords: non-small cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR) mutation, HSP90 Inhibitor AUY922

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-40 ABP 215 AND BEVACIZUMAB IN NSCLC PATIENTS: TIME COURSE AND MAGNITUDE OF RESPONSE IN THE PHASE 3 COMPARATIVE TRIAL (MAPLE)

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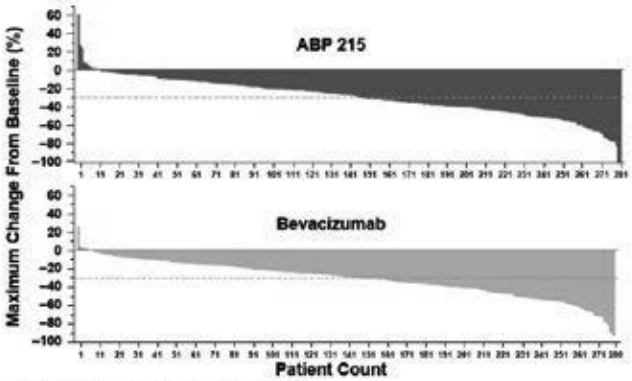
Background: ABP 215 (MVASI™ (bevacizumab-awwb)) has been approved as the first biosimilar to bevacizumab. Here we present the results of efficacy analyses from the phase 3 comparative trial of ABP 215 and bevacizumab. **Method:** The phase 3 study was a double-blind trial designed to demonstrate clinical equivalence of ABP 215 and bevacizumab (BEV) in patients with NSCLC. Adult patients with non-squamous NSCLC receiving first-line chemotherapy with carboplatin and paclitaxel were randomized 1:1 to ABP 215 or BEV (15 mg/kg IV Q3W for up to 6 cycles). Clinical evaluations included efficacy, safety, PK, and immunogenicity. Results of the primary analysis have been reported previously. A post hoc analysis of individual patient response data was performed using independent, central radiologists' evaluations of the time course and magnitude of tumor response. Imaging assessments of tumor response were completed using RECIST v1.1 to generate waterfall plots for the magnitude of target lesion response. **Result:** The proportion of patients with an objective response was similar between ABP 215 and BEV treatment groups by week 7, 13, 19, and overall. By week 19, 36.9% of patients receiving ABP 215 and 39.2% of patients receiving BEV had a first objective response. The risk difference in ORR by week 19 was -2.6% (95% CI: -10.05%, 4.93%). Both groups had a highly similar magnitude of target lesion response, as depicted in the Figure below.



Based on central tumor review using RECIST v1.1.

Conclusion: The analyses of the time to response and the magnitude of reduction of target lesions in the phase 3 comparative trial provide further support for clinical similarity of ABP 215 and bevacizumab.

Keywords: Biosimilar, ABP 215, bevacizumab

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-41 A NOVEL MITOCHONDRIA-BASED TARGETING TO RESTORE THERAPEUTIC RESPONSE IN CISPLATIN- AND GEFITINIB-RESISTANT HUMAN LUNG CANCER CELLS

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Background: Lung cancer is the leading cause of cancer related death accounting for up to 25% of all cancer mortality world-wide, with an estimated 1.2 million deaths each year. The major challenge of lung cancer is that approximately 50% of patients diagnosed present with advanced disease, and are likely resistant to chemo- and targeted tyrosine kinase inhibitor (TKI) therapies upon disease progression or acquired during therapeutic intervention. We devised a new approach to target specifically tumor mitochondria and observed that lung cancer cells, resistant to chemo- and TKI, therapies, Cisplatin (CIS) and Gefitinib (GF), respectively, can be overcome by DZ-191, a Simvastatin (SIM)-heptamethine carbocyanine (DZ) conjugate, or DZ-SIM, but not by the unconjugated SIM. **Method:** (1) Cell viability assay was used to detect the IC50 of the lung cancer cells treated with DZ or DZ-SIM. (2) flow cytometry was used to determine apoptosis of the lung cancer cells. (3) The mitochondrial membrane potential of DZ-SIM- or SIM- treated cells were assayed by using rhodamine123 staining. (4)The expression of PARP, Cleaved PARP, ProCaspase3, cCaspase3, ProCaspase9, cCaspase9, pH2AX and CHOP were detected by Western blot. (5)The Mitochondrial and lysosome staining was photographed by a Keyence microscope. (5) The tumor sizes and tumor volumes were determined by Nude mouse

xenograft of lung cancer cells treated by cells with Tween 80), DZ, DZ-SIM or GF (20 mg/kg) and DZ-SIM plus. **Result: (1)**DZ-SIM can significantly inhibits lung cancer cell growth of A549, A549-^{DDP}, 95D, 95C, YTMLC and H446 in vitro. **(2)**DZ-SIM can remarkably sensitizes CIS/TKI-induced lung cancer cell death in vivo and vitro. **(2)**DZ-SIM induced apoptosis of lung cancer cells via caspase activation and decreased mitochondrial membrane potential**. (3)**DZ-SIM can remarkably inhibits tumor growth in H1650-xenograft in nude mice**. (4)**The mechanisms of DZ-SIM restore therapeutic response in cisplatin- and gefitinib-resistant human lung cancer cells was that It co-localizes with mitochondrial and lysosomal subcellular organelles. **Conclusion:** (1)DZ-SIM, but not SIM, kills lung cancer cells *in vitro* and vivo inhibits lung tumors in vivo by inducing programmed cell death. DZ-SIM also sensitizes anti-tumor responses in CIS- and GF-resistant lung cancer cells in culture and tumors in mice. (2)DZ-SIM accumulates in mitochondrial and lysosomal organelles and interrupts mitochondrial membrane potential, activates caspases, apoptosis and DNA fragmentation in lung cancer cells in culture. (3) DZ-SIM can be employed as a promising targeting agent for killing and sensitizing therapeutically-resistant lung tumors to therapy in patients in the future.

Keywords: lung cancer, target therapy, therapeutic resistant, lung cancer, traget therapy, therapeutic resistant

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-42 OSIMERTINIB TREATMENT FOR PATIENTS WITH EGFR EXON 20 INSERTION POSITIVE NON-SMALL-CELL LUNG CANCER

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Background: Epidermal growth factor receptor (*EGFR*) exon 20 insertions are identified in 4-10% of al *EGFR* mutations in non-small cell lung cancer (NSCLC) and are generally associated with primary resistance to first and second generation EGFR tyrosine kinase inhibitors (TKIs). *In vitro* and preclinical animal studies have shown that osimertinib exerts antitumor activity in *EGFR* exon 20 insertion positive NSCLC cell lines. We report on a cohort of advanced stage NSCLC patients, harboring an *EGFR* exon 20 insertion, that was treated with osimertinib. **Method:** 17 patients with advanced NSCLC harboring an *EGFR* exon 20 insertion were treated with osimertinib 80 mg once daily, in four institutions in the Netherlands. Data were obtained retrospectively. *EGFR* mutation status was assessed by next-generation sequencing. Progression free survival (PFS), disease control rate (DCR) and objective response rate (ORR) were assessed using RECIST v1.1. **Result:** Median age was 63 years (range 35 – 81), 71% was female and median number of prior systemic treatments was 1 (range 0 – 3). Ten patients (59%) received prior platinum-based chemotherapy, and 2 patients afatinib, one patient experienced stable disease for 11 months, the other patient showed progression. Among all patients treated with osimertinib, we observed 1 partial response, 13 patients with stable diseases and 3 with progressive disease as best response (ORR 6%). Two patients were still on osimertinib treatment at the cut-off date. Median PFS was 3.7 months (95% CI: 2.3 – 5.4 months). Six of seventeen patients (35%) achieved DCR at five months.

Patient	Number of prior treatments	Prior platinum based chemotherapy	Prior EGFR TKI	Best RECIST response	PFS (months)
1	2	Yes	no	SD	4.0
2	1	Yes	no	SD	1.6
3	2	Yes	no	PR	0.7
4	1	Yes	no	PR	0.7
5	2	Yes	no	SD	3.8
6	1	Yes	no	SD	3.0
7	3	Yes	no	SD	9.3
8	1	Yes	no	SD	17.0
9	1	No	no	SD	3.7
10	1	Yes	no	SD	17.2
11	0	No	no	PR	3.1
12	0	No	no	SD	2.6
13	0	No	no	SD	6.5
14	3	Yes	afatinib (SD)	SD	7.9
15	1	No	afatinib (PD)	PD	1.7
16	0	no	no	SD	8.3
17	0	no	no	SD	1.4

EGFR, epidermal growth factor receptor; RECIST: Response Evaluation Criteria in Solid Tumors; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression free survival

Conclusion: Osimertinib has limited antitumor activity in patients with *EGFR* exon 20 mutated NSCLC, with an ORR of 6%. A subset of patients (35%) seems to derive benefit from osimertinib treatment with durable disease control for more than five months.

Keywords: EGFR Exon 20 Insertion, Osimertinib

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-43 PHASE 1 STUDY OF THE ANTI-HER3 ANTIBODY DRUG CONJUGATE U3-1402 IN METASTATIC OR UNRESECTABLE EGFR-MUTANT NSCLC

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Background: While outcomes for patients with EGFR-mutant NSCLC have significantly improved with the use of EGFR tyrosine kinase inhibitors, there remain limited treatment options for many patients once they develop resistance to these agents. The HER3/ERBB3 oncogene is overexpressed in many cancers, including NSCLC, and higher expression is correlated with poor outcomes. U3-1402 is a novel HER3-targeting antibody-drug conjugate (ADC) comprised of a recombinant fully human anti-HER3 antibody (patritumab) covalently conjugated via a cleavable peptide linker to a derivative of the topoisomerase I inhibitor exatecan. After U3-1402 binds to HER3 on the tumor cell surface, it is internalized and leads to apoptosis via inhibition of topoisomerase I. This ADC achieves a high drug-to-antibody ratio (DAR) of ~8:1. In vivo xenograft mouse model studies with human tumor cell lines indicate that U3-1402 exhibits HER3 expression-dependent tumor growth inhibition activity. **Method:** This is a multicenter Phase 1, Dose Escalation and Dose Expansion study of U3-1402 in metastatic or unresectable adenocarcinoma NSCLC subjects harboring EGFR-activating mutation who (a) are T790M mutation-negative after disease progression during treatment with erlotinib, gefitinib, or afatinib or (b) develop disease progression while on osimertinib. Eligible subjects are at least 18 years of age, have ECOG PS 0 or 1, have radiological documentation of disease progression while receiving continuous treatment with an EGFR TKI, have at least one measurable lesion per RECIST v1.1, have adequate bone marrow and organ function, do not have LVEF < 45%, do not have QTc prolongation, and do not have spinal cord compression or clinically active brain metastases. In Dose Escalation, subjects receive U3-1402 via intravenous infusion in 21-day cycles. In Dose Escalation, escalation of U3-1402 dosing is based on dose-limiting toxicity data in subjects, guided by the modified Continuous Reassessment Method (mCRM) using a Bayesian logistic regression model (BLRM) following the escalation with overdose control (EWOC) principle. Additionally, intra-subject dose escalation may be considered in subjects who have completed at least 4 cycles of treatment without ≥ Grade 2 treatment-emergent adverse events. In Dose Expansion, subjects receive U3-1402 at the recommended dose for expansion (RDE) determined in Dose Escalation. Primary objectives are to determine the safety, tolerability, and RDE of U3-1402. Secondary objectives are to assess the pharmacokinetic parameters of U3-1402 and its components, and to assess antitumor

activity of U3-1402 (RECIST v1.1). Enrollment to Dose Escalation cohort 1 was completed in April 2018. Clinicaltrials.gov identifier: NCT03260491 **Result:** Section not applicable - CTIP **Conclusion:** Section no applicable

Keywords: EGFR mutation, Drug resistance, HER3

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-44 TARGETING NFE2L2 MUTATIONS IN ADVANCED SQUAMOUS CELL LUNG CANCERS WITH THE TORC1/2 INHIBITOR TAK-228

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Background: Despite research efforts over the past decade, no targeted therapy options exist for patients with SQCLC. Analyses by TCGA and others (Paik Cancer Disc 2015) have identified a heretofore untargeted, frequently mutated oncogene (NFE2L2)/tumor suppressor (KEAP1) pair, each mutated in ~20% of patients with SQCLC. NFE2L2 encodes Nrf2, a transcription factor involved in the oxidative stress response which is targeted for degradation by Keap1. NFE2L2 mutations occur exclusively in an exon 2 hotspot that encodes the Neh2 domain (~aa.1-86), which is the binding site for Keap1. Mutations in this region disrupt Keap1 binding, leading to Nrf2 nuclear translocation and increased mTOR signaling through regulation of RagD (Shibata Cancer Res 2010). We now report translational studies and preliminary results from a phase 2 trial of the oral TORC1/2 inhibitor TAK-228 in SQCLC patients with these mutations. **Method:** Cytotoxicity, signaling, and xenograft experiments were performed using LK-2 SQCLC cells harboring an NFE2L2 E79K mutation treated with TAK-228, everolimus, rapamycin, or deforolimus with requisite vehicle controls. Patients with stage IV SQCLC harboring NFE2L2 mutations were treated on an NCI CTEP- single-institution phase 2 study of TAK228 3mg po qd (continuous, 28 day cycles; NCT02417701). Primary endpoint: ORR. Secondary endpoints: PFS/OS. The study utilizes a Simon 2-stage design with H0=5% (N≥1/5 responses), HA=40% (N≥2/10 responses). **Result:** TAK-228 exhibited significantly increased anti-tumor activity over TORC1 rapalogs in LK-2 cells. TAK-228 alone was cytotoxic at sub-[μM] (IC50 68nM); all other rapalogs exhibited IC50s >10μM. This was associated with an 80% decrease in downstream S6 phosphorylation. Tumor response (-55% shrinkage) was also seen in an LK-2 xenograft treated with TAK228. No anti-tumor/growth inhibitory response was seen with any other rapalog tested. N=4 patients have been treated on study (exon 2 del, D29H, F37V, W24C). 3 are evaluable for response. 2 related-SAEs (G3 hyperglycemia, G3 confusion) were seen; no other G3 AEs reported. ORR=67% (2 PR, 1 SD, 0 PD). Prolonged disease response is present, with DOR= 12mo, 10mo (ongoing), 8mo (ongoing). **Conclusion:** TAK228 is tolerable with evidence of pre-clinical and clinical activity in this biomarker-selected population. The trial has met its first-stage endpoint and has expanded to N=10 patients. The trial has also expanded to included patients with KRAS mutant lung cancers harboring co-alterations in NFE2L2 or KEAP1.

Keywords: squamous, NFE2L2, KEAP1

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-45 SHERLOC: A PHASE 2 STUDY OF SERIBANTUMAB IN COMBINATION WITH DOCETAXEL IN PATIENTS WITH HEREGULIN POSITIVE, ADVANCED NSCLC

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Background: HER3 and its ligand, heregulin (HRG), have been identified as a critical activator of PI3K and Akt signaling and a key pro-survival pathway in cancer cells. Seribantumab (MM-121) is a fully human, monoclonal IgG2 antibody that binds to the HRG domain of HER3, blocking HER3 activity. Preclinical data suggest that seribantumab reverses HRG-mediated drug resistance across multiple cancer models. In retrospective analyses of prior seribantumab Phase 2 studies, high levels of HRG mRNA appeared to predict poor outcome to standard of care (SOC) treatment. Addition of seribantumab to SOC appeared to improve progression-free survival (PFS) in patients with HRG positive (HRG+) tumors, consistent with the hypothesis that the blockade of HRG-induced HER3 signaling by seribantumab can restore drug sensitivity. **Method:** In the current randomized, open-label, international, Phase 2 study, patients with locally advanced or metastatic NSCLC histologically classified as adenocarcinoma are screened for HRG using an RNA *in situ* hybridization assay on a recent biopsy tissue sample. Approximately 100 HRG+ patients will be enrolled and randomized in a 2:1 ratio to receive seribantumab plus docetaxel (experimental treatment Arm), or docetaxel alone (control Arm). Eligible patients must have no EGFR and ALK mutations and have progressed following one to two SOC for locally advanced and/or metastatic disease, including platinum-based therapy and anti-PD-1/PD-L1 therapy where available and clinically indicated. Primary trial endpoint is PFS. Secondary endpoints include overall survival, objective response rate, time to progression, and pharmacokinetic profile. The study has ≥ 80% power to detect a 3-month improvement in median PFS over 3 months (hazard ratio ≤ 0.50), using a one-sided, stratified log-rank test at a significance level of 0.025. Study is ongoing and enrolling patients in seventy nine sites worldwide. Clinical trial information: NCT02387216 **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Heregulin, Antibody, biomarker

P2.13 TARGETED THERAPY
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.13-46 COMPREHENSIVE INVESTIGATION OF ERBB2 TRANSMEMBRANE DOMAIN MUTATIONS (V659/G660) IN 12,833 CHINESE LUNG CANCER PATIENTS

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Background: The ERBB2/HER2 receptor tyrosine kinase belongs to the human EGFR family and is a known oncogenic driver in many cancers including lung cancer. Majority of *ERBB2* mutations are within its kinase domain in non-small cell lung cancer (NSCLC). Rare transmembrane domain (TMD) mutations of *ERBB2* have also been identified at V659/G660 residues, which potentially stabilize ERBB2 heterodimerization with EGFR, favour a kinase activating conformation, and have shown to respond to afatinib (Ou et al, JTO 2017). **Method:** We interrogated next-generation sequencing data from 19,800 Chinese cancer patients, including 12,833 lung cancers between 2014 and 2017. Sample types include formalin-fixed paraffin-embedded (FFPE) or fresh tumor samples, and/or circulating tumor DNA (ctDNA) from pleural effusion or plasma. Patients' demographic and clinical data were further analyzed. **Result:** *ERBB2* TMD mutations at V659 were identified in twelve adenocarcinomas patients (five with V659D and seven with V659E), accounting for 0.14% of lung adenocarcinomas and 0.09% of all lung cancers. However, no G660 mutations were observed in this patient cohort. There is no gender preference for patients carrying such mutations (50%:50%). The median age of these patients is 56 with a trend to be younger in female patients. Two cases also carry other known driver alterations, *EGFR* L858R mutation and *PIK3CA* amplification, respectively. One case has two tumor tissue samples from the right upper and lower lobe of the lung, respectively. One lobe harbors *EGFR* exon19del mutation and *EGFR* amplification, whereas the other lobe carries *ERBB2* V596D and *EGFR* G719A mutation. No other driver mutations were identified in the remaining cases. Interestingly, a novel TMD mutation I649R on *ERBB3* was found in two patients together with *ERBB2* V659D mutation, which might involve in the regulation of heterodimerization between ERBB2 and ERBB3. All these ERBB2 TMD mutations present at a relatively high mutant allele frequency (MAF) in tumor tissues, ranging from 15% to 71%, as well as liquid biopsy samples up to 47.5% of MAF, indicating a high tumor burden in these patients and potential *ERBB2* amplification. Three patients received afatinib treatment though with progressive disease for various potential reasons, and the details of their treatment course will be presented. **Conclusion:** Among Chinese patients, *ERBB2* TMD mutation V659D/E is rare and unique to lung adenocarcinomas (0.14%). The efficacy of ERBB2-specific targeted therapy on these patients especially ERBB2 antibody and/or TKI need to be further investigated.

Keywords: ERBB2, lung adenocarcinomas, transmembrane domain mutation

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-01 CANSCRIPT™ AS A PATIENT-DERIVED PREDICTIVE PLATFORM FOR INDIVIDUALIZING TREATMENT IN LUNG CANCER

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Background: Lung cancer causes nearly 1.69 million deaths globally and 5-year survival rate is less than 20%[1]. Several predictive and prognostic biomarkers have been identified, such as mutations in *EGFR* and *KRAS,* -rearrangement of *ALK* and *ROS1*, and PD-L1 expression status amongst others, which have improved treatment selection and overall prognosis in lung cancer to some extent[2]. However, clinical relevance of these biomarkers is limited to only a small percentage of patients who potentially benefit from these signatures[2]. Hence, there is a need for a personalized tool that can accurately predict an individual's response to a therapy, especially in scenarios where there is a choice of equivalent treatment regimens. **References:** http://www.who.int/en/news-room/fact-sheets/detail/cancer J. Natl. Compr. Canc. Netw. 2017;15(4):504 Nat. Commun. 2014, 6:6169 doi: 10.1038/ncomms7169 **Method:** We have developed a platform technology (CANscript™), using multi-disciplinary systems biology-based approach that effectively recreates a patient's tumor microenvironment *ex vivo* by preserving the native contexture and heterogeneity. The platform provides phenotypic assessment of response to the drug(s) tested for a given tumor and generates clinically relevant predictions for real-time treatment selection[3]. **Result:** In the current study, 21 lung cancer patient tumors were evaluated using the CANscript™, were treated with one or more FDA approved regimens including targeted therapy and chemotherapy. We did not observe any advantage of targeted therapy (erlotinib and gefitinib) over chemotherapeutic agents used. Six tumors, which were non-responder to gefitinib, were predicted responders to chemotherapy (carboplatin/pemetrexed and/or carboplatin/docetaxel). Further, out of 4 gefitinib responders, 3 were predicted to respond to chemotherapies carboplatin/pemetrexed or carboplatin/docetaxel. Highest efficacy was observed in carboplatin/pemetrexed and carboplatin/docetaxel arms (47% and 46% respectively). One out of 4 tumors treated with anti-PD1 responded to the therapy showing a response rate of 25%, matching the reported clinical response rate of anti-PD-1 therapy. **Conclusion:** CANscript™ is used as an *ex-vivo*, personalized platform that can predict an individual's response to various classes of anticancer drugs. The platform has been validated over a large number of clinical samples and the current study indicates that CANscript is a preferred platform for selecting individualized drug responses for treatment of lung cancer.

Keywords: Lung Cancer, CANscript, TKI vs PD1 inhibitor

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-02 GENDER-ASSOCIATED DIFFERENCES IN PATIENTS WITH LUNG CANCER TREATED AT AN ARGENTINEAN UNIVERSITY HOSPITAL IN THE LAST 10 YEARS

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Background: In the last 20 years, lung cancer became in the first cause of death worldwide among women and is responsible for 20,000 deaths yearly in Argentinean women. Retrospective data suggest differences in incidence and outcome according to gender. We report the clinicopathologic profile and outcome of lung cancer patients assisted in our institution in the last decade according to gender. **Method:** We retrospectively, relieved the female population with lung cancer with available data treated at Institute of oncology Angel H. Roffo in the last 10 years to compare their clinical, pathological and epidemiologic variables such as: age, gender, histology ,molecular testing (EGFR mutations, ALK rearrangement), PET-TC at diagnosis ,stage, ECOG, PS and weight loss, with a cohort of male patients in the same period of time and their outcome (OS). **Result:** From a total of 395 charts reviewed, 180 (45.6%) women and 215 (54.4%) men shared no differences in the median age of lung cancer diagnosis; 62 (30-92) and 63 (28-84) year, respectively (p=0,16). Differing from men, more women come from Buenos Aires urban and suburban areas (89 vs 79%) (p=0,003). Compared to men, women had a lower incidence of: SCC (squamous cell carcinoma) (24/180, 13% vs 38/215, 18%)(p=0,020), advanced disease (stage III-IV)(136/180, 75% vs 190/215 88%)(p=0,001), smoking history (126/180, 70% vs 203/215, 94%)(p=0,000), consumption of tobacco (Mean 24 pack/year ±30 vs 41±33) (p=0,000)and presence of symptoms at diagnosis (141/180, 78% vs 193/215, 90%)(p=0,006). At the molecular level, women had more positive EGFRm cases (28, 15% vs 13 6%) (p=0,008) than men. Overall, median survival was superior for women (24 months; IC95%, 20-28 vs 20 months; IC95% 15-24) (p=0,15), especially in stage IV disease, but it was not statistically significant. **Conclusion:** Our data confirms gender-associated differences in the clinical and pathologic profile of lung cancer in an Argentinean cohort of patients. Although not statistically significant, women would also had a better outcome than men. This analysis represents the first step of a prospective project to determine the clinic, epidemiological and molecular characteristics related to gender in lung cancer in our population

Keywords: Women Gender

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-03 AVAILABILITY AND REIMBURSEMENT OF DIAGNOSTIC TESTING AND NOVEL ANTI-CANCER DRUGS FOR NSCLC IN CEE: RESULTS OF A CECOG SURVEY

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Background: Current guidelines recommend routine molecular testing for EGFR, ALK, ROS1 and BRAF alterations in patients with advanced non-squamous non-small cell lung cancer (NSCLC) and in squamous NSCLC presenting specific clinical features. Precision medicine reflects the selection of appropriate targeted therapies (TTs) and immune-oncology (IO) treatment based on molecular testing. **Method:** To provide an overview of current situation, the Central European Cooperative Oncology Group (CECOG) has developed a survey with participation of national experts in the field of molecular pathology and oncology from 10 countries: Austria, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia, and Slovenia. First part of the survey referred to availability and reimbursement of molecular diagnosis in NSCLC, including testing policy ("reflex" vs "on demand", parallel vs subsequent) and turnaround times. The second part evaluated the access and reimbursement of targeted and IO therapies. **Result:** There is large variability regarding molecular testing for NSCLC patients in CEE countries, both from access and reimbursement, and from the pattern of recommendation by oncologists. EGFR testing is reflex in Austria, Slovenia, Croatia, Czech Republic, and Slovakia and on demand in Bulgaria, Hungary, Poland, Romania, and Serbia, being fully covered by the public health system only in Austria and Slovenia. Similar situation is reported for ALK testing. ROS1, BRAF and PD-L1 are mainly tested on demand, once testing results for EGFR and ALK are found negative. Turnaround time ranges between 5 and 10 days for reflex testing influenced by technology, with delays for on demand testing. In the first line, EGFR TKIs are available and reimbursed, while IO is reimbursed only in 5 out of 10 countries. The majority of second line TTs and IOs are registered, but not yet reimbursed in many CEE markets, despite the unmet medical need. Austria can be a model in CEE, having rapid access and implementation of the new standards in testing and treatment (all second line TTs and IO available). Slovenia and Hungary follow with 7 out of 10 second line available novel treatments. Time from registration to reimbursement of targeted treatment is usually long, lasting 1 year or more. **Conclusion:** This survey provides updated overview on availability and reimbursement of molecular diagnostic and precision medicines in CEE countries, for NSCLC patients. There is a strong need to standardize management and to facilitate access to novel therapies in routine clinical practice for better patient outcomes. Experts network, like CECOG, can facilitate regional dialogue.

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-04 COSTS OF CARES ON THE MONTH BEFORE DEATH OF PATIENTS WITH LUNG CANCER: A FRENCH NATIONAL DATABASE SURVEY

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Background: There is a few data's on the burden of the last month of life of patient with lung cancer and on impact of end of life (EOL) aggressiveness of cares. The aim of this study was to assess the costs of the month before death in patients with lung cancer and the impact of aggressiveness of cares during this period. **Method:** Using a French hospital discharge database (PMSI, *Programme de Médicalisation des Systèmes d'Information*), all adult patients with lung cancer who death between January 1, 2010 and December 31, 2011 (cohort 1) and between January 1, 2015 and December 31, 2016 (cohort 2) were identified through the International Classification of Diseases 10th version (ICD-10). Aggressiveness of EOL cares was assessed by the following criteria's 1) chemotherapy administrated within last 14 days of life (DOL); 2) > 1 hospitalizations within 30 DOL; 3) ICU admission within 30 DOL; and 4) palliative care < 3 days before death.Direct hospital costs were assessed from the French public health insurer perspective based on DRG tariffs. Costs were expressed in 2017 Euros. **Result:** A total of 90,827 i patients were identified: men: 74%, median age: 67 years [59-77], metastatic at diagnosis: 70%;57% have at least one marker of aggressiveness of EOL cares (repeated hospitalization: 49%, ICU admissions: 12%, chemotherapy within 14 DOL: 9%, and palliative care < 3 days before death: 5%). The mean cost of last month of EOL was € 8,152 ± 5,117 (346 - 91,537) per patient, significantly more important in patients with at least one aggressiveness marker of EOL cares (€ 9,480±5,946 vs € 6,376±2,898, p <0.001). These over-costs were explained in large part by hospitalizations and intensives cares costs (€ 8,080 ± 4,296 vs € 6,228 ±2,752 and € 1,063 ± 2,948 vs € 92 ± 546). The cost of expensive drugs (€ 285 ± 888 vs € 39 ± 330), radiotherapy (€ 14 ± 138 vs € 6 ± 84) and medical devices (€ 38 ± 352 vs € 11 ± 137) does not impact the extra costs of patients with markers of aggressiveness of cares. **Conclusion:** The EOL economic burden is major for the healthcare system, with extra costs of more than € 3,000 per patient in case of EOL aggressiveness markers. Organizing a precocious palliative care system may improve the quality of cares of EOL and reduce the financial costs of the last days of life of lung cancers patients.

Keywords: Population Based-Study, Aggressiveness of End-of-Life, Costs of End-Of-Life

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-05 PRESCRIBING PATTERNS OF PHYSICIANS AND FINANCIAL IMPLICATIONS FOR LUNG CANCER TREATMENT AT THE END OF LIFE

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Background: Rates of systemic chemotherapy use at the end of life are estimated to be above 44%. Limited information exists on prescribing patterns of intravenous and oral treatments (immunotherapy, chemotherapy, and tyrosine kinase inhibitors) at the end of life. Use of systemic therapy in the last month of life may have a significant clinical and financial impact. This study aimed to evaluate prescribing patterns and costs associated with lung cancer treatments in the last month of life in two large academic institutions. **Method:** Patients (n=184) deceased between July 2016 and June 2017 who received lung cancer treatment were included in this analysis. The primary objective was characterization of prescribing patterns associated with end of life care. Patient, disease, and treatment related factors were recorded. Patient characteristics were compared between those who did and did not receive treatment in the final month of life using Wilcoxon and chi-square tests, respectively. **Result:** Forty-three (23%) patients received treatment in the last 28 days of life. Patient-related factors were similar between patients who did and did not receive therapy at the end of life. Patients who did not receive therapy at the end of life were more likely to be enrolled in hospice (72% vs 40%; p =0.0035, chi-square test). Of therapies given within the last month of life, 47% were oral therapies, 35% were intravenous chemotherapy, and 16% were immunotherapy (p = <0.0001, chi-square test). Using average wholesale price, overall drug costs given in the last month of life were $422,454, of which oral agents accounted for $326,400. There were no statistical differences in patient factors, including age, creatinine, albumin, hemoglobin, Charlson Index, and ECOG performance status between patients who received therapy at the end of life and those that did not (all p-values >0.05). **Conclusion:** Oral therapies are the most commonly prescribed modality of treatment at the end of life compared to intravenous chemotherapy or intravenous immunotherapy. Oral therapies pose a significant financial burden to patients at the end of life. Using patient factors to determine candidates for therapy at the end of life continues to be an area of exploration. Further studies are warranted to identify when therapies should be discontinued or to identify patients who may not benefit from systemic therapy.

Keywords: financial toxicity, oral therapy, end of life

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P2.15-06 EXAMINATION OF OPTIMAL TIMING OF POST-SURGICAL SURVEILLANCE FOR EARLY STAGE LUNG CANCER PATIENTS AND ASSOCIATION WITH OUTCOMES

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Background: Guidelines for post-operative surveillance for NSCLC are variable. Historically, surgeons have used a one-size fits all approach, such that surveillance guidelines incorporate few important prognostic indicators for recurrence and survival. Recent NCCN guidelines recommend surveillance CT every 6 months for both stage I and II patients. This is in contrast to the recent IFCT-0302 Trial suggesting that CT scans every 6 months are not useful within the first 2 years following surgery. The goal of this study was to determine optimal timing for detection of recurrence by CT scan and the association between surveillance CT and overall survival. **Method:** This was a retrospective, single institution series of patients undergoing surgical resection (2008-2012) with stage I or II disease (AJCC 7thedition) with at least 6 months of follow-up. Guideline adherence was defined as receipt of CT every 6 months for the first two years and annually thereafter. **Result:** The cohort consisted of 162 patients (80% stage I 20% stage II) with median follow-up 57 months. Recurrence occurred in 27.5% of patients at a median of 29.5 months following surgery. The rate of adherence to guideline recommended surveillance ranged 61%-76.3%with the majority of all CT scans done for surveillance purposes (87%-98%). The percentage of CT scans with suspicious findings was relatively stable over time (30-35%), however, the rate of CT scans with recurrence was variable, peaking at 2-3 years following surgery. For those detected on CT scan, stage I recurrences peaked at 25-36 months whereas stage II peaked at 19-24 months. Timing of recurrences differed significantly based on stage with 81% of recurrences occurring > 24 months following surgery for Stage I patients compared to 41% of a Stage II patients. (p<0.01) Overall, higher rates of surveillance CT were associated with a reduced risk of death (HR 0.14 [95% CI 0.06-0.36] p<0.01). **Conclusion:** The majority of CT imaging performed within 5 years following surgery was done for surveillance purposes rather than symptoms. The timing of recurrence differs significantly based on stage such that few stage I patients have recurrences within 2 years following surgical resection. Additionally, rates of recurrence detected by surveillance CT scans performed less than 24 months following surgery is lower for stage I patients.These results should be examined within a larger cohort with longer longitudinal follow-up as timing of CT surveillance based on peak recurrence rates has the potential to eliminate unnecessary testing and expense for healthcare systems.

Keywords: early stage NSCLC, Surveillance

P2.15-07 LUNG CANCER IN THE YOUNG

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Background: Lung cancer is the leading cause of cancer related death worldwide. Median age at diagnosis is 70 years. Its presentation in patients 40 or younger is uncommon and it has been proposed that maybe is a different disease due to its clinical characteristics and genetic makeup. There are a limited number of studies in this population and they report different clinico-pathological characteristics in comparison with older patients. **Method:** This is a retrospective analysis of patients 40 years or younger diagnosed with lung cancer between 2009 and 2015 at Instituto Nacional de Enfermedades Neoplasicas (INEN) in Lima, Peru. Patient characteristics such as age, sex, smoking history, family history, symptoms, histological type, stage at diagnosis, and overall survival were collected from clinical files. **Result:** During the study period, we identified 2946 patients with lung cancer. Among these, 107 (3.63%) patients were 40 years or younger. Median age at diagnosis was 36 years and 58% of patients were female. Most patients (77.5%) lacked family history of cancer. A smoking history was present in 13.3% of patients and exposition to biomass fumes from inhouse cooking was reported in 16.3%. Mean time from onset of symptoms to diagnosis was 2 months. Frequent symptoms at diagnosis were cough (59.2%), weight loss (56.1%), chest pain (50%), dyspnea (44.2%), hemoptysis (18.4%) and fever (9.6%). Most patients (59.8%) had performance status (PS) of 1. Adenocarcinoma was the most histological type (64.5%), followed by not otherwise specified (NOS) lung cancer (13.1%), squamous carcinoma (10.3%) and neuroendocrine carcinoma (5.6%). Almost all patients (96.9%) had unresectable disease at diagnosis (7.3%, stage III; 89.6% stage IV). The median overall survival was 7 months (range 4.4 – 9.5). **Conclusion:** The proportion of young patients with lung cancer in our population is higher than that reported in the literature. Lung cancer in the young is mostly sporadic, more frequent in women and usually of adenocarcinoma type. Young patients tend to present with advanced disease at diagnosis, resulting in a very poor survival. The molecular characterization of this cohort of patients is ongoing.

Keywords: lung cancer, Incidence, young

P2.15-08 IMPACT AND FEASIBILITY OF A SUPPORT GROUP FOR WOMEN WITH LUNG CANCER

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Background: Patients with lung cancer have limited psychosocial supports in the community. Participation in support groups provides emotional, social and educational support and may be beneficial for cancer patients. In our city there are no support groups for patients with lung cancer. We assessed the impact and feasibility of a lung cancer support group for women. **Method:** We conducted a weekly, 1.5-hour psycho-education support group for 6 sessions in 2017. Sessions were facilitated by a trained social worker with long experience in psychosocial oncology. Pre- and post-intervention quality of life tools were administered: the Canadian Problem Checklist (CPC), Functional Assessment of Cancer Therapy-Lung (FACT-L), Impact of Events Scale (IES), and the Hospital Anxiety and Depression Scale (HADS). Median changes in scores were calculated. A negative (-) change represents improvement in the domain. **Result:** 10 women were enrolled, 60% completed the program. Demographics were available for 8 participants: median age 68 (range 26-80); median diagnosis year 2016 (range 2000-2017); 3 vs 5 women were ECOG PS 0 vs 1; 1 current smoker, 2 past smokers; 5 with metastatic disease; 5 undergoing palliative systemic therapy, 1 undergoing curative therapy, 1 had completed curative therapy,1 receiving best supportive care. Both pre- and post-intervention tools were completed by 60% of participants. The CPC showed that 67% had reduced/stable problems after the intervention. The FACT-L, IES and HADS tools and their sub-scales generally showed a favourable change after the intervention. See Table 1 for the median pre- and post-intervention scores and median change in scores. 100% of participants agreed or strongly agreed that the group helped them cope with lung cancer.

Table 1

Scale	Pre-intervention score, median [IQR]	Post-intervention score, median [IQR]	Change in score, median [IQR]
FACT-L	1.4 [1.0-1.9]	1.9 [0.8-2.1]	0 [-0.1-0.6]
Physical wellbeing	1.1 [1.0-1.7]	1.6 [0.9-2.6]	0 [0-0]
Social/ family well-being	0.6 [0.3-1]	0.7 [0.2-1.0]	-0.1 [-0.3-0.4]
Emotional wellbeing	0.3 [0.3-1]	0.7 [0-1.0]	0.3 [-0.7-0.3]
Functional wellbeing	1.6 [1.2-2]	1.7 [1.1-2.4]	0.4 [-0.3-0.6]
Additional concerns	1.7 [0.6-2.5]	2.1 [0.4-2.4]	-0.1 [-0.3-0.4]
Impact of Events	1.2 [0.6-1.9]	0.5 [0.2-1.4]	-0.4 [-0.7-0.1]
Avoidance	1.9 [0.4-2.3]	0.5 [0.2-1.4]	-0.2 [-0.8-0.5]
Intrusion	1.6 [1.1-1.9]	0.9 [0.3-1.3]	-0.8 [-1.0-(-0.4)]
Hyper-arousal	0.7 [0.2-1.0]	0.3 [0.2-1.3]	0 [-0.3-0]
HADS	0.7 [0.3-1.1]	0.9 [0.8-1.1]	0 [-3-0.6]
Depression	0.6 [0.4-1.0]	0.9 [0.6-1.1]	-0.1 [-0.3-0.6]
Anxiety	0.6 [0.2-1.3]	1.0 [0.6-1.5]	0 [-0.3-0.3]

Conclusion: A support group for women with lung cancer was feasible and quality of life improved in several domains. Support groups and other community resources should be more widely available for patients with lung cancer.

Keywords: support group, community resources, lung cancer

P2.15-09 THE IMPACT OF TREATMENT EVOLUTION IN NSCLC (ITEN) MODEL: SURVIVAL AND COST OF TREATING PATIENTS WITH ADVANCED NSCLC IN 2017

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Background: The life expectancy and healthcare costs of treating advanced NSCLC (aNSCLC) patients are expected to rise as new targeted and immuno-oncology (IO) therapies are approved for clinical practice. Here, we have used the iTEN model to estimate the cost of managing aNSCLC patients in Canada in 2017. **Method:** The iTEN model development and validation are presented in an accompanying abstract ("The iTEN model: Development and Validation"). A treatment algorithm for EGFRm, T790m, ALK re-arrangement and PD-L1+ aNSCLC patients in 2017 was generated through a modified Delphi process based on anonymous responses from Canadian clinical experts. The generated treatment algorithm was used to estimate the survival and life-time costs of managing patients. Health resource use and cost estimates included drug acquisition and administration, adverse events, laboratory and radiologic monitoring, physician visits and end of life costs (2018 costs). Cost estimates were based on published literature, Ontario formulary listings, Cancer Care Ontario recommendations and the Ontario Case Costing Initiative. The estimation of survival is described in the companion abstract. **Result:** Survey responses indicated that first-line

therapy is consistent with current guideline recommended practice, but that care beyond the second-line is variable, particularly with respect to IO usage. Modelled life expectancy varied based on the molecular subtype of aNSCLC. Costs over the span of an average aNSCLC patient's life-time were estimated to be $89,899 (range: $61,134-$194,158). In comparison, the life-time cost of treating a Canadian lung cancer patient in 2007 (ie, prior to the introduction of IOs and ALK TKIs), inflated to 2018 dollars, was an estimated $60,678 (de Oliveira *et al.,* 2016).

Source	Period examined	Treatment Mix	Overall Survival (months)					Predicted life-time cost per patient ($CAD)[c]
			12	24	36	48	60	
iTEN estimate	Current (2017)[a]	All patients[b]	46%	20%	10%	5%	2%	$89,899
iTEN estimate	Current (2017)[a]	EGFR+ Patients	65%	28%	11%	3%	1%	$63,906
iTEN estimate	Current (2017)[a]	EGFR+T790M+ Patients	75%	41%	18%	9%	4%	$119,251
iTEN estimate	Current (2017)[a]	ALK+ Patients	73%	48%	26%	14%	7%	$194,158
iTEN estimate	Current (2017)[a]	PD-L1+ (>50%) patients	51%	25%	13%	7%	4%	$126,281
iTEN estimate	Current (2017)[a]	PD-L1+ (>1-49%) patients	46%	22%	9%	4%	2%	$61,068
iTEN estimate	Current (2017)[a]	PD-L1+ (<1%) patients	32%	10%	5%	2%	1%	$61,134

Notes: [a] Estimates representative of patients receiving a treatment algorithm reflective of Canadian clinical practice in 2017; [b] represents the weighted average survival and cost of patients receiving each of the subtype-specific treatment mixes. [c] Assumes all approved drugs are publicly funded.

Conclusion: Results suggest that aNSCLC patient survival increases in conjunction with increased expenditure. The iTEN model may be used to assess the impacts of evolving treatment paradigms in aNSCLC.

Keywords: aNSCLC, Cost of Treatment, overall survival

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P2.15-10 DETERMINANTS OF HEALTH UTILITY SCORES (HUS) IN PATIENTS WITH ALK REARRANGED NON-SMALL CELL LUNG CANCER.

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Background: Despite an increasing number of available treatment options for patients with advanced ALK-rearranged (ALKr) NSCLC, the goals of care remain to improve survival whilst maintaining quality of life. With rapidly changing management and prognosis, understanding the impact of treatments on quality of life becomes important. We evaluated factors affecting health utility scores (HUS) in this generally younger cohort of patients with NSCLC. **Method:** An ongoing prospective observational/real-world cohort study at the Princess Margaret Cancer Centre is enrolling patients with advanced NSCLC. Patients are asked to complete the EQ5D questionnaire at each outpatient visit. During the period from November, 2014 to March, 2018, patients with ALKr who participated were analyzed. Baseline clinical characteristics, oncological treatment, and outcomes were extracted from chart review. Factors associated with HUS were identified using ANOVA. **Result:** 272 encounters (follow-up visits) in 43 ALK+ patients were analysed. The median age at diagnosis was 56 years (range: 31-79 years). Half the patients in our sample were female (49%), and the majority were never-smokers (84%); 44% of the cohort were Asian. During the study period, 24 patients (56%) presented with or developed brain metastases. The median number of HUS collected per person was 4 (range: 1-20). Among patients who were stable on treatment, there were no statistically significant differences in mean HUS (mHUS) between different ALK inhibitors: mHUS [SD, standard deviation] were: mHUS of crizotinib=0.82 [0.08] (n=25, 92 encounters); mHUS of ceritinib=0.79 [0.14] (n=17, 102 encounters); and mHUS of other ALK inhibitors=0.80 [0.17] (n=12, 25 encounters), which included mHUS of alectinib=0.79 [0.20] (n=8, 10 encounters). The number of previous lines of treatment did not impact HUS (p=0.85). Patients stable on treatment who received prior whole brain radiation (n=14) had lower mHUS compared to those who never had WBRT (mHUS=0.78 [0.14] vs. 0.84 [0.10]; p=0.05), which may partly explain differences in mHUS by sex (64% of patients who had received WBRT were female vs 41% who did not receive WBRT): males=0.84 [0.10] vs females=0.78 [0.14], p=0.04. In 11 stable patients who had received radiation to bone metastases mHUS was 0.75 [0.16] vs. 0.84 [0.09] in those who did not (p=0.006). **Conclusion:** In this study, mean HUS were similar across different ALK inhibitors. Female patients and those receiving whole brain radiation or radiation to bone had lower HUS. This highlights specific factors that influence health-related quality of life in this subset of patients with advanced NSCLC

Keywords: ALK, NSCLC, health utility scores

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P2.15-11 CLINICAL OUTCOME OF PULMONARY RESECTION FOR NON-SMALL CELL LUNG CANCER IN EXTREMELY ELDERLY PATIENTS (85-YEAR-OLD OR OVER)

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Background: Surgical resection is considered to be an effective therapy in the elderly patients. In Japan, the number of surgical operations performed in the elderly patients has been increasing. We reviewed the outcome of surgical treatment and the determining indication of pulmonary surgery in patients aged 85 years or over. **Method:** We performed surgical resection for 27 lung cancer patients aged 85 years or over in our hospital from January 2007 to December 2016. The patients' operative procedure, histological type, comorbidity, surgery-related complications, prognosis, and recurrence were retrospectively reviewed. We performed pulmonary surgery for elderly patients who have to be able to undergo pulmonary physiotherapy, have good performance status (0-1 in ECOG scale), and be free from psychological disorder such as dementia. **Result:** There were 19 males and 8 females. Their mean age was 87.0 years (range: 85-93 years). The mean follow-up period after operation was 1585 days (range: 395-3255 days). Operative procedures include lobectomy (N=10), segmentectomy (N=8), and wedge resection (N=9). Histological type include adenocarcinoma (N=18), squamous cell carcinoma (N=7), adenosquamous carcinoma (N=1), and LCNEC (N=1). Pathological stage was IA in 20 patients, IB in 4patients, IIB in 2 patients, and IIIA in 1 patient. 17 patients had comorbidity including coincidence of other malignancy, anti-coagulant therapy, history of the lobectomy, and others. No patients died from surgery or post-surgical complications. Morbidity rate was 14.8% (e.g. refractory pulmonary fistula, Atrial fibrillation, heart failure, atelectasis). 14 patients are alive, whereas 11 patients died from other diseases than lung cancer. 4 patients experienced recurrence, and 2 patients of those died. 5-year survival rate was 71.4%, and 3-year survival rate was 87.5%. **Conclusion:** Our study indicates that the surgical resection of non-small cell lung cancer benefits patients, even with extremely elder age (85-year-old or older). We consider patients with clinical stageI are good candidates. The long-term prognosis is expected if we chose the patients in elderly people lung cancer definitely.

Keywords: Elderly patients, Lung cancer, 85 years or over

P2.15-12 EXPAREL VS. BUPIVICAINE FOR POSTOPERATIVE ANALGESIA AFTER VATS LUNG RESECTION: RESULTS OF A RANDOMIZED CONTROL TRIAL

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Background: Postoperative pain control practices are highly variable and opioid use is of considerable interest to clinicians and patients. This thoracic surgery program focuses on minimally invasive interventions and sought an optimal pain control regimen. Previously, tunneled pleural catheters with a continuous Bupivicaine infusion for 7 days were used. The shortened length of stay (LOS) and excellent patient satisfaction observed were attributed to this technique, however a prior randomized controlled trial (RCT) at this institution showed no differences in opioid use between catheters or singular injections of Bupivicaine. Exparel (Liposomal Bupivacaine formulation) reports local anesthesia up to 72 hours. Exparel's emergence removed the catheter burden and compares local infiltration of Exparel with standard 0.25% Bupivacaine injections into the subcutaneous space. **Method:** This RCT compares both injections' analgesic effects on opioid use. Adult VATS lung resection patients from 2015-2017 were eligible. Patients with: chronic opioid use, pain medication allergies, liver or renal dysfunction, severe COPD, peptic ulcerative disease, or pregnancy were excluded. The primary endpoint measured differences in opioid utilization in postoperative days (POD) 0-7, via chart review and self-reported pain medication use post-discharge. Hydromorphone equivalents were utilized for opioid conversions. Wilcoxon rank-sum and Fisher's exact tests compared all appropriate endpoints. **Result:** Sample sizes, opioid utilization, and pain scores are demonstrated in Table 1. No differences were observed for opioid utilization between groups for all PODs. No differences in pain scores (except for POD4), 30-day patient satisfaction (98% vs. 90% very satisfied), or LOS (0 [0-1] vs. 0 [0-1]) were observed.

Table 1: Comparisons of opioid utilization and self-reported pain scores between Exparel and 0.25% Bupivacaine groups, stratified by postoperative day[1].

Postoperative Day	Total Opioid Utilization (mg)				Self-reported Pain Scores[4]			
	All	0.25% Bupivacaine	Exparel	*P*	All	0.25% Bupivacaine	Exparel	*P*
Day 0	2 [0 - 10.38][2]	2 [0 - 10.38]	2 [0 - 8.22]	0.599	5 [3 - 7][3]	5 [3.5 - 7]	5 [3 - 7]	0.876
Day 1	0 [0 - 20]	0 [0 - 20]	0 [0 - 12.38]	0.621	4 [2 - 5]	4 [3 - 5]	4 [2 - 5]	0.813
Day 2	0 [0 - 18]	0 [0 - 18]	0 [0 - 12]	0.789	3 [2 - 5]	3 [1.25 - 5]	3.5 [2.25 - 5]	0.202
Day 3	0 [0 - 20]	0 [0 - 20]	0 [0 - 8]	0.507	3 [2 - 4]	3 [1 - 4]	3 [2 - 5]	0.190
Day 4	0 [0 - 16]	0 [0 - 16]	0 [0 - 6]	0.679	2 [1 - 4]	2 [1 - 3]	2 [2 - 5]	0.049
Day 5	0 [0 - 20]	0 [0 - 20]	0 [0 - 6]	0.052	2 [1 - 3]	2 [1 - 3]	2 [1 - 4]	0.518
Day 6	0 [0 - 20]	0 [0 - 20]	0 [0 - 4]	0.150	2 [1 - 3]	2 [1 - 2]	2 [1 - 3]	0.415
Day 7	0 [0 - 12]	0 [0 - 12]	0 [0 - 4]	0.169	1 [0.5 - 2]	1 [0 - 2]	2 [1 - 2]	0.112

[1] Total dosages of opioid for each postoperative day of utilizing Hydromorphone equivalents in milligrams (mg) to convert all postoperative opioid usage from day of surgery through postoperative day 7.
[2] Median [range] was calculated for opioid usage at each postoperative day given that most IQRs were [0 – 0] and less informative than ranges.
[3] Median [IQR] was calculated for pain scores at each postoperative day.
[4] Pain scores were based on a numerical scale of 0 to 10 where 0 = no amount of pain, 10 = maximum amount of pain.
[2] P-values are not adjusted for multiple comparisons.

Conclusion: These results suggest clinical equipoise between Exparel and Bupivicaine and practitioners cannot justify routine use of Exparel in this patient population for improved postoperative pain control. Appropriate preoperative preparation and attention to proven evidence-based metrics designed to decrease morbidity, such as ambulation, should take precedence over a focus on pain management.

Keywords: Exparel (Liposomal Bupivacaine), Pain Managemnet, VATS Lung Resections

P2.15-13 IMPLEMENTATION OF A DEMOCRATIZED APPROACH TO MULTI-OMIC MOLECULAR PROFILING VIA THE LUNGMATCH PROGRAM.

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Background: For metastatic non-small cell lung cancer (NSCLC) guidelines include molecular testing for actionable biomarkers and recommend broad profile testing. Previous studies indicate that many patients with NSCLC are not receiving testing, even for actionable changes in EGFR, ALK, and ROS, BRAF, and PD-L1. There are widespread gaps in the community setting and Lung Cancer Alliance data shows that less than 50% of callers to the patient HelpLine have had molecular testing on their lung cancer. **Method:** The LungMATCH molecular testing program is operationalized via a turn-key precision medicine (PM) operation system. This approach provides a standardized workflow from tissue acquisition through multi-omic molecular profiling, treatment history integration, and AI-based computational analysis to produce a treatment decision support tool of therapeutic options matched to the patient. Longitudinal outcome is collected on every patient along with treatment decisions and patient experience. **Result:** The majority of the patient referrals (72%) came from non-academic centers across a wide geographic region that covered nearly 75% of the United States (36/50 states). Barriers to signing informed consent and completing biopsy have been identified including: patients in poor health, cost concerns, unsupportive physicians, and patient loyalty to the physician (discomfort with advocating for testing). For patients who have received reports, 72% (12/17) had actionable genomic alterations that indicated either a standard of care agent or a clinical trial. An additional 82% (9/11) had actionable proteomic findings and 31% (5/16) had high tumor mutational burden. **Conclusion:** There is broad patient interest in accessing PM information but still many barriers to widespread adoption. The LungMATCH program provides a turn-key solution to help provide a facile means to "democratize" access to PM information unbound by geography or community/academic setting. Importantly, the majority of patients who received a completed profiling report had actionable molecular alterations, which underscores the potential impact of testing. Treatment decisions and patient outcomes continue to be followed.

Keywords: molecular testing, biomarker, decision support

P2.15-14 SURVIVORSHIP OF ADVANCED LUNG CANCER PATIENTS WITH PSYCHIATRIC DISORDERS AND MALNUTRITION RISK

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Background: Advanced lung cancer (aLC) is often accompanied by anxiety and/or depression and malnutrition risk. The above stated burdens have a huge influence on patients' lives during the disease trajectory. Aim of this study was to assess the influence of depression and/or anxiety and malnutrition risk on overall survival (OS) in advanced lung cancer patients. **Method:** This prospective trial was conducted at the Institute for Pulmonary Diseases of Vojvodina, Serbia. Patients with advanced lung cancer were included in this study regardless of lung cancer type and therapy regimen. Patients rated themselves on the Hospital Anxiety and Depression Scale (HADS). Malnutrition universal screening tool (MUST) was used for assessment of malnutrition risk. Univariate and multivariate analysis was performed in order to correlate the data. **Result:** Out of total 134 patients, 76.9% were male and 23.1% female. Majority of patients were current smokers (58.2%), average age 61, with ECOG performance status 1 (79.9%) and diagnosed lung adenocarcinoma (48.5%). A psychiatric disorder was confirmed in 41.8% of patients (anxiety in 3.0%, depression in 19.4%, combined disorder in 19.4%). Malnutrition risk was observed in 35.0% of patients (low risk in 13.4%, high risk in 21.6%). Malnutrition risk was significantly related to education level (p=0.010) and age (p=0.040). Median OS of included patients was 17.8 months. We observed a significant relation between OS and psychiatric disorder (p=0.029) and OS and malnutrition risk (p=0.001). Median OS of patients without psychiatric disorders was 20.3, with depression 12.2 and with combined psychiatric disorders 13.9 months. Median OS of patients with low malnutrition risk was 20.6, for medium risk 12.3 and for high risk 13.2 months. Median OS of patients with any psychiatric disorder accompanied by increased malnutrition risk was 5.9 months (p=0.000). One-year survival was 71.7% in patients without burdens, 73.5% in patients with psychiatric disorder, 64.0% in patients with malnutrition risk and in 36.4% (p=0.018) in patients with combined burdens. Five-year survival was 5.7%, all these patients were without disorders. **Conclusion:** Depression and/or anxiety and malnutrition risk are present in large number of aLC patients and have great influence on not only quality of life but also overall survival. Effort should be done to implement easy-to-use screening tools in daily routine for early recognition of patients' burdens and concerns which can improve comprehensive care of incurable lung cancer.

Keywords: malnutrition, advanced lung cancer, Depression and Anxiety

P2.15-15 DIFFERENTIATING CHARACTERISTICS OF PATIENTS SEEKING A SECOND OPINION: A SURVEY ON NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Data on second-opinion seeking characteristics and behaviors is limited, especially for non-small cell lung cancer (NSCLC) patients. Seeking a second opinion could influence future treatment decisions, treatment satisfaction, and the patient-provider relationship. As patients are more involved in the decision-making process and care is more personalized than ever before, it is important to understand factors associated with seeking a second opinion. This research aims to determine and describe differentiating characteristics of NSCLC second-opinion seekers. **Method:** An online survey was conducted with NSCLC patients (N=542) to gain insights on second opinion seeking characteristics. Measures included single-answer and multiple-answer multiple-choice questions, including self-reported risk factors. Responses were evaluated using descriptive statistics and comparisons using a Chi-square test. **Result:** Among NSCLC patients surveyed, 29% (N=158) indicated that they sought a second opinion when initially diagnosed. Second-opinion seekers were less likely to identify smoking as a personal risk factor than non-second opinion-seekers, (66% vs. 78%, X^2=7.68, p <.01). Analyses then examined second-opinion seekers versus non-second opinion seekers separately to look for distinct patterns among ever-smokers and never-smokers. Among never-smokers, those who sought a second opinion were more likely to have been diagnosed with Stage IV NSCLC compared to those who did not seek a second opinion (56% vs. 29%, - X^2=9.39, p <.01), and to say they were interested at time of diagnosis in information about treatment options (46%, X^2=11.66, p=.001) and clinical trials (33%, X^2=7.74, p <.01). **Conclusion:** Late stage never-smokers are more likely to seek a second opinion, and they are more interested in information about treatment options and clinical trials. Stigma among ever-smokers may be preventing them from seeking a second opinion. Understanding these characteristics and potential bias or stigma related to smoking may help to tailor the conversation between patient and provider to ensure patient needs are met at initial diagnosis.

Keywords: stigma among ever-smokers, second-opinion seeking, patient-provider relationship

P2.15-16 CLINICAL ECONOMIC IMPACT OF IMPROVED GENOTYPING IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG ADENOCARCINOMA (NSCLC)

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Background: Comprehensive genomic profiling (CGP) at diagnosis and progression identifies NSCLC patients who may benefit from targeted therapies and are unlikely to respond to immunotherapy, however many patients are incompletely or undergenotyped. We developed a cost benefit model to evaluate the clinical and economic impact of using plasma-based cfDNA CGP to guide treatment decisions in first- and second-line advanced NSCLC. **Method:** The model compares the clinical and economic impact of an NCCN guideline driven care paradigm, utilizing Guardant360ª (G360), a CLIA certified, CAP accredited, NYSDOH approved cfDNA CGP test, for stage IIIB/IV NSCLC patients versus the current care paradigm and assesses the impact of additional genomic information to aid in therapy selection and subsequent effects on biopsy rates, drug costs, and clinical outcomes (RR, PFS, and median OS). The model targeted patients with NSCLC receiving first or second line treatment enrolled in a U.S. Commercial Health Plan with 10 million lives. Frequency of NCCN genomic targets in first-line patients was per The Cancer Genome Atlas with second-line frequencies modified to reflect the first-line testing, genotyping QNS, biopsy, and undergenotyping rates. Therapy current care distributions were derived from 2017 Integra Connect's proprietary database. **Result:** Under the guideline directed care, immunotherapy and chemotherapy use decreased as patients are re-assigned to targeted therapy in both first line QNS and second line progression settings, resulting in improved clinical outcomes, including a second line repeat tissue biopsy rate reduction. Individual and overall cost savings were observed in both settings

(See next page)

	First-Line QNS Patients			Second-Line Patients		
	Current	Guideline Directed	Difference	Current	Guideline Directed	Difference
Overall Patient Cohort						
Immunotherapy Monotherapy	19.2%	13.2%	- 6.00%	52.5%	42.9%	- 9.6%
Immunotherapy + Chemotherapy	5.6%	3.9%	- 1.7%	3.3%	2.7%	- 0.6%
Chemotherapy +/- Biologics	75.2%	51.7%	- 23.5%	35.7%	29.2%	- 6.5%
Targeted Therapy	0%	31.3%	+ 31.3%	8.6%	25.3%	+ 16.7%
Overall Clinical Outcome Measures						
Response Rate	18.1%	28.3%	+ 10.2%	20.9%	25.7%	+ 4.8%
Progression Free Survival (months)	4.7	6.0	+ 1.3	4.7	5.6	+ 0.9
Overall Survival (months)	11.1	12.6	+ 1.5	11.0	12.1	+ 1.1
Reassigned Patient Cohort						
Immunotherapy Monotherapy	6.0%	-	-6.0%	9.6%	-	- 9.6%
Immunotherapy + Chemotherapy	1.8%	-	- 1.8%	0.6%%	-	- 0.6%
Chemotherapy +/- Biologics	23.5%	-	- 23.5%	6.5%	-	- 6.5%
Targeted Therapy	-	31.3%	+ 31.3%	-	16.7%	+ 16.7%
Clinical Outcome Measures for Reassigned Patients						
Response Rate	18.1%	50.7%	+ 32.6%	17.7%	49.5%	+ 31.8%
Progression Free Survival (months)	4.7	8.8	+ 4.0	4.2	9.7	+ 5.5
Overall Survival (months)	11.1	15.9	+ 4.9	10.3	17.3	+ 7.0
Second-line re-biopsy rate	-	-	-	25%	11%	-14%
Overall Cost per Patient	$140,950	$130,141	-$10,809	$175,563	$161,810	- $13,753
Overall Total Cost	$55,516,110	$51,258,713	-$4,257,397	$209,553,002	$193,136,843	- $16,416,159

Conclusion: cfDNA CGP application in first line tissue QNS and second line progressing advanced NSCLC patients improved outcomes and cost savings. Shifting from chemotherapy and immunotherapy to relatively more efficacious, less toxic, and less expensive targeted therapies resulted in improved patient outcomes. Cost savings are driven by decrease in immunotherapy, infusion costs, emergency room/hospital visits, and avoidance of tissue biopsy.

Keywords: cfDNA, NSCLC, Health Economics

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-17 PATIENT CARE IN ADVANCED LUNG CANCER: UNMET NEEDS

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Background: Comprehensive cancer care uses complementary approaches alongside specific anticancer therapy. Using a dedicated questionnaire, the Calista2 survey sought to assess the importance of supportive care and activities among lung cancer (LC) patients, how often these services are made available and offered, the utilization rate, and the frequency of unmet needs. **Method:** The 25 physicians who accepted to take part in the survey recruited 198 patients of whom 143 answered the patient-reported questionnaire. Patients meeting the inclusion criteria were adults already on specific therapy for advanced LC. The patient-reported questionnaires covered drug management of pain, fatigue, adverse effects of treatments (AE), and sleep disorders, social and psychological support, physical activities, and complementary and alternative medicines. Items were rated on a 0 – 10 scale. Questionnaires were collected between September 2016 and October 2017. **Result:** After exclusion of non-valid patient questionnaires, 134 were analyzed. The mean age of these patients was 64.3 years (SD:8.5). There were 62% men and 37% women. Patients perceived the management of pain, AE and fatigue as the three most important items (7.5, 7.2, 6.0) while counselling with regards to employment (1.7), spiritual support (2.6), art therapy (2.6), and support groups for patients' children (2.6) were the least important. Although most of the facilities were available at the point of care, complementary medicines, art therapy, and professional counselling were accessible for 29%, 33%, and 21%, respectively. Physicians frequently suggested pain and AE management (78%, and 75%, respectively), and diet counselling (51%). In contrast, fatigue management, sleep disorders, and sexual issues were less frequently addressed (35%, 44%, and 6%, respectively). Paradoxically, the four main unmet needs were management of fatigue, complementary medicines, psychological support for the patient's family and friends and relaxation techniques (32%, 25%, 20%, and 20%, respectively). **Conclusion:** These key findings highlight the fact that support for pain and for the AE of cancer treatment are available, suggested and used. In contrast, unmet needs expressed by the patients were either available but not used

(fatigue management and psychological support for the patient's family and friends) or rarely available (complementary medicines and relaxation techniques).

Keywords: Patient comfort, palliative care, Complementary therapies

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-18 COST-EFFECTIVENESS ANALYSIS OF SECOND-LINE IMMUNE CHECKPOINT INHIBITORS FOR ADVANCED NSCLC IN COLOMBIA

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Background: Immune checkpoint inhibitors improve outcomes compared with chemotherapy in lung cancer. Tumor PD-L1 receptor expression is being studied as a predictive biomarker. The greatest challenge in oncology today is how to reconcile improvements in the management of cancer with the exponentially increasing costs of new treatment and this is a very important barrier in low and middle income countries. The objective of this study was to assess the cost-effectiveness and economic impact of second-line treatment with nivolumab and pembrolizumab with and without the use of PD-L1 testing for patient selection in Colombia . **Method:** We designed a decision-analytic model to evaluate the cost-effectiveness of second-line immunotherapy versus docetaxel for advanced NSCLC. We considered the outcomes from randomized clinical trials (RCTs). Direct and indirect costs were retrieved with a colombian perspective. We followed standard recommendations for the conduct and reporting of health economic analyses. Primary endpoint were Incremental Cost Effectiveness Ratios (ICER), for treatment with nivolumab and pembrolizumab with and without PDL1 testing. **Result:** Nivolumab improved quality-adjusted life-years (QALY) by 0.417 among squamous tumors and 0.287 among non squamous tumors. The ICER were $135,093 COP and $179,391 COP, respectively. Pembrolizumab achieved a QALY gain of 0.346 and the ICER was $146,022 COP. The use of PD-L1 expression as a tailor biomarker for nivolumab among non-squamous tumors improved incremental QALY by up to 157% and decreased the ICER by up to 61% compared with treating all patients. Considering a willingness to pay threshold of three times the Colombian Gross Domestic Product per capita, second-line immunotherapy was not cost-effective with or without patient selection by PD-L1 expression. **Conclusion:** Patient selection by PD-L1 expression increased cost-effectiveness of immunotherapy. Second-line immunotherapy was not cost-effective in Colombia due to its high cost. Taking into account the disparities in access to cancer innovative therapies, there is a need to promote strategies to reduce drug acquisition costs, such as price discrimination and the use of biosimilars or generics.

Keywords: cost effectiveness, pharmacoeconomics, Inmunotherapy

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-19 INEQUALITY OF ACCESS TO NOVEL LUNG CANCER THERAPIES IN EUROPE

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Background: With an estimated incidence of over 449,000 cases per year, lung cancer is one of the most common malignancies in Europe. Over the last decade the landscape of lung cancer treatment has evolved. We have entered a new era of lung cancer treatment and high costs has led to disparities in lung cancer care among different European countries. There is evidence of discrepancy in access to cancer therapies in Europe however access to contemporary targeted agents and immunotherapy for lung cancer hasn't been studied. We analysed the reimbursement dates of novel lung cancer therapies in Europe. **Method:** The lung cancer therapies investigated include the tyrosine kinase inhibitors (TKI) alectinib, ceritinib, and crizotinib. Immunotherapy agents nivolumab, pembrolizumab and atezolizumab were also researched. National reimbursement dates of these drugs of these drugs in 29 European countries were obtained from national resources and from the pharmaceutical companies' affiliates. **Result:** As of February 2018, Crizotinib was reimbursed in 24/29 (83%) of countries. Ceritinib was reimbursed in 21/29 (72%) of countries while Alectinib was reimbursed in 12/29 (41%) countries. Pembrolizumab and Nivolumab were reimbursed for previously treated NSCLC in 21/29 (72%) and 18/29 (62%) countries respectively. Atezolizumab was reimbursed in 7/29 (24%) countries for previously treated NSCLC patients. Pembrolizumab for first line treatment of NSCLC was reimbursed in 20/29 (69%) countries, while in 9/29 (31%) (all Eastern European Countries) not reimbursed. Eastern European countries reimbursed these drugs later than Western European countries. **Conclusion:** The time from European Medicines Agency approval to reimbursement of these novel lung cancer treatments differs throughout Europe. Eastern European countries were less likely to have novel lung cancer therapies reimbursed. This research shows access to novel lung cancer therapeutics is unbalanced in Europe.

Keywords: NSCLC, Access to therapy, Immunotherapy

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-20 EDUCATING THE MULTISPECIALTY TEAM ON MOLECULAR TESTING RELATED TO IMMUNOTHERAPY

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Background: Clinical guidelines for metastatic non-small cell lung cancer (NSCLC) increasingly include molecular testing for actionable biomarkers related to immuno-oncology (IO) use in lung cancer patients. While precision therapies targeting the PD-1/PD-L1 pathway have the potential to improve patient response rates, there is ambiguity regarding optimal biomarker testing and care coordination for NSCLC patients. To address this disparity in health care delivery, an online education program on molecular testing related to immunotherapies was developed for multispecialty providers. Learner responses were evaluated to determine the educational impact. **Method:** A thoracic surgeon, medical oncologist and pathologist developed a curriculum to address the current diagnostic landscape in IO, the value of testing and patient response rates, and how to optimize care coordination and communication among multispecialty team members. In February 2018, a live-online 1-hour video panel discussion with slides, participant polling, and live questions was produced and made available on-demand. Survey responses (pre-test, post-test, 4 weeks post-activity), polling responses, and live questions were tracked to measure knowledge gaps, lessons learned, and educational needs. Demographic information was collected for generalizability. **Result:** Seventy-one learners participated in the live webinar; 64 learners on-demand (n=135). Learners were actively engaged for an average of 35.19 minutes (out of 52 minutes). Learners represented 11 unique disciplines and specialties. Most learners indicated specializing in oncology (55%), were practicing physicians (31%), and saw 1-10 new patients on an IO therapy each week (72%) in a hospital-based setting (35%). Seven audience questions were asked prior to, and during the live session. Thirty of 135 learners completed all pre/post/follow-up surveys, 96% of which reported they will actively utilize the knowledge gained into their clinical practice. Because of the education provided, learners reported improvements in their ability to: identify patients to test and treat with IO (75%), comprehend the current diagnostic landscape in IO (100%), and optimize communication and coordination of IO testing (100%). Learners also demonstrated improved comprehension via case study by identifying the optimal next step for a NSCLC clinical stage I patient referred by an oncologist for surgical resection who was found to have pleural disease intraoperatively. **Conclusion:** The rapid expansion of cancer immunotherapy-based options for patients with lung cancer requires providers to stay abreast on guidelines related to molecular testing. Continued refinement of care coordination practices between multispecialty team members and education on the value of molecular testing is recommended to improve the diagnosis and appropriate treatment decisions for patients with lung cancer.

Keywords: Provider education, Immunotherapy, molecular testing

P2.15-21 POST RESECTION LUNG CANCER SURVEILLANCE: COMPARISONS OF PRACTICE BETWEEN STS, ESTS AND JACS MEMBERS

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Background: We recently investigated contemporary practice in post-resection lung cancer surveillance, between the Society of Thoracic Surgeons (STS) and the European Society of Thoracic Surgeons (ESTS) updating a published STS survey and showed a wide variance of practice. In order to understand better the role of socio-demographics on this divergence, we aim to compare these patterns to those of members of the Japanese Association for Chest Surgery(JACS) as well as surveillance attitudes across these regions. **Method:** A survey identical to the one conducted in 1995 among STS members was administered via mail or electronically to members of the STS, ESTS and JACS requesting responses from those treating NSCLC. Goodness of fit tests were used to compare profiles of respondents and attitudes toward testing between groups. Multivariable logistic regression was performed to examine for predictors of guideline concordant surveillance with CT. **Result:** A total of 2978 STS member (response rate 7.8%, n=234), 1450 ESTS members (response rate 8.4%, n=122) and 272 JACS (response rate 40,8%, n=111) members were surveyed. All three societies reported similar use of history and physical examination for asymptomatic patients (75%vs78%vs73%p=0.52). Rate of guideline-recommended surveillance CT was reported highest among ESTS respondents for stage I patients (22% ESTS, 3% STS and 6% JACS members, p<0.01). However, both JACS and ESTS respondents reported higher rates of use of non-guidelines-recommended tests compared to STS respondents which persisted on adjusted analyses. In particular, JACS and ESTS respondents reported significantly higher use of brain MRI (JACS AOR 13.85 [7.46-25.73] ESTS AOR 2.81 [1.59-4.99], p<0.01), Bone Scan (ESTS AOR 3.00 [1.68-5.36] JACS AOR 5.69 [3.21-10.08], p<0.01) and bronchoscopy for post-resection surveillance (JACS AOR 3.51 [1.99-6.20] ESTS AOR 3.25 [1.83-5.79], p<0.01) compared to STS respondents. Regarding attitudes towards surveillance, more JACS and ESTS members either "agree" or "strongly agree" that routine testing for NSCLC recurrence results in potentially curative treatment (ESTS:86%, STS:70%, JACS:90% p<0.01). Similarly, JACS and ESTS respondents believe that surveillance would identify a curable second primary NSCLC (ESTS:94%, STS:84%, JACS:100% p<0.01) and that current literature documents definitive survival benefits from routine follow-up testing (ESTS:57%, STS:30%, JACS:62% p<0.01). **Conclusion:** The Japanese attitude towards surveillance is similar to that of ESTS members potentially highlighting significant differences between European and Asian surgeons compared to STS members and may be the underpinnings of routine use of non-guideline concordant surveillance. These differences clearly highlight the need of better prospective studies and joint recommendations to standardize practice globally.

Keywords: CT-follow-up, Surveillance

P2.15-22 OPTIMAL GLYCEMIC CONTROL IMPROVES PROGNOSIS FOR LUNG CANCER PATIENTS WITH DIABETES MELLITUS

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Background: Diabetes mellitus (DM) is a common comorbidity in patients with lung cancer (LC). This study aimed to evaluate the prognostic value of DM comorbidity for LC patients with DM and to assess whether an optimal glycemic control improves survival. **Method:** A total of 4390 patients diagnosed with LC between 2012 and 2013 at Shanghai Chest Hospital were retrospectively reviewed, 491 patients with DM and 3899 without DM. The relationship between hemoglobin A1c (HbA1c) level and the overal survival (OS) was plotted by a smooth curve. LC patients with DM were subdivided into the well-controlled group (HbA1c < 7%, n=438) and uncontrolled group (HbA1c ≥ 7%, n=53). OS differences among patients without DM, with well-controlled DM, and uncontrolled DM were evaluated by multivariate Cox regression analysis with adjustment for stage, sex, age, histology, smoking history and EGFR mutation status. The survival benefit of well-controlled DM was compared across subgroups. **Result:** The median follow-up of the entire cohort was 35.8 months. DM patients (11.2%) had a significantly worse OS than nondiabetic patients [median (95% CI): 47.5 (39.0-56.1) vs. 73.6 (54.8-92.4) months, P<0.001]. The risk of mortality increased along with the elevation of HbA1c level. Uncontrolled DM patients tended to be male, elder, non-adenocarcinoma, with smoking history, wide-type EGFR mutations and advanced stage. Well-controlled DM patients had a worse OS [HR (95% CI): 2.3 (1.9-2.7), P<0.001] compared to nondiabetic patients without adjustment but a similar OS with adjustment for stage, sex, age, histology, smoking history and EGFR mutation status [HR (95% CI): 0.9 (0.8-1.1), P=0.185]. Benefit of well-controlled DM was more obviously seen in patients with advanced stage (III-IV) [HR (95% CI): 0.8 (0.6-1.1), P=0.130] or EGFR mutations [HR (95% CI): 1.2 (0.9-1.5), P=0.262]. **Conclusion:** Elevated glycemic status negatively affected OS for patients with LC. LC patients with DM is recommended to have a glycemic control (HbA1c < 7%) especially for those with advanced stage and EGFR mutations.

Keywords: Diabetes, lung cancer, glycemic

P2.15-23 ARE THERE ETHNIC DISPARITIES IN THE CLINICAL OUTCOMES OF NON-SMALL CELL LUNG CANCER HISPANIC PATIENTS TREATED WITH IMMUNOTHERAPY?

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Background: Immunotherapy outcomes in non-small cell lung cancer (NSCLC) are widely available thanks to studies that got the approval of PD-1/PD-L1 inhibitors. However a careful review of ethnicity can find that most of the studies were done in Non-Hispanic White or Asian populations. There is little known about the outcomes in Hispanics (H). It is well known that Hispanics (H) in the US seem to have a lower age-adjusted mortality in NSCLC and have a different gene expression profile than NHW with higher prevalence of EGFR mutations. **Method:** We reviewed clinical outcomes in 216 H pts with NSCLC stage IV treated with atezolizumab, nivolumab or pembrolizumab at 4 large cancer centers (Memorial Cancer Institute, University of Miami and Moffitt Cancer Center all of them in Florida (US), and the National Cancer Institute in Peru. These patients have failed at least one line of chemotherapy previously. All of these patients did not have actionable genes (EGFR. ALK, ROS-1). We assessed overall response rate ORR (CR+PR) as main objective and disease control rate (DCR: ORR+SD), median PFS (progression free survival) & overall survival (OS) and PFS at 6m and 12m as secondary objectives. **Result:** Most of the pts were males: 116 (54%), 82% adenocarcinomas and the median age was 65 years (range: 37-88y). The ORR was 16% and the DCR that shows the clinical benefit was 67%. ORR and DCR were similar in adenocarcinomas (20%/68%) and squamous cell carcinomas (17%/64%). The progression free survival (PFS) at 6 months (m) and 12m were 80% and 56% respectively. Median PFS 14.5m and median overall survival were 19m, respectively. **Conclusion:** ORR for NSCLC pts treated with immunotherapy is 16% in Hispanics treated at 4 cancer centers compared to an expected 20% ORR for NHW as reported in the literature. Therefore it appears that Hispanics might not have a benefit from immunotherapy to the extent that NHWs do. We need a larger cohort and prospective studies to validate these findings.

Keywords: PDL-1, Hispanics, EGFR

P2.15-24 COMPARISON OF PEMETREXED ADMINISTERED Q 3 WEEKS VS Q 4 WEEKS AS MAINTENANCE THERAPY IN NSCLC: ANALYSIS OF REAL WORLD DATA FROM A SINGLE INSTITUTION

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Background: Pemetrexed maintenance q 3 weeks has shown survival benefit in patients with advanced stage nonsquamous NSCLC. We sought to compare treatment outcomes in patients receiving alternate maintenance schedule (q 4 weeks) in real-world practice. **Method:** This is a single-center, IRB-approved retrospective study of over 500 advanced stage (IIIB&IV) nonsquamous NSCLC patients receiving pemetrexed between May 1, 2011 to June 30, 2016 as standard of care. Patients who received at least two doses of maintenance pemetrexed were included in the analysis. Tumor response was assessed with CT scan imaging every 6-9 weeks. Hematologic indices, hepatic, renal function, performance status, dose changes, subsequent dosing or schedule changes, duration on therapy (discontinuation due to toxicity, switch in therapy or death) and overall survival data were obtained. Summary statistical analyses are provided for the demographic features of the patients included in this study in both. The difference between the two groups are evaluated using Fisher's Test /Chi-Square Test / Logistic regression analyses for categorical variable, and T-Test / Generalized Linear regression analyses for continuous variables. Generalized Linear regression model are applied to compare outcomes between outcomes SAS version 9.4 (SAS Institute, Cary, NC) will be used for statistical analyses. All tests were two-sided and performed at a nominal significance level of 0.05. **Result:** 138 patients were eligible to be included in the analysis. There were 90 and 48 patients who received pemetrexed q 3 weeks (group A) and q 4 weeks (group B), respectively. There were no differences in gender or ECOG performance status (PS) at baseline between the groups. Most common reasons documented for q4 week schedule are either patient preference or cumulative toxicities (lab abnormalities, poor tolerance or fatigue after induction treatment). Duration on therapy was longer in group B than in group A (282 days vs 156 days, $p < 0.001$). There were no differences in pre- and post-treatment changes in hemoglobin, ANC, creatinine clearance, ALT or AST levels between the two groups. There was also no difference in the change in PS between groups. Platelet count was higher at the end of therapy in group A compared to group B ($p<0.01$) . Survival outcomes and molecular profiling data will be presented in the meeting. **Conclusion:** Alternate q 4 week dosing schedule of pemetrexed is feasible and associated with longer time on treatment. There appears to be no difference in toxicities experienced between the two treatment schedules in this cohort.

Keywords: maintenance pemetrexed, alternate schedule, Real world data

P2.15-25 NIVEX TRIAL (GECP 1605): NIVOLUMAB IN THE REAL WORLD: SPANISH EXPANDED ACCESS PROGRAM EXPERIENCE IN PRETREATED ADVANCED NSCLC PATIENTS

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Background: Nivolumab is a standard treatment for pretreated patients with advanced non-small cell lung cancer (NSCLC). Real world data about toxicity and efficacy of nivolumab is needed. **Method:** We have analyzed patients from the Expanded Access Program in Spain that included patients with advanced pretreated NSCLC. We have retrospectively analyzed 665 patients that had received at least 1 dose of nivolumab 3mg/kg q2w from 01/2015 for squamous (Sq) and 06/2015 for non-Sq NSCLC, to 11/2017. **Result:** Median age was 61 (32-85) years, 73% were men, 85% had ECOG 0-1, 88% were current or former smokers and 15% presented brain metastases. 128 (19,2%) patients presented Sq NSCLC and 537 (80,8%) patients Non-Sq NSCLC. 7% of patients presented EGFR mutation. PD-L1 was ≥ 1% in 32,9% of analyzed patients. Best response was complete response 1,7%, partial response 22,4%, stable disease 24,1%, and progressive disease 37,1%, and was not assessed in 14,7% of patients. No differences in response rate were observed according to histology. After a median follow-up of 8,2 months, the median OS was 8,97 (95%CI 7,69-10,24) months, and the median PFS was 3,23 (95%CI 2,77-3,70) months. Estimated 1-year OS was 42,4% (95%CI 38,5-42,8%) and estimated 1-year PFS was 22,2% (95%CI 19,1-25,3%). No differences in OS or PFS according to histologies were observed. 296 (44,5%) patients presented toxicity related to Nivolumab, that was grade ≥3 in 69 (10,4%) patients. Grade ≥3 diarrhea was reported in 1,2% of patients and pneumonitis occurred in 1,2% of patients (1 patient presented a grade 5 pneumonitis). According to the presence of grade ≥3 toxicity, the median OS was 14,57 (CI95% 8,45-20,68) months for patients with grade ≥3 toxicity and 8,73 (CI95% 7,50-9,96) months for patients without grade ≥3 toxicity (p= 0,074). Additional efficacy data including treatment lines, presence of immune-related adverse events, PS2, brain metastasis, response to first line, or post-nivolumab treatment will be presented. **Conclusion:** Efficacy and safety of nivolumab was in line with previously shown data. There was a trend to a better OS for those patients experiencing grade ≥3 toxicity.

Keywords: real world, nivolumab, NSCLC

P2.15-26 RATES AND ECONOMIC BURDEN OF ADVERSE EVENTS IN PATIENTS WITH METASTATIC NSCLC TREATED WITH EGFR-TKIS

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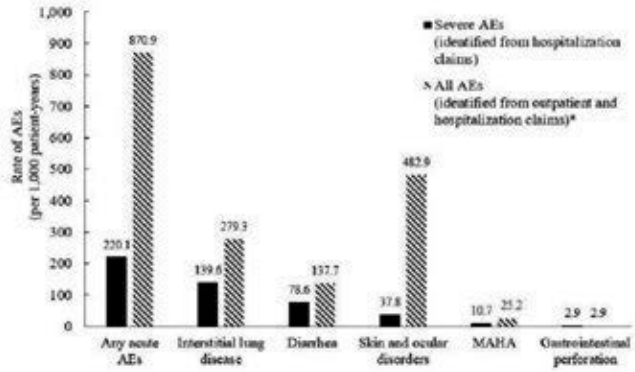
Background: Trials of first- and second-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) have reported severe adverse events (SAEs) in 6%–49% of patients with *EGFR*-mutant (*EGFR*m) metastatic non-small cell lung cancer (mNSCLC). This study describes the real-world rates and incremental cost of AEs in this population. **Method:** Adults with mNSCLC treated with EGFR-TKIs as first-line therapy (first dispensing defined as the index date) with ≥1 lung cancer diagnosis code, no claim for a lung surgery, and no administration of other NSCLC therapies during 3 months pre-index date were identified from the IQVIA™ Real-World Data Adjudicated Claims – US database (Q2/2012–Q1/2017). The select AEs identified from prescribing information of EGFR-TKIs were skin and ocular disorders, interstitial lung disease (ILD), diarrhea, microangiopathic hemolytic anemia, gastrointestinal perforation, cardiac and cerebrovascular events, renal failure, and hepatotoxicity. AE rates per 1,000 patient-years and healthcare cost per-patient-per-month (PPPM) were calculated during first-line therapy. Multivariate linear regression was used to assess cost differences (CD) for patients with and without AEs, adjusting for baseline characteristics. All AEs (outpatient and hospitalization claims) and a subgroup of SAEs (hospitalization claims) were analyzed. **Result:** Among 1,646 patients, 86.1% were treated with erlotinib, 12.1% with afatinib, and 1.0% with gefitinib. During first-line therapy, 549 patients had ≥1 acute AE (33.4%, 870.9 per 1,000 patient-years) and 200 patients had ≥1 acute SAE (12.2%, 220.1 per 1,000 patient-years). Skin and ocular disorders (17.6%, 482.9 per 1,000 patient-years) and ILD (4.5%, 139.6 per 1,000 patient-years) had the highest rate among all AEs and SAEs, respectively (**Figure**). Patients with AEs had higher PPPM healthcare costs than patients without AEs (all AEs: CD=$1,079, $p<0.001$; SAEs: CD=$4,700, $p<0.001$).

(See next page)

Figure. Rate of occurrence of acute AEs during treatment period



AEs: adverse events; MAHA: microangiopathic hemolytic anemia

* For the category of all AEs, only first diagnosis or admission diagnosis (i.e., "primary" diagnoses) were considered for AEs identified from outpatient claims. All diagnoses were considered for the identification of AEs from hospitalization claims.

Conclusion: Over one-tenth of patients suffered from SAEs, resulting in a sizeable economic burden. EGFR-TKIs with more favorable safety profiles may reduce substantial healthcare costs in this patient population.

Keywords: NSCLC, adverse events

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-27 LUNG VOLUME CHANGE AFTER LOBECTOMY ESTIMATED BY THREE-DIMENSIONAL IMAGE ANALYSIS SYSTEM

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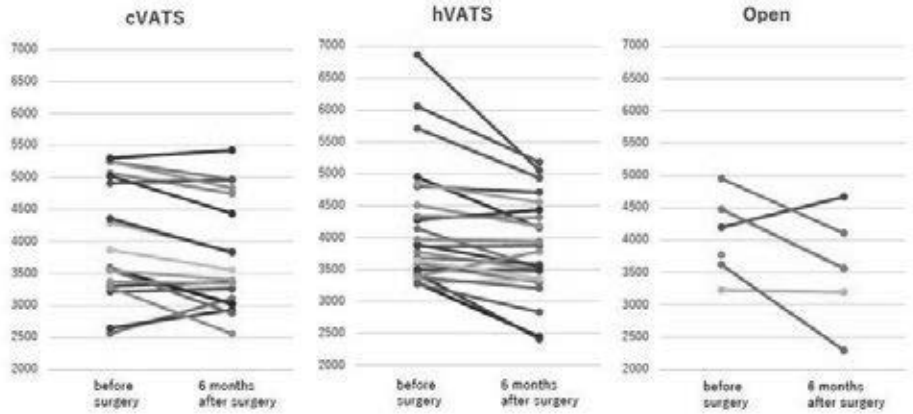
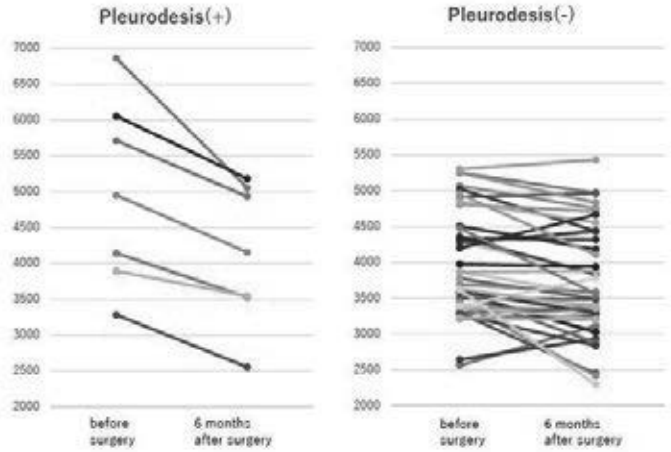
Background: High-precision three-dimensional (3D) image analysis system has been used for preoperative planning in various fields including thoracic surgery. Such software has made us quite easy to measure lung volume. Change of pulmonary function after surgery has been surveyed in some reports, but there are few reports about lung volume change after surgery. **Method:** We conducted a retrospective review of 49 patients who underwent lobectomy between January 2014 and June 2016 at General Hospital of Japan Railway Company. We used 3D image analysis system (SYNAPSE VINCENT, Fujifilm Corp, Tokyo, Japan) to calculate lung volume of each patient from computed tomography (CT) images which were taken twice, before surgery and 6 months after surgery. We estimated lung volume change from the difference between those two values. **Result:** There were 19 right upper lobectomies (RUL), 7 right middle lobectomies (RML), 8 right lower lobectomies (RLL), 5 left upper lobectomies (LUL), and 10 left lower lobectomies (LLL). We performed lobectomies in three different surgical approaches; Thoracotomy (n=5), Hybrid Video-assisted thoracic surgery (VATS) (n=24), Complete VATS (n=20). 7 patients needed pleurodesis after surgery to treat air leakage. The average of total lung volume change was -10.4%. Right lobectomies showed 11.45% decrease of lung volume in average, while left lobectomies showed 5.34% decrease (p=0.18). Decrease ratio seemed to depend on the way of approaches; Thoracotomy was -19.98% and VATS (hybrid and complete) was -8.58% (p=0.12). Volume change of patients who underwent pleurodesis after surgery was -20.37%, while the ratio of the others was -7.84% (p=0.03).





Conclusion: VATS seemed to be better in the point of lung volume after lobectomy than thoracotomy. Pleurodesis turned out to reduce lung volume significantly. For furthur study, we will compare lung volume with pulmonary function on a lager aomount of data .

Keywords: lung volume, lobectomy, 3D imagge analysis

P2.15-28 EFFECT OF INSURANCE TYPES ON TUMOR RECURRENCE AND OVERALL SURVIVAL IN RESECTABLE NON-SMALL LUNG CANCER PATIENTS IN NORTHERN THAILAND

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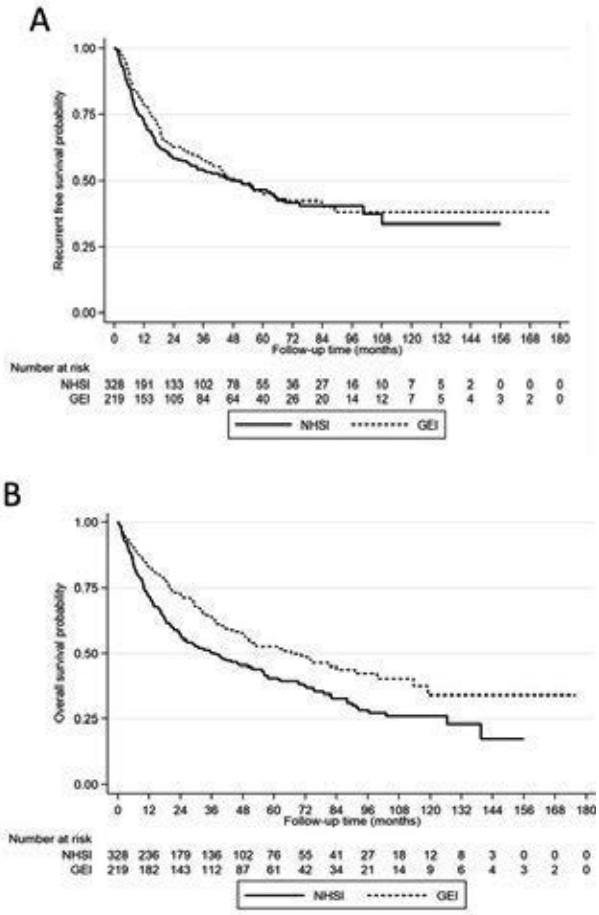
Background: The effect of insurance types on tumor recurrence and overall survival in resectable non-small cell lung cancer in northern Thailand have never been reported. The aim of this study is to identify the association between Thailand's insurance types and long-term outcomes of treatment. **Method:** Medical records of patients with non-small cell lung cancer (NSCLC) who underwent pulmonary resection at Chiang Mai University Hospital from January 2002 through December 2016 were retrospectively reviewed. Patients were divided into two groups; patients with National Health Security insurance (NHSI) and patients with Government/State Enterprise insurance or private insurance (GEI). Patient characteristics, pathologic findings and long-term outcomes were assessed. Primary outcome was overall survival; secondary outcome was tumor recurrence. Multivariable cox's regression analysis were used to analyze data. **Result:** This study included 583 patients; 344 with NHSI and 239 with GEI. Patients with NHSI were more likely to be active smokers, lower % predicted FEV1, present with higher stage tumor, having moderately and poorly differentiated tumor, present with tumor necrosis, and undergo open surgical approach than those with GEI. There were no differences between the two groups in term of lymph node dissection, chemotherapy and post-operative complications. At multivariable analysis, tumor recurrence in patients with GEI was not statistically different from what observed in patients with NHSI (adjusted hazard ratio ($HR_{adj)}$=1.03, 95% CI=0.51-2.11), however patients with NHSI was more likely to die (HR_{adj}=2.45, 95%CI=1.11-5.42).



Conclusion: Thai NSCLC patients with NHSI coverage were more likely to experience shorter overall survival than those with GEI. The difference in medical coverage in each type of insurance, especially in term of regimens of chemotherapy, targeted therapy and immunotherapy may be associated with overall survival of patients. The Thai government should take into account this difference.

Keywords: Coverage, treatment outcome, Thai insurance

P2.15-29 ELIGIBILITY FOR ANTI-ANGIOGENIC TREATMENTS IN PATIENTS WITH SQUAMOUS NON-SMALL CELL LUNG CANCER (SQ-NSCLC): EPISQUAMAB STUDY (GFPC 2015-01)

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Background: Antiangiogenic treatments are today restricted to non-squamous NSCLC. New drugs, like ramucirumab, have been approved in second line setting for advanced NSCLC regardless histology but there is little information about the rate of squamous NSLC eligible to these treatments. This descriptive, prospective, observational study aimed to assess the rate of squamous advanced NSCLC patients eligible to anti-angiogenic treatments. **Method:** Each participating center had to include consecutive relapsed advanced SQ-NSCLC and to assess the presence of common criteria which restricted the use of antiangiogenic treatments (hemoptysis, cardiovascular diseases, tumoral extension to blood vessels and tumoral cavitation). **Result:** From july 2016 to july 2017, 317 patients were included: 256 (80.8%) men, PS0/1/2 in 30.5%/54.5%/14.9% patients, stage IV in 74.5% of cases. Ineligibility criteria for anti-angiogenic therapy were found in 53.6% of patients (one single criteria in 29,3%, two criteria in 19,9%, three in 3.5%). The main reasons for ineligibility was as followed: blood vessel extension 39.8%, cavitation 20.5%, hemoptysis 7.2%, cardiovascular diseases 12.1%. Table described patients characteristics according to the ineligibility criteria: Cavitation had the highest number of metastatic disease, cardiovascular diseases the highest number of men and number of metastatic site.

(See next page)

	Blood vessel extension n=105	Cavitation n=54	Hemoptysis n=19	cardiovascular diseases n=29
Men/women (%)	81.9 / 18.1	77.8 /22.2	89.5 / 10.5	93.1 / 6.9
Stage IV/ Others (%)	65.7 / 34.3	75.9 / 24.1	63.2 / 36.8	72.4 / 27.6
Number of mestastatic site >1 vs ≤ 1 (%)	60.9 / 39/1	65.9 / 34.1	58.3 / 41.7	71.4 / 28.6
chemotherapy 1st line (%)	99.1	100	94.7	100
chemotherapy 2nd line (%)	87	79.7	73.7	79.3

Conclusion: In a non-selected advanced SQ-NSCLC population, only half of these patients are ineligible to a second line anti-angiogenic treatments with a wide majority of tumoral blood vessel extensions and cavitations.

In collaboration with the GFPC team and supported by an academic grant from Lilly pharmaceuticals. *GFPC: French Lung Cancer Group*

Keywords: Squamous non small cell lung cancer, Antiangiogenic eligibility, Observational study

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-30 MARITAL STATUS AND SURVIVAL IN PATIENTS WITH LUNG CANCER

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Background: Multiple studies have shown that marital status is associated with the survival of various types of cancer patients. Majority of the findings support high survival rate for married patients is closely related to well social support and family care. However, another conclusion that there is no correlation between marital status and the length of cancer survival makes it controversial when talking about the survival benefit of cancer patients. To better explain the issue, here we did further investigation to study the effect of marital status on survival of lung cancer patients. **Method:** In this study, we retrospectively extracted 136535 eligible lung cancer patients from the Surveillance, Epidemiology, and End Results (SEER) database in the period from 2010 to 2014. Marital status was categorized as married, divorced/separated, widowed, and Single/Partner. The latter three are classified as unmarried. Meanwhile, 1:1 propensity scores for marital status, which were calculated for each patient using a multivariable logistic regression model, were used to match 64749 unmarried patients with 71786 married patients. With accurate matching, the fault tolerance rate is set to 0. Chi-square tests were used to investigate the association between marital status and other variables. The Kaplan-Meier test was adopted to compare survival curves of different groups. Multivariate Cox regression analyses were conducted to estimate the effect of marital status on OS and CSS. **Result:** We exactly matched 37105 unmarried patients with 37105 married patients. Married patients had higher OS than unmarried patients before matching (OS: HR: 0.903(0.891-0.916), P<0.001; CSS: HR: 0.917(0.904-0.931), P<0.001). But after matching, the OS is undifferentiated between married patients and unmarried patients (OS: HR: 0.985(0.967-1.003), P=0.1; CSS: HR: 1.004(0.985-1.024), P =0.695). Then we carried out subgroup COX analyses stratified by AJCC stage for OS and CSS. Result hints that the prognosis of married patients is better than that of unmarried patients in Stage III and IV, there is no significant difference between the stage I and II patients in lung cancer. **Conclusion:** Marital status affects the prognosis of patients with advanced lung cancer. the prognosis of married patients is better than that of unmarried patients.

Keywords: lung cancer, SEER database, Marital status

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-31 THE EVOLUTION OF COSTS IN THE TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) IN ONTARIO, CANADA BETWEEN 1999 TO 2014

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Background: Treatment options for patients with advanced non-small cell lung cancer (NSCLC) have evolved substantially since the 1990s. Newer agents are more expensive to acquire and administer and the perception is the cost of lung cancer care has increased considerably in the last two decades. We conducted a cost analysis study to evaluate changes in the total cost of NSCLC care over time. **Method:** We conducted a retrospective cohort study of all NSCLC patients diagnosed in Ontario from Apr 1, 1999 to Mar 30, 2014, who received palliative chemotherapy for advanced disease. Variables of interest were extracted from provincial registry data electronically linked by the Institute for Clinical Evaluative Sciences (ICES). The use of oral systemic therapy is not universally captured in these databases. The mean total cost of care including, systemic therapy, and supportive care (hospitalizations, physician billings, lab tests, out-patient visits, emergency visits, home care, and most prescription medications), was calculated in 2015 CAD dollars by fiscal year of diagnosis. Regression analysis was used to project costs in years with missing supportive care costs. **Result:** Of all NSCLC cases diagnosed in Ontario (n=89,936), 21.6% (n=19,447) received any chemotherapy for advanced disease. In this population, median age ranged from 65 to 69 years, 54.9% were male, 15.4% resided rurally, 45.0% were adenocarcinoma, 58.6% with de novo stage IV disease, and 25.8% received second line chemotherapy. At the time of the data analysis, 6.8% of patients are presumed to be alive. The average cost of care per patient treated rose from $85,339 to $102,026. The cost of systemic therapy rose from $3,856 to $12,554. During the same time period, average supportive care costs changed from $84,732 to $93,495. The proportion of total costs of systemic therapy changed from 4.5% to 12.3%. Utilization of palliative chemotherapy in only those with de novo stage IV disease remained stable over time (29.8%). Patients who received second line chemotherapy cost 5.9 times that of patients who did not ($11,342 and $1,924 respectively). Costs in the final year of life increased from 61.9% to 68.0% of total lifetime costs from 2003 to 2014. **Conclusion:** The cost of systemic therapy for lung cancer patients is rising disproportionately to that of supportive care. Ongoing analyses are assessing the main drivers of cost of care and model the impact of oral targeted therapies and immunotherapies on the cost of lung cancer care.

Keywords: registry data, Cost analysis, advanced NSCLC

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-32 NOVICE TRAINING : THE TIME COURSE FOR DEVELOPING COMPETENCE IN SINGLE PORT VIDEO-ASSISTED THORACOSCOPIC LOBECTOMY

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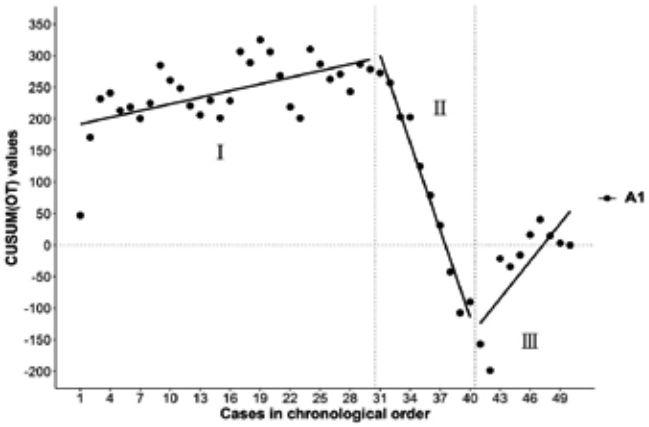
Background: The competency in video-assisted thoracoscopic (VATS) lobectomy is expected to be achieved after surgeons practiced 30 to 50 cases according to previous reports. Does single port video-assisted thoracoscopic (SPVATS) lobectomy have a steeper learning curve and being harder to perform correctly, leading to long development times and high defect rates? **Method:** From January,2014 to Febreary,2017, 8 individual surgeons (3 were novices, 5 were pioneers in SPVATS surgery) submitted their cases chronologically to evaluate the learning curve of SPVATS lobectomy. Propensity score match between two groups and cumulative sum(CUSUM) method were used to explore evolution of learning curve **Result:** Before propensity-score matching, a total of 356 cases were included (93 in junior consultant group (group A), 263 in senior consultant group (group B). There were no differences between the groups in operative time, conversion rate, postoperative complication rate, 30 and 90 day mortality rate. After propensity- score matching, operative time was longer in group A (214.33±62.18 v.s 183.62±61.25 mins, p=0.001). 2-year overall survival rate was similar among two groups (p=0.409). Competency was reached after junior surgeon completed 30th case of SPVATS lobectomy.



Conclusion: SPVATS lobectomy is safe for the novice surgeon who wants to adopt this new surgical approach under well- developed training program. The learning curves for competence in SPVATS lobectomy is similar to VATS lobectomy in our series.

Keywords: Single port VATS, learning curve, novice

P2.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.15-33 EVALUATION OF LIQUID BIOPSIES FOR MOLECULAR PROFILING IN PATIENTS (PTS) WITH ADVANCED NSCLC: WHAT HAPPENS AFTER PANEL TESTING BY NGS?

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Background: Molecular profiling is limited by tumor heterogeneity and access to sufficient tissue for comprehensive analysis. Circulating tumor DNA (ctDNA) is promising as a minimally-invasive liquid biopsy for testing gene alterations and monitoring personalised treatment strategies. Because of its high expense, translation of the sensitive and accurate next generation sequencing (NGS) into routine cancer care has been slow. **Method:** We retrospectively reviewed 60 advanced NSCLC pts who were performed gene test prior to treatment using tissue by ARMS. Blood collections (10ml K2-EDTA) were performed after disease progression and analysed by NGS using a 10-gene panel (EGFR, KRAS, BRAF, HER2, PIK3CA, ALK, ROS1, RET, MET and TP53). We evaluated the significance of the outcome of panel testing by NGS in guiding the subsequent treatment in clinical practice. **Result:** Among 60 NSCLC pts, 39 were male, 28 were never-smokers, and 56 were adenocarcinoma. ctDNA profiling detected alterations in 50 pts (83%). TP53 (53%), EGFR (48%) and KRAS (15%) were the most common abnormalities detected. Additionally, MET (8%), ALK (3%), HER2 (3%) and PIK3CA (2%) mutations were detected, respectively. Sensitizing mutations were detected in 22 pts (37%) prior to treatment using tissue by the method of ARMS, including 20 EGFR mutations and 2 ALK fusions, and all pts received tyrosine kinase inhibitor (TKI) as first-line therapy. Among 20 EGFR mutant pts, T790M mutation was detected in 9 pts (45%), KRAS mutation was detected in 4 pts (20%), and TP53 mutation was detected in 12 pts (60%), while MET amplification was found in 1 pt (5%). 1 KRAS mutation and 1 TP53 mutation were detected in 2 ALK –TKI resistant pts, respectively. 28 pts (47%) reported as tissue negative had a positive liquid biopsy, including 4 MET 14 exon skipping mutations, 2 EGFR 19 DEL, 4 EGFR L858R and 1 EGFR L861Q, and 2 EGFR T790M mutations. The mutation abundance is all below 1%, except 2 EGFR 19 DEL and 4 L858R. Ten pts received TKIs; 2 got parcial responses, 5 stable diseases and 3 progressive disease. **Conclusion:** ctDNA can be used as a 'liquid biopsy' for molecular profiling of NSCLC pts, and NGS, as a highly sensitive method to detect mutations with low mutation abundance, can provide more chances to pts to receive precise treatment.

Keywords: next generation sequencing, non-small cell lung cancer, liquid biopsy

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-01 PROGNOSTIC SIGNIFICANCE OF PREOPERATIVE CONSOLIDATION TO MAXIMUM TUMOR DIAMETER RATIO AND SUV-MAX IN PATHOLOGICAL STAGE I LUNG ADENOCARCINOMA

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Background: Findings on computed tomography like tumor size, amount of consolidation and ground glass opacity, size of the solid component, maximum standardized uptake value by 18F-fluorodeoxyglucose positron emission tomography/CT and the ratio of the size of solid attenuation to the maximum tumor dimension (consolidation/ tumor [C/T] ratio) are predictive for pathologic subtypes and prognosis after resection. There are many number of study about clinical early stage lung cancer in terms of C/T ratio. We aimed to investigate prognostic value of C/T ratio and SUVmax among patients with pathological stage I lung adenocarcinoma **Method:** 258 patients were reviewed by using institution's records who had undergone surgery for early stage lung adenocarcinoma. Only patients with pathological stage I (T1a, T1b and T2a without lymph node metastasis) were included. Synchronous tumor, oligometastatic disease and history of other organ malignancy was exclusion criteria. Seventh TNM edition was used. Totally 168 patients' demographic data, surgery types, clinical and pathological stage, pre-operative SUVmax and C/T ratio was recorded. Differences between patients with recurrence after surgery and without recurrence was demonstrated. Survival rates were analysed by divided into 3 groups according to C/T ratio (0.25-0.5, 0.5-0.75, 0.75-1.0) and cut-off value 50% of C/T ratio. **Result:** Two groups (C/T<0.5 and C/T=0.5-1) did not differ according to comparable factors like visceral pleural invasion, subtype of adenocarcinoma, median SUVmax. Median follow up time was 35 months. 54 patients were died of whom 8 (68%) patients were in C/T ratio<0.5 and 46 patients (67.8%) were in C/T=0.5-1 group. OS was 44.9±5.07 and PFS was 50.8±5.42 in C/T<0.5 group. OS was 69.7±3.34 and PFS was 77.2±3.23 in C/T=0.5-1 group (p>0.05). Three-year survival rate was 50% for C/T <0.5 and 72% for C/T=0.5-1 group (p>0.05). Mean SUVmax is 8.05±6.04 for C/T<0.5 and 10.07±6.85 for C/T≥50% (p= 0.43). Existence of visceral pleura invasion was higher in patients with C/T≥50% (69 patients vs 6 patients, p=0.05). In univariate analyses age, gender and SUVmax value and in multivariate analyses only surgery type and SUV max value were predictors for OS (Surgery type: HR:1.33 (1.04-1.70), p=0.02 and SUVmax: HR:1.04(1.00-1.08), p=0.04).For PFS, only surgery type had significance both unıvariate and multivariate analyses (Univariate: HR: 1.47 (1.15-1.89), p=0.002 and multivariate: HR: 1.67 (1.25-2.23), p=<0.001). **Conclusion:** In pathological stage 1 lung adenocarcinomas, SUVmax and surgery type are important predictors for OS. For PFS only surgery type has significance. Even visceral pleura invasion rates are higher in C/T≥0.5 group, SUVmax is superior to the C/T ratio for predicting prognosis particularly for solid type lung cancer.

Keywords: Consolidation/tumor ratio, SUVmax, Prognosis

P2.16-02 PREDICTING PATHOLOGICAL NONINVASIVENESS IN T1 NON-SMALL CELL LUNG CANCER ON CHEST CT SCAN USING DEEP LEARNING ALGORITHM

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Background: Because of the risk of recurrence, lobectomy is indicated even for small lung cancers. If we could accurately predict and classify noninvasive small lung cancers on CT images using deep learning algorithm prior to surgery, a more refined selection of candidates who would benefit from limited resection without increasing the risk of recurrence would be possible. The purpose of this study was to evaluate the ability of an artificial intelligence (deep learning algorithm) to predict pathological noninvasiveness of T1 non-small cell lung cancer (NSCLC) using computed tomography (CT) images. **Method:** 468 preoperative CT images of NSCLC smaller than 3 cm, resected at our institution from 2008 to 2015 were used to train and validate the deep learning algorithm. Noninvasiveness was defined as the absence of nodal involvement, vascular invasion, and lymphatic invasion, and NSCLCs were classified as either noninvasive or invasive according to the pathological reports. A deep 3D convolutional neural network (CNN) was trained using 5-fold cross-validation method. To normalize input data, we rescaled CT image to let one voxel size be represented as (1mm,1mm,1mm). Input cube size was (32mm, 32mm,32mm). Horizontal flip and vertical flip augmentation were applied, and max-pooling and dropout layer were used to avoid overfitting. Receiver operating characteristic (ROC) curves and areas under the curve (AUCs), accuracy, and sensitivity/specificity were used to assess the performance of 3D CNN. We also added tumor size as an external feature to the 3D CNN model and evaluated the performance of the combined model using Xgboost classifier. **Result:** 157 out of 486 samples (33.5%) were invasive. A subsample group composed of 10% of the data (32 noninvasive and 16 invasive samples) was retained for the validation set. The 3D CNN showed an AUC of 0.826, 77.08% accuracy, 68.7% sensitivity, and 81.2 % specificity. Adding tumor size to the 3D CNN model showed an AUC of 0.855, 81.25% accuracy, 87.5% sensitivity, and 78.1% specificity. **Conclusion:** Artificial intelligence can accurately predict pathological noninvasiveness in T1 size NSCLC on CT images.

Keywords: Artificial Intelligence, Deep learning, NSCLC

P2.16-03 CHECKMATE 816: A PHASE 3 TRIAL OF NEOADJUVANT NIVOLUMAB PLUS IPILIMUMAB OR CHEMOTHERAPY VS CHEMOTHERAPY IN EARLY-STAGE NSCLC

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Background: Approximately 20–25% of patients with NSCLC are diagnosed with early or localized disease, which has a relapse rate of 30–80% with surgery. Although neoadjuvant chemotherapy can reduce the risk of relapse, it only provides a pathological complete response (pCR; no viable tumor cells) rate of 4%. The neoadjuvant setting presents abundant tumor-associated neoantigens derived from the primary tumor that may allow immunotherapy to prime a long-lasting immune response. Clinical trial results support the use of immuno-oncology agents as neoadjuvant treatment for early-stage NSCLC. In a pilot study in patients with untreated, surgically resectable early-stage (stage I–IIIA) NSCLC, nivolumab (a fully human PD-1 immune checkpoint inhibitor antibody) administered as neoadjuvant treatment (3 mg/kg for 2 cycles during the 4 weeks prior to surgery) induced a pCR in 10% of patients and a major pathological response (MPR; ≤10% residual viable tumor cells in resected primary tumor) in 45% of patients, did not delay surgery, and was associated with an acceptable safety profile. Combining immuno-oncology agents with distinct mechanisms of action, such as PD-1 and CTLA-4 inhibitors, offers the possibility of a synergistic response and may improve antitumor activity compared with either agent alone. The combination of an immuno-oncology agent and chemotherapy may also offer synergistic activity, given that chemotherapy results in tumor cell death and subsequent antigen release that can activate an immune response. Promising results have been noted with nivolumab plus ipilimumab (a CTLA-4 immune checkpoint inhibitor antibody) and nivolumab plus chemotherapy in patients with treatment-naïve stage IIIB/IV NSCLC in the multicohort phase 1 CheckMate 012 study. CheckMate 816 (NCT02998528) is a phase 3 study evaluating nivolumab plus ipilimumab, nivolumab plus platinum-doublet chemotherapy, and platinum-doublet chemotherapy as neoadjuvant treatment for early-stage NSCLC. **Method:** Approximately 642 patients aged ≥18 years with early-stage (stages IB–IIIA) resectable NSCLC, ECOG performance status 0–1, pulmonary function capable of tolerating lung resection, and available lung tumor tissue will be enrolled in North America, South America, Europe, Asia, and Africa. Patients are ineligible if they have active autoimmune disease or had received prior treatment with immune checkpoint inhibitors. Patients will be randomized (1:1:1) to receive neoadjuvant nivolumab plus ipilimumab, nivolumab plus platinum-doublet chemotherapy, or platinum-doublet chemotherapy. Primary endpoints are event-free survival and pCR. Key secondary endpoints are overall survival and MPR (<10% residual tumor in lung and lymph nodes). The start date was January 2017. The estimated primary completion date is May 2023. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: neoadjuvant, Nivolumab, NSCLC

P2.16-04 PROGNOSTIC VALUE OF LYMPHOVASCULAR INVASION AND ITS EFFECT ON PATTERNS OF RECURRENCE IN T1-3N0 NON-SMALL CELL LUNG CANCER

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Background: The purpose of this study is to clarify the prognostic value of lymphovascular invasion (LVI) in patients with surgically resected T1-3N0 non-small cell lung cancer (NSCLC) according to the eighth edition of the TNM Classification of the American Joint Committee on Cancer (AJCC). **Method:** A total of 442 NSCLC patients who received curative surgery and were confirmed with pathologic T1-3N0 between March 2000 and August 2015 were reviewed. The pathological stages were re-evaluated according to the eighth edition of the TNM Classification of the AJCC. **Result:** The 5-year recurrence-free survival (RFS) rate for total cohort was 69.7%, and the 5-year overall survival (OS) rate was 78.0%. LVI was present in 89 patients (19.9%). The presence of LVI decreased the 5-year RFS rate significantly (47.5% vs. 72.3%, $p < 0.001$) and the 5-year OS rate (62.5% vs. 81.1%, $p < 0.001$). The differences between LVI group and non-LVI group were more remarkable in T2a-bN0 staged patients compared with T1a-c staged patients (T1a-c patients: 63.6% vs. 78.0%, $p = 0.004$; T2a-b patients: 31.7% vs. 64.9%, $p = 0.027$, respectively). Multivariate analysis revealed that the presence of LVI was a significant predictor for RFS ($p < 0.001$) but an insignificant factor for OS. In T2a-bN0 staged patients, the 5-year OS rate was significantly lower in patients with LVI than in patients without LVI (50.0% vs. 74.4%, $p = 0.045$), whereas T1a-c staged patients did not show a significant difference in 5-year OS according to the presence of LVI ($p = 0.196$). **Conclusion:** LVI is a significant associated factor for RFS in patients with stage T1-3N0 NSCLC. Prognostic impact of LVI is more remarkable in patients with more than T2N0 stage compared to patients with the T1N0 disease.

Keywords: non small cell lung cancer, lymphovascular invasion, patterns of recurrence

P2.16-05 HYPERMETHYLATION OF SOX1, RASSF1A, HOXA9, CDH13 AND DAPK GENES PLAYS A ROLE IN NSCLC PATHOGENESIS

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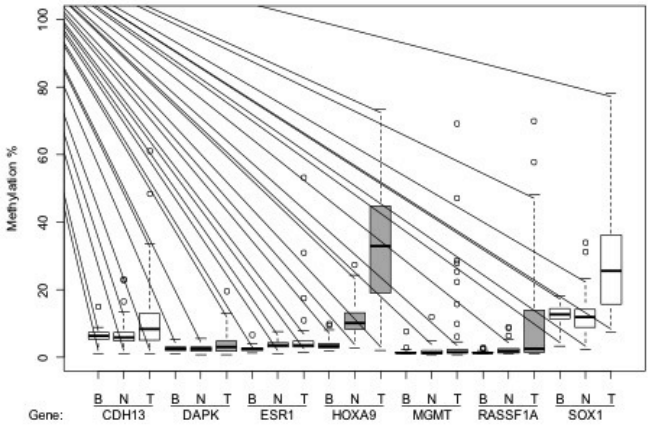
Background: A number of genes have been reported as aberrantly methylated in lung tumors. Here, we investigate the relationship between gene methylation in lung tumors relative to matching normal lung tissue,

and whether DNA methylation changes can be detected in paired blood samples. **Method:** Primary tumor samples (n=65), corresponding nonmalignant lung tissues (n=65) and maching blood samples (n=51) were obtained from NSCLC patients undergoing curative resectional surgery. Using bisulfite pyrosequencing, CpG methylation was quantified at seven genes (RASSF1A, CDH13, MGMT, ESR1, HOXA9, SOX1 and DAPK) in lung tumor, matching pathologically normal lung tissue, and circulating blood samples. We wanted to determine whether these methylation changes are specific to lung tumors, and test whether these changes are detectable in patients' blood samples. We also analyzed possible associations between DNA methylation and clinicopathologic features. **Result:** We observed that genes SOX1, RASSF1A, HOXA9, CDH13 and DAPK were significantly hypermethylated in lung tumors compared to match normal tissue. However, these changes could not be detected in patients' blood samples, indicating a low feasibility of detecting lung cancer by analyzing these genes in a blood-based test. We confirmed that hypermethylation of SOX1, RASSF1A, HOXA9, CDH13 and DAPK play a role in NSCLC pathogenesis, but also showed that these genes are not suitable markers for early detection of NSCLC. Lastly, we found that histology and gender were associated with methylation at the CDH13 gene, while stage was associated with methylation at MGMT.



Conclusion: Our results show higher methylation of SOX1, RASSF1A, HOXA9, CDH13 and DAPK genes in lung tumors compared to matching normal lung tissue. The lack of reflection of these methylation changes in blood samples from patients with NSCLC indicates their poor suitability for a screening test.

Keywords: Hypermethylation, NSCLC, carcinogenesis, genes

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-06 DEVELOPMENT AND VALIDATION OF A GENE EXPRESSION-BASED NOMOGRAM TO PREDICT RELAPSE IN STAGE I NSCLC: A RETROSPECTIVE, MULTI-COHORT STUDY

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Background: Increasing patients were diagnosed with stage I non-small cell lung cancer (NSCLC), and in 30% of diagnosed patients, recurrence will develop within 5 years. Optimal postoperative adjuvant therapy is still ambiguous for stage I NSCLC. Here, we aimed to develop and validate a feasible tool for recurrent risk assessment of stage I NSCLC. **Method:** This retrospective study incorporated the gene expression profiles from 14 public NSCLC cohorts, including 13 microarray data sets and 1 RNA-Seq data set for The Cancer Genome Atlas (TCGA) lung adenocarcinoma cohort. In discovery phase, multiple eligible microarray data sets were used to select statistically significant genes thought to be predictive by two algorithms, Least Absolute Shrinkage and Selector Operation and Support Vector Machine-Recursive Feature Elimination. In the training phase, candidate genes were used to generate a recurrence related signature in TCGA cohort by penalized Cox regression. Recurrence related signature and other clinical variables were selected to develop a nomogram by back stepwise variable selection. In validation phase, the performance of nomogram was further tested via two independent cohorts. **Result:** In this retrospective study, 14 eligible datasets and 7 published signatures were included. In discovery phase, 42 significant genes were highlighted as candidate predictors by two algorithms. A 13-gene based signature related to recurrence were generated by penalized cox regression and categorized training cohort into high-risk and low risk subgroups with significantly different recurrence free survival (HR = 8.873, 95% CI:4.228-18.480 *P*<0.001). The performance of signature was tested in two external cohorts (HR=3.556, 95%CI:1.587-7.996, *P*=0.001; HR=2.586, 95%CI:1.226-5.286, *P*=0.007). Furthermore, a nomogram integrating recurrence related signature, age, and histology was developed to predict the recurrence-free survival in the training cohort, and it performed well in the two external validation cohorts (concordance index: 0.737, 95%CI:0.732-0.742, *P*<0.001; 0.666, 95%CI: 0.650-0.682, *P*<0.001; 0.651, 95%CI:0.637-0.665, *P*<0.001 respectively). **Conclusion:** The proposed nomogram is a promising tool for estimating recurrence free survival in stage I NSCLC, which might have tremendous value in guiding adjuvant therapy. Prospective studies are needed to test the clinical utility of the nomogram in individualized management of stage I NSCLC.

Keywords: Stage I NSCLC, Nomogram, recurrence

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-07 IMPACT OF DE NOVO T790M ON OUTCOME FOR RESECTED NSCLC FROM EGFR MUTANT COHORT OF JAPAN MOLECULAR EPIDEMIOLOGY (JME) STUDY

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Background: We conducted a prospective multicenter molecular epidemiology study (JME study; Kawaguchi T, J Clin Oncol 2016), collecting 876 surgically resected non-small-cell lung cancer (NSCLC) including 373 EGFR mutated cases and examining 72-gene somatic mutations status using the next generation sequencing. We also previously reported pretreatment T790M mutation was detected in 298 (79.9%) of these EGFR mutated NSCLC patients from JME study cohort utilizing the ultra-sensitive droplet digital PCR (Watanabe M, Clin Cancer Res 2015). Here, we report follow-up data and clinical outcomes in the EGFR mutant cohort of JME study and the impact of pretreatment T790M on recurrence free survival (RFS) and overall survival (OS). **Method:** All the patients were enrolled from July 2012 to December 2013, and clinical and prognostic data were obtained until the end of November 2017. Cox proportional hazards model were applied to assess the impact of pretreatment T790M on RFS and OS, considering age, gender, smoking history, histology, stage, history of adjuvant chemotherapy, EGFR mutation status, TP53 and number of coexisting mutations. **Result:** Median follow up time was 48.6 months, and 373 patients were analyzed: 182 were ≥70 years; 97 were men; 93 had smoking history; 361 were adenocarcinoma; 290/43/40 were stage I/II/III-IV; 120 received the adjuvant chemotherapy, 19 had uncommon EGFR mutation, 92/11 had one/two somatic mutations and 69 had TP53 mutation. In RFS, univariate analysis showed event risk tended to be higher in pretreatment T790M positive group than negative group (HR=1.76, 95%CI: 0.98-3.15, p=0.06), but multivariate analysis also couldn't show significance (HR=1.62, 95%CI: 0.89-2.94, p=0.12). Multivariate analysis showed age (≥70 vs. <70, HR=2.07, 95%CI: 1.34-3.19), gender (male vs. female, HR=1.88, 95%CI: 1.03-3.44), pathological stage (II vs. I, HR=4.10, 95%CI: 2.32-7.21; ≥III vs. I, HR=10.49, 95%CI: 6.07-18.15) and the number of coexisting mutations (2 vs. 0, HR=2.77, 95%CI: 1.07-7.17) were significantly associated with RFS. In OS, although pathological stage (II vs. I, HR=3.61, 95%CI: 1.45-8.96; ≥III vs. I, HR=6.64, 95%CI: 2.92-15.12) was significant prognostic factor, pretreatment T790M positive was not associated with event (HR=1.32, 95%CI: 0.53-3.27, p=0.55). **Conclusion:** Our study showed pretreatment EGFR-T790M was not a prognostic factor for RFS and OS in surgically resected NSCLC. Cases in younger age, female and less number of coexisting mutations were associated with longer RFS, while earlier stage was significantly associated with both improved RFS and OS in resected NSCLC.

Keywords: non-small cell lung cancer, digital PCR, pretreatment T790M

P2.16-08 INFLUENCE OF TUMOUR LOCATION AND HISTOLOGICAL SUB-TYPE OF NON-SMALL CELL LUNG CANCER ON PATIENT SURVIVAL

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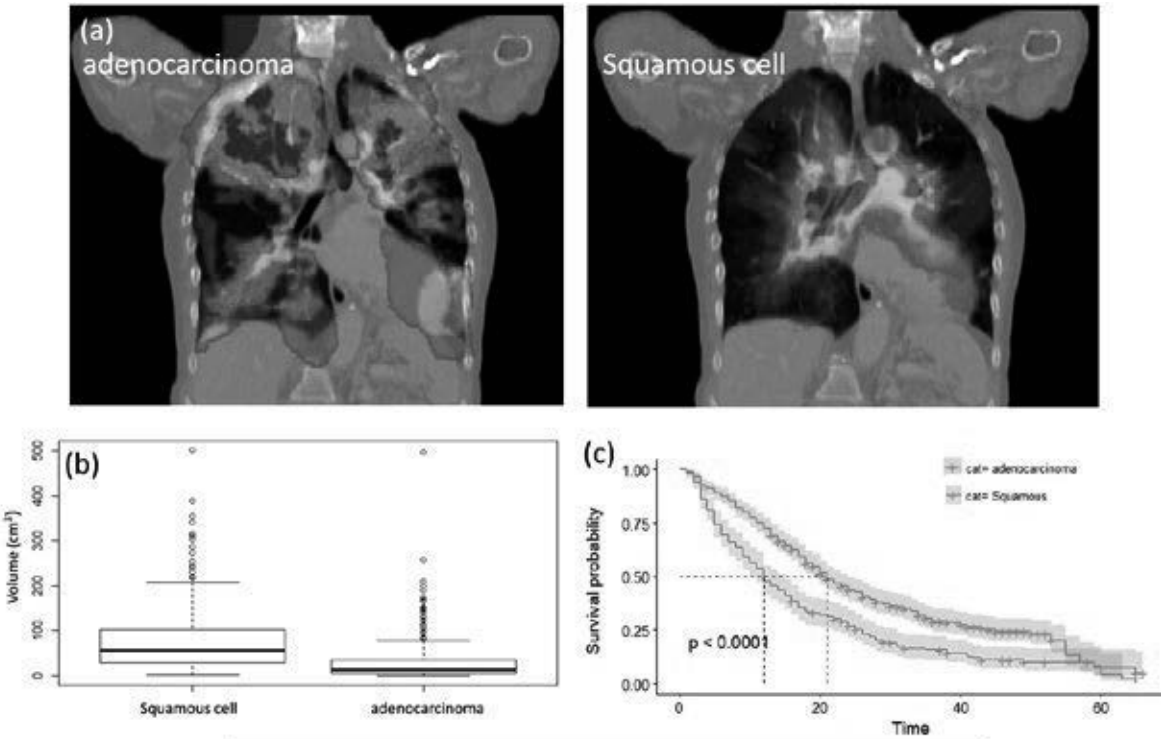
Background: In non-small cell lung cancer (NSCLC), adenocarcinomas tend to arise peripherally and squamous cell carcinomas (SCC) centrally. Tumour location is known to impact patient survival: in previous work, we showed that right-sided tumours show worse survival, n=1101; HR=1.25, p<0.01. In this study we extended the laterality analysis by including histological sub-type and explore its correlation with overall survival. **Method:** 529 unselected NSCLC patients (treated with 55Gy/20fr), with confirmed adenocarcinoma or SCC, were included. All patients were spatially normalised using non-rigid registration to a reference anatomy, allowing tumour probability maps to be created from the outlined tumours. A Kolmogorov-Smirnov test assessed differences in distributions. Kaplan-Meier curves, grouped by histological sub-type, were plotted. Tumour volumes were extracted for all patients and included in a multi-variate analysis including N-stage, performance status, gender and median dose to left and right lungs, encoding laterality. **Result:** 326 adenocarcinomas and 203 SCC were found. Tumour probability maps show a clear separation in tumour locations between the sub-types (Fig.1a, p<0.001) and a general location of SCC tumours along the major airways. Tumour volumes were significantly different (SCC larger, median 56cm^3 versus 14cm^3, p<0.001, Fig.1b). Histology also influences nodal involvement, 20% adenocarcinomas versus 80% SCC are N+. Location and volume impacts on normal tissue doses, mean lung and heart doses: 8.8Gy and 4.9Gy for adenocarcinomas, 15.6Gy and 18.8Gy for SCC. SCC patients showed worse survival (median 12 versus 21 months, Fig.1c). Multivariate analysis shows right lung mean doses significantly correlate with survival for adenocarcinomas, p=0.04, but not for SCC, p=0.2, indicating the spatial location of the tumour may have an interaction with our previously described laterality effect.



	Multi-variable adenocarcinoma			Multi-variable Squamous cell	
	HR (95% CI)		p	HR (95% CI)	P
Tumour volume (continuous)	1.01 (1.01 – 1.01)		<0.001	1.01 (1.00 – 1.01)	<0.001
Left lung mean dose (continuous)	1.00 (0.99 – 1.01)		0.4	1.00 (0.97 – 1.03)	0.87
Right lung mean dose (continuous)	1.03 (1.02-1.06)		0.03	1.02 (0.99 – 1.05)	0.21
Gender (Male vs. female)	1.77 (1.3 – 2.4)		<0.001	0.80 (0.56 – 1.15)	0.22
N-stage					
(N0 reference)	**N1**	0.95 (0.56 – 1.57)	0.83	0.62 (0.31 – 1.24)	0.18
	N2	0.99 (0.57 – 1.70)	0.97	0.82 (0.48 – 1.39)	0.47
	N3	3.10 (0.98 – 10.1)	0.05	1.50 (0.83 – 2.72)	0.18
Performance status					
(PS 0 reference)	**1**	0.85 (0.53 – 1.37)	0.50	1.90 (1.11 – 3.26)	0.02
	2	1.09 (0.69 – 1.73)	0.72	2.25 (1.25 – 4.05)	0.01
	3	1.50 (0.72 – 3.12)	0.27	2.11 (0.88 – 5.06)	0.09

Conclusion: Differences in the spatial locations and volumes of histological sub-types influence normal tissue doses including the effect of tumour laterality on survival. Further work will explore possible mechanisms, including ventilation/perfusion variation in the lungs.

Keywords: Radiotherapy, histology, normal tissue dose

P2.16-09 PATTERNS OF BRAIN METASTASES IN STAGE I-III NON-SMALL CELL LUNG CANCER: AN NCDB ANALYSIS

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Background: We have submitted single institution data suggesting nodal size is most associated with the development of brain metastases at diagnosis of non-small cell lung cancer, and seek to investigate the applicability of NCCN recommendations for brain magnetic resonance imaging (MRI) for non-small cell lung cancer (NSCLC) to evaluate rates brain metastases in patients with Stage I-III non-small cell lung cancer (NSCLC) in a population based cohort. **Method:** Results of patients diagnosed with NSCLC in the NCDB were evaluated between the years 2010 and 2013. Patients were included if they were AJCC 7th edition Stage I-III, or Stage IV patients on the basis of brain metastases alone. Exclusion criteria included those with bone, lung, or liver metastases at diagnosis. Due to heterogeneity in reporting in the NCDB, characterization of Stage IB, IIA, and IIB is difficult to discern. To account for this, we present rates of brain metastases for patients with T2N0, T1/2N1, and T3N0 disease within this cohort. Statistical evaluation included incidence of brain metastases per stage as well as logistic regression of baseline factors predictive of brain metastases (SPSS V21). **Result:** A total of 256,340 patients were included in the analysis. Overall rates of brain metastases were 6.4% (16,333/256,340). Brain metastases were identified in 1.6% (1457/89,868) of Stage IA patients, 5.5% (4038/73,233) of patients with Stage IB-II disease (4.6% (2025/44,026), 8.2% (1162/14,118), and 5.6% (851/15,089) for stages T2N0, T1/2 N1, and T3N0, respectively), 11.0% (6945/63,127) of Stage IIIA patients, and 12.9% (3893/30,112) of Stage IIIB patients. On multivariate analysis, younger age was associated with increased risk of brain metastases (p<0.01). When compared to Stage IIIB, patients with T1/2 N1 disease and Stage IIIA disease were most likely to have brain metastases (p<0.01 for both and HR 0.823 and 0.959, respectively). Poorly differentiated tumors were most associated with brain metastases (p<0.01 for both; HR 0.652 vs 0.187). Additionally, women were more likely to have brain metastases than men (p<0.01, HR 1.065). Adenocarcinoma histology was most likely to have brain metastases in our population (p<0.01, HR 1.162). **Conclusion:** This series shows that young age, adenocarcinoma histology, female gender, higher clinical stage disease, and younger age were associated with the development of brain metastases. Future analysis will be focused on developing a RPA classification of this data to further prognosticate most important features associated with the development of brain metastases in newly diagnosed NSCLC.

Keywords: Brain metastases, lung, cancer

P2.16-10 PROGNOSTIC IMPACT OF POSTOPERATIVE C-REACTIVE PROTEIN FOR NON-SMALL CELL LUNG CANCER FOLLOWING LOBECTOMY

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Background: C-reactive protein (CRP) is suggested to be associated with cancer progression; however, the prognostic impact of elevated CRP on postoperative course are not highlighted. We investigated whether the peak level of postoperative CRP could serve as a prognostic marker in patients with non-small cell lung cancer who underwent lobectomy. **Method:** We retrospectively reviewed 198 consecutive patients with non-small cell lung cancer who underwent lobectomy at a single institution between April 2007 and March 2015. Patients with infection before surgery, missing CRP data, induction therapy, postoperative infectious complications, and non-curative resection were excluded. CRP was measured on postoperative days 1, 3, and 5. Patients were equally divided into two groups according to the median of CRP on postoperative day 3 (CRP_3); the high and low CRP_3 groups (n=99, respectively).Survival analysis for OS and recurrence-free survival (RFS) was conducted with the Kaplan-Meier method, and the estimates were compared with the log-rank test. A Cox proportional hazards model was used for multivariate analysis to evaluate prognostic factor for OS.Baseline variables with p<0.10 in the univariate analysis were included in the multivariate analysis. **Result:** In this study, 148 patients (74.7%) were alive and 50 had deceased (25.3%). The median length of follow-up for all cases was 61.3 months (IQR=42.6–85.8). Pathological staging were significantly higher in the high CRP_3 group (p=0.003). There were no significant differences in 30-day mortality, 90-day mortality, and postoperative complications between two groups. Five-year overall survival (OS) was significantly higher in the high CRP_3 group than the low CRP_3 (75.3% vs. 86.5%; P=0.016), as was the 5-year recurrence-free survival (62.7% vs. 73.0%; P=0.016). Among the pathological stage I patients, the 5-year OS of the high CRP_3 group was higher than that of low CRP_3 group (80.5% [95%CI=66.8–88.2] *vs*. 90.3% [95%CI=78.0–95.9]; p=0.023). This was also same for the pathological stage II and III patients (61.2% [95%CI=38.8–77.5] *vs*. 81.0% [95% CI=63.9–90.6]; p=0.045). A Cox hazard proportional model for OS adjusted for age, sex, smoking history, pathological staging, and Glasgow prognostic score revealed high CRP_3 was associated with a favorable prognosis (hazard ratio, 0.36; 95%CI=0.20–0.65; P<0.001). **Conclusion:** Our findings indicate that high CRP_3 may be a favorable prognostic predictor in patients with non-small cell lung cancer following lobectomy. Evaluating the change in postoperative CRP levels should be considered as a prognostic marker of OS.

Keywords: Prognosis, non-small cell lung cancer, C-reactive protein

P2.16-11 PROGNOSTIC ROLE OF COMBINED PULMONARY FIBROSIS AND EMPHYSEMA (CPFE) IN PATIENTS WITH CLINICAL STAGE I LUNG CANCER.

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Background: The prognostic role of CPFE in lung cancer is not fully understood. The purpose of this study is to evaluate the prognostic role of combined pulmonary fibrosis and emphysema (CPFE) in patients with clinical stage I primary lung cancer with interstitial pneumonia (IP). **Method:** CPFE was defined as the presence of both emphysema and IP on high-resolution computed tomography (HRCT). Of 836 consecutive patients with clinical stage I primary lung cancer who underwent complete resection between April 2007 and March 2016, 65 patients with CPFE were identified. The log-rank tests and Cox proportional hazard models were used to test for survival differences. **Result:** There was a significant difference in overall survival (OS) between patients with CPFE (n = 65: 5 y-OS rates, 62.6%) and those without CPFE (n = 771: 5 y-OS rates, 86.5%, P <0.001). However, in patients with interstitial pneumonia on HRCT (n = 115), there was no significant difference in OS between patients with CPFE (n = 65: 5 y-OS rates, 62.5%) and those without CPFE (n = 50: 5 y-OS rates, 59.4%, P = 0.84). In patients with interstitial pneumonia, multivariable backward stepwise Cox analysis revealed that histology, %DLCO, radiologic IP pattern, and surgical procedure were independent prognostic factors for OS, but the presence of CPFE was not. **Conclusion:** CPFE was not an independent prognostic factor for OS in patients with clinical stage I lung cancer with IP. The presence of interstitial pneumonia pattern may explain poor survival in patients with CPFE.

Keywords: Combined pulmonary fibrosis and emphysema, lung cancer, Interstitial pneumonia

P2.16-12 EXPANDED DATA CONFIRM MOLECULAR TESTING IDENTIFIES LUNG ADENOCARCINOMA PATIENTS, INCLUDING STAGE IA, WHO BENEFIT FROM ADJUVANT CHEMOTHERAPY

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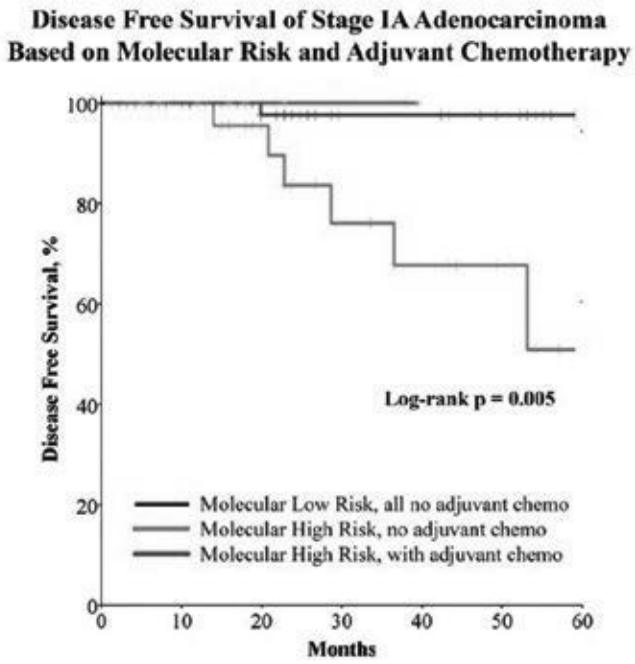
Background: A clinically certified, 14-gene quantitative PCR expression assay has been validated to assess mortality risk in early-stage lung adenocarcinoma. Molecular stratification may identify those stage I-IIA patients who are in most need of potentially life-saving intervention after resection, including stage IA patients for whom chemotherapy is never recommended. **Method:** Prospective molecular risk-stratification by the 14-gene assay was performed on 200 consecutive patients with stage I-IIA lung adenocarcinoma after complete surgical resection at a single institution. Adjuvant chemotherapy was recommended for molecular high-risk patients. Kaplan-Meier analysis and log-rank tests were used to evaluate differences in disease free survival. **Result:** Average age of

patients was 68 +/- 10 years, 62% were female and mean follow up was 24 months. The recurrence rate among all patients was 9%. However, 87 patients (44%) were found to be molecular high-risk and had a recurrence rate of 17%, whereas the 113 patients (56%) who were molecular low-risk had a recurrence rate of only 3% (p<0.0001). Even among the stage IA patients, 41 (33%) were found to be molecular high-risk. The recurrence rate in molecular low-risk stage IA patients was only 1%, compared to 15% in stage IA patients who were identified as molecular high-risk (log-rank p=0.003). Of the 41 stage IA patients found to be molecular high-risk, 24% agreed to undergo adjuvant chemotherapy; there have been no recurrences among these treated high-risk patients. In contrast, the KM estimate of 5-year disease free survival among stage IA high-risk patients who did not receive adjuvant chemotherapy was 51% (log-rank p=0.005).



Conclusion: This prospective, single-institution study further demonstrates the clinical utility of the 14-gene molecular prognostic assay in the management of early stage lung adenocarcinoma. Adjuvant chemotherapy guided by molecular prognosis in the earliest stages of disease, including stage IA, may prevent a significant number of recurrences and deaths.

Keywords: molecular testing, Early Stage Lung Adenocarcinoma, adjuvant chemotherapy

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-13 A PROPOSAL OF CLASSIFICATION FOR SUBSOLID NODULE: PROGNOSTIC IMPACT OF T DESCRIPTOR

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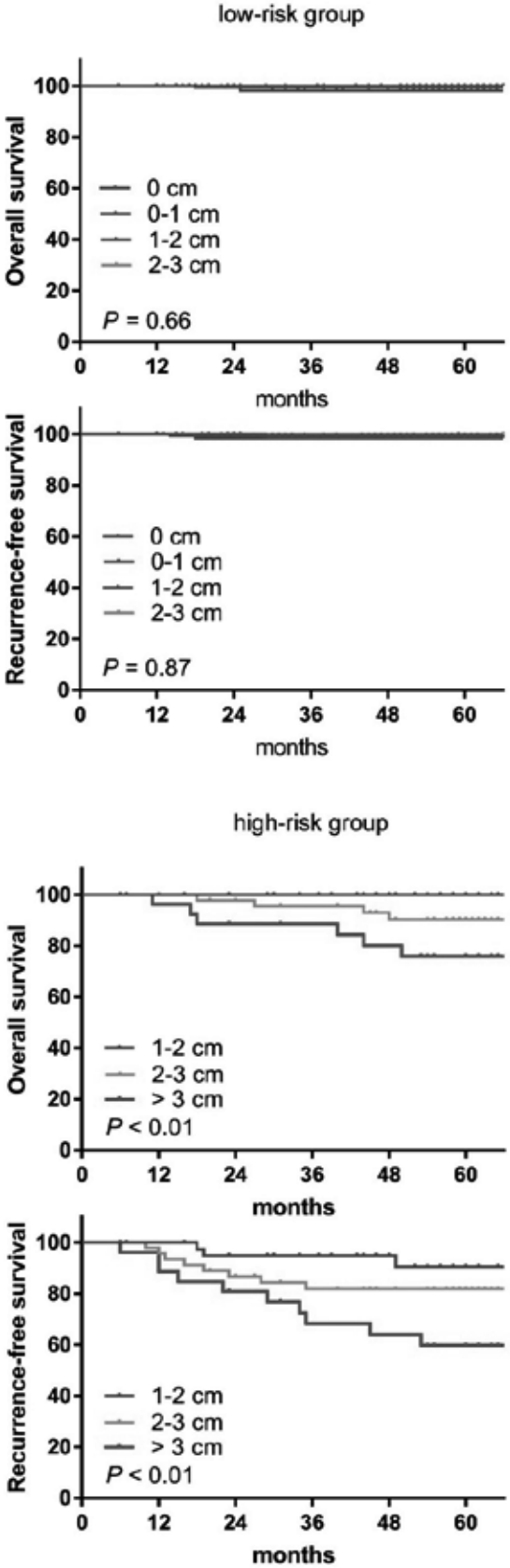
Background: Prognosis of lung cancer presenting as subsolid nodule is satisfying, and prognostic impact of tumor size for subsolid nodules is not so clear as pure-solid nodule. Our study aimed to find whether T staging is suitable for subsolid nodule. **Method:** We retrospectively reviewed 431 cTis-T3N0M0 subsolid nodules in our hospital. Maximum tumor size, solid component size, consolidation/tumor ratio (CTR) were measured. **Result:** Five year recurrence-free survival (RFS) and overall survival (OS) were 94.2% and 97.0%. Nodules with maximum tumor size < 2 cm & CTR ≤ 0.5, maximum tumor size < 2 cm & CTR > 0.5 and maximum tumor size > 2 cm & CTR ≤ 0.5 were defined as low-risk group. Nodules with maximum tumor size > 2 and CTR > 0.5 were defined as high-risk group. Five year RFS and OS were both 99.0% for low-risk group, 81.0% and 91.4% for high-risk group. Maximum tumor size, solid component size and CTR were not the prognosticator for low-risk nodules but were significant for high-risk nodules.



Conclusion: We suggest using T descriptor only for clinical high-risk subsolid nodule. Prognosis of low-risk nodules is excellent, no clear relationship with tumor size or CTR.

Keywords: ground-glass opacity, Tumor size, Prognosis

P2.16-14 RESULTS OF STEREOTACTIC RADIATION THERAPY (SABR) IN EARLY STAGE LUNG CANCER: TURKISH RADIATION ONCOLOGY GROUP (TROG) STUDY

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Background: To determine factors affecting treatment outcomes for SABR in inoperable early stage lung cancer (ESLC) patients treated by TROG member centers. **Method:** A total of 386 ESLC patients treated with SABR between 2009-2017 were retrospectively analyzed. Factors related to disease, treatment and patients' characteristics were recorded. Primary endpoints were overall survival (OS), progression free survival (PFS), local control (LC), regional control (RC) and radiation-related toxicities. **Result:** Median follow-up was 21 months. Median SABR dose was 54Gy (30-70Gy), corresponding to a biological equivalent dose (BED) of 112Gy (48-180Gy) administered in median 5 fractions. Patient and treatment characteristics are in Table 1. Response evaluation was made in median 3 months after SABR and complete response; partial response, stable disease and progression rates were 48%, 36%, 5.7% and 0.5%, respectively. One and 3 years LC and RC rates were 97%, 91% and 93%, 86%, respectively. On multivariate analyzes BED10<90 Gy (HR 3.6;1.3-9.9), SCC histology (HR 2.2;1.2-4) and less than complete response (HR 3.5; 1.6-7.5) were predictive of worse LC. Tumor size >3cm was the only predictor of low RC (HR 2.1; 1.1-4.2). One and 3 years PFS and OS were 88%, 72% and 90%, 65%, respectively. T2 tumor (HR 2.5; 1.5-3.6), BED10<90Gy (HR 2.1; 1.1-4) and SCC (HR 1.4; 1.0-1.8) had lower PFS. OS was negatively affected by tumor size >28mm (HR1.6; 1.0-2.5). No severe acute side effects were observed. Overall 18 patients experienced =grade 3 pneumonitis, 11 chest wall pain and 1 rib fracture.

Table 1: Patient Characteristics

Age	Median 72 (43-93)
Female/male ratio:	21/79
Tumor Diameter	Median 30mm (2 – 78)
Histopathology (280/386 patients)	Adenocarcinoma 113 (40.3%) Squamouscell carcinoma 97 (34.6%) Non-smallcell carcinoma75 (26.8%)
T stage	T1, 215 (55.6%) T2, 166 (43%) T3, 2 (0.5%) T4 , 3 (0.7%) [bilateral tumor]
Central /Peripheral	%30.5/%69.5
SABR dose	Median 54 Gy (30-70 Gy)
Fraction	Median 5 (1-10 fr)
BED_{10}	Median 112 Gy (48-180 Gy)
BED_3	Median 256 Gy (90-460 Gy)
Response evaluation method (median 3. months)	39% PET/CT 38% CT

Conclusion: Results of this retrospective study have shown that SABR is an encouraging technique with satisfactory LC and OS rates and minimal toxicity in patients with inoperable ESLC. Higher dose and intensification of treatment in patient with large tumors, SCC histology and less than complete response may result in better LC, PFS and OS.

Keywords: lung cancer, early stage, SBRT, prognostic factors, toxicity

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-15 TOXICITIES AND SURVIVAL AFTER STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR) FOR CENTRALLY LOCATED LUNG TUMORS

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Background: To evaluate factors associated with local control (LC), overall survival (OS) and toxicities after SABR to centrally located primary non-small cell lung (PL) and oligometastatic (OM) tumors. **Method:** Seventy centrally located tumors (abutting tracheobronchial tree [TBT], <2cm from TBT, or intersecting mediastinum) in 65 patients treated with linear accelerator-based SABR between 2009 and 2016 were retrospectively studied. Impact of patient, tumor, and treatment parameters on LC, OS and toxicity-free survival (TFS) were evaluated by multivariate analyses. **Result:** Forty-eight PL and 22 OM lesions were analyzed, including 20 (28%) re-irradiation (Re-RT) cases. Median total, fractionated, and biological equivalent doses in BED10 and BED3 were 55 (30-60), 9.75 (4-18), 110 (41-151), and 228 (90-378) Gy, respectively. Doses given as Re-RT were lower (median Re-RT BED10 dose 94 vs. 110 Gy, P=0.009). Complete response (CR) was obtained in 43 (61%) lesions. None of the analyzed factors correlated to CR. After a median follow-up of 57 (48-65, 95%CI) months, 10 (14%) lesions had relapsed and 37 (57%) patients had died (2 and 5-year LC and OS rates were 84/70% and 52/28%, respectively). In univariate analysis, 2-year LC was lower for lesions with no CR and for colorectal cancer lesions. Only "no CR" was significant (100 vs. 51%; HR=18.2, CI 2.3-146, P=0.006) in final multivariate analyses. Median OS was significantly lower in patients with grade 3+ toxicity (5 months after grade 3+ toxicity, vs. 39 months in others [HR 4.7, CI 2-11.2,P<0.0001]). OS was marginally lower in patients with primary lung cancer compared to patients with OM tumors (19 vs. 49 months, HR 2.3, CI 1-5.6, P=0.06). Among 17 toxicities, 5 reached grade 5. For patients with grade 3+ toxicities, TFS was lower after Re-RT (2-year TFS 63% vs. 96%, HR 5.1, CI 1.3-20.3, P=0.022) but did not differ significantly for lesions abutting TBT (2-year TFS 69% vs. 93.4%, HR 3.5, CI 0.9-13.9, P=0.08). **Conclusion:** SABR is an effective treatment modality in centrally located lung tumors. SABR to re-irradiated lesions and possibly lesions abutting TBT may have the higher risks for serious toxicities. Further studies are indicated.

Keywords: lung tumors, stereotactic radiotherapy, toxicity

P2.16-16 SABRTOOTH: A FASIBILITY STUDY OF SABR VERSUS SURGERY IN PATIENTS WITH PERIPHERAL STAGE I NSCLC CONSIDERED TO BE AT HIGHER RISK FOR SURGERY.

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Background: Stage I NSCLC is curable by surgery and Stereotactic Ablative Radiotherapy (SABR). Many patients have co-morbidities that place them at higher risk of surgical complications. For such patients it is unknown whether the potential benefits of surgery are outweighed by the risks since published randomised trials comparing surgery with SABR have been underpowered. The SABRTooth study was designed to determine the feasibility of randomising patients between the two treatments and thus performing a larger RCT. **Method:** Four thoracic oncology centres and a referral site participated. Patients with peripheral (>2cm from the main airways) stage T1-T2bN0M0 NSCLC were considered for study entry. Patients at higher risk were identified using several criteria including Thoracoscore and the Nottingham Risk Score and confirmed by multidisciplinary team consensus. Eligible patients were approached by a respiratory physician and research nurse, consented and randomised (1:1) before consulting a surgeon or oncologist. Surgery was preferably by lobectomy with lymph node sampling/resection although sub-lobar resection was permitted. SABR was delivered as per the UK SABR guidelines. An average recruitment rate of 3 patients/month from the 5 centres over a formal monitoring period was set to prove feasibility of a larger RCT. Meetings with the trial sites and patient representatives were held through-out to improve recruitment. Qualitative research was embedded into the study with interviews for patients who declined participation or randomised treatment. **Result:** Between July 2015-January 2017 318 patients were assessed for eligibility of which 106 were initially considered eligible. 84 patients were approached for the study and 24 (29%) were randomised (10 surgery, 14 SABR); a mean recruitment rate of 1.7 per month. The median age was 75 (range 54-88). The main reason for declining the study was patient preference with 29% preferring surgery and 42% SABR. Overall 9/24 (38%) did not receive their randomised treatment. Of 7 patients randomised to surgery, 6 received SABR, 1 radical radiotherapy and of 2 patients randomised to SABR, 1 received radical radiotherapy, 1 was lost to follow-up. **Conclusion:** Despite recruiting at higher rate/centre than previous SABR versus surgery trials, the SABRTooth study failed to meet its recruitment target and the majority of patients randomised to surgery subsequently underwent SABR. Therefore, conducting a large RCT in the UK was shown not to be feasible. However, establishing which patients should have surgery or SABR for early stage NSCLC remains a critical question and alternative study designs are being developed to provide an answer for patients and clinicians.

Keywords: Randomised Controlled trial, SABR, Surgery

P2.16-17 HYPO-FRACTIONATED ACCELERATED RADIOTHERAPY IN CENTRAL EARLY NON-SMALL CELL LUNG CANCER: LEEDS CANCER CENTRE EXPERIENCE.

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Background: Centrally located early stage lung cancers in patients who are unfit for surgery and stereotactic ablative body radiotherapy (SABR) are routinely treated with radical radiotherapy. There are no standard dose regimens but evidence seems to favour acceleration. We present the outcomes of a moderately hypo-fractionated accelerated dose regimen of 50Gy in 15 fractions (BED $_{(a/b=10)}$ corrected for time = 58.85Gy) from a single centre in the UK. **Method:** Electronic case notes and radiotherapy records of lung cancer patients treated between January 2014 to December 2016 were retrospectively reviewed. Adult Comorbidity Evaluation-27 (ACE-27) score was used to evaluate comorbidities. Survival outcomes were estimated using Kaplan-Meier curves and compared using log-rank test. **Result:** Fifty-three patients were treated with 50Gy in 15 fractions with a median age of 74.0 years (IQR: 69.5–79). 4 patients had a poor WHO PS of 3. Thirty-seven (69.8%) were females. A similar number had Grade 2 or 3 ACE-27 score while one had Grade 0. Forty-six patients were stage I, whilst four and three patients were stage II and III respectively. Thirty-seven (70%) patients had a radiological diagnosis. The treatment was well tolerated, 90-day mortality rate after radiotherapy was 3.8% (n=2). Grade 2 pneumonitis was seen in 5 patients while no grade 3 or 4 pneumonitis was observed. At the time of cut-off for analysis, the median follow-up was 20.2 months. The median progression-free survival (PFS) and overall survival (OS) were 18.5 months (95% CI 12.2–24.8) and 28.2 months (95%CI 14.4–42.1) respectively. The estimated 1 and 2 year PFS were 62.3% and 41.3% respectively and OS were 77.4% and 56.6% respectively. Only PS significantly impacted survival on univariate analysis, while PS and ACE-27 both were shown to have significant effect on multivariate analysis. Of the nineteen patients who relapsed, 4 (7.5%) had infield recurrence, 10 had out-of-field lung recurrence and the rest had distant metastases. One patient underwent salvage surgery. 6 patients received further radical therapy with 3 each being treated with conventional and SABR. **Conclusion:** This moderately hypo-fractionated accelerated radiotherapy regimen for central early stage lung cancer seems similar in efficacy but is associated with significantly less toxicity when compared to SABR.

Keywords: 50 Gy in 15 fractions, Hypo-fractionated accelerated radiotherapy, central early non-small cell lung cancer

P2.16-18 STUDY OF INTERSTITIAL LUNG DISEASE AND ACUTE EXACERBATION IN PATIENTS RECEIVING RADIATION THERAPY FOR LUNG CANCER IN JAPAN.

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Background: Radiation therapy (RT) for lung cancer in patients who have interstitial lung disease (ILD) is considered to be a risk for acute exacerbation (AE). The indication for RT in such patients is determined in each facility. The ratio of patients with ILD who have received RT for lung cancer, the incidence of AE in such patients, and the risk factors for AE are unclear. To clarify these, a nationwide survey was carried out by the Lung and Mediastinal Tumor Committee of the Japan Radiation Oncology Study Group (JROSG). **Method:** (1) Questionnaire survey on the diagnosis of ILD, determination of the indication for RT and the state of implementation. (2) Multi-institutional retrospective cohort study in fiscal year 2014. Statistical analysis of risk factors for AE. ILD confirmation using CT images by two central radiation diagnosticians. These two studies were included. **Result:** (1) Questionnaires were returned by 47 institutes. RT was not an option for patients with ILD in 8 of the institutes. Some of the institutes excluded RT from options because of experience of severe adverse events. RT was an option even for patients with ILD depending on conditions of the case in 39 of the institutes. In 37 of the institutes, 3.7% of lung cancer patients (78/2128 patients) in fiscal year 2014 had ILD. (2) Sixty-seven patients were enrolled. AE occurred in 5 cases including 4 photon RT cases. AE occurred in 4 (7.7%) of 52 cases in which photon RT was performed, and there was one RT-induced AE-related death (25.0%). Regarding risk factors for AE, in the t-test, grade

of radiation pneumonitis, FEV1, and lung V30 were significant. Age, lung mean dose, lung V20, and DLco were marginally significant. However, they were not significant in multivariate analysis. AE occurred in 1 of 15 cases in which particle RT was performed. In a review of CT images, 59 cases were analyzable. ILD was confirmed in 58 cases (98.3%). Diagnosis of ILD by each institute was almost the same as that in the review by central radiation diagnosticians. Post-irradiation exacerbation of ILD (PIE-ILD) on CT was revealed in 23 (43.4%) of 53 cases. We considered that PIE-ILD does not necessarily progress to AE. **Conclusion:** We surveyed actual conditions of RT for patients with ILD in Japan. RT was an option even for patients with ILD in many institutes, though cases in which it was actually implemented were limited.

Keywords: radiation therapy, acute exacerbation, interstitial lung disease

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-19 FEASIBILITY AND OUTCOMES OF RADIOFREQUENCY ABLATION AS SALVAGE MODALITY AFTER HYPOFRACTIONATED RADIATION/SBRT FOR EARLY NSCLC

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Background: Local recurrences after radiotherapy (RT) for early non-small cell lung cancers (NSCLC) may be amenable to curative treatments. One such modality is Radio Frequency Ablation (RFA). There is paucity of data about outcomes after RFA salvage. We aim to evaluate the feasibility and outcomes of RFA when used as salvage therapy after hypo-fractionated radiation for early NSCLC. **Method:** We retrospectively reviewed consecutive early NSCLC patients treated with SBRT or hypo-fractionated radiation followed by RFA salvage in an ethics board approved study. RFAs were performed using CT guidance and under general anesthesia using LeVeenTM needle. Its immediate and follow up complications were assessed. The end points of interest were local recurrence free survival (LRFS), distant relapse free survival (DRFS) and overall survival (OS). The end points were compared by the tumour size and Positron Emission Tomography (PET) maximum Standardized Uptake Value (SUVmax) **Result:** 20 individuals with 21 tumours were treated with salvage RFA after RT for early tumours between 2005 and 2017. The median age was 76 years(52-94). Initial treatment was SBRT in 55%(11/20) tumours. 55%(11) tumours were adenocarcinomas, 25%(5) were squamous and 20%(4) were NSCLC- not otherwise specified. The median tumour size (long axis diameter) was 31.5mms. PET was available for 16 tumours and the median SUVmax was 6.15. The median interval since prior radiation was 24 months(8-56). The procedure was well tolerated. One individual developed pneumothorax requiring pigtail catheter drainage. The median hospitalization period was 1 day. One procedure was aborted midway due to lancinating ipsilateral arm pain. Two patients required 3 and 5 days of hospitalization respectively because of post-procedural pain. Chronically, one individual developed tissue necrosis syndrome, one individual developed hydropneumothorax and one individual developed dysphonia. The median LRFS was 31.8 months. When stratified by ≤ or >30 mms, there was no statistically significant difference in mean LRFS, but a trend was noted. Onset of distant metastases was slightly earlier in larger tumors but not statistically significant. The median overall survival for tumours ≤ or >30 mms was 42.8 months and 17.4 months respectively (p-0.015). THE LRFS was 27.7 and 60.45 months (p-0.29), DMFS was 27.8 and 54.7 months (p-0.11) for patients with PET SUV >5 and ≤5 respectively . **Conclusion:** RFA is an effective and feasible salvage modality in early NSCLC after radiation. This study is limited by its retrospective nature and limited numbers. A larger prospective analysis will help ascertain its role.

Keywords: Stereotactic body radiation therapy, Radio Frequency ablation, hypofractionated radiation therapy

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-20 PROGNOSTIC UTILITY OF PET IN NON-SMALL CELL LUNG CANCER AFTER EMPIRIC STEREOTACTIC BODY RADIOTHERAPY (SBRT)

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Background: Positron emission tomography (PET-CT) is valuable for diagnosing early stage non-small cell lung cancer (NSCLC) in the absence of biopsy. Here we investigate the diagnostic, prognostic, and treatment response of PET-CT in NSCLC treated with empiric stereotactic body radiotherapy (SBRT). **Method:** We retrospectively reviewed 78 empiric lung SBRT cases with pre-treatment PET scans treated to biologic equivalent dose≥100 Gy_{10}. We correlated pre and post-treatment standard uptake values (SUV) with local, regional, and distant control. Statistical analysis was conducted via SPSS v20. **Result:** A total of 44 males and 34 females median age 77 were treated to 48 Gy in 4 fractions (n=47) or 50 Gy in 5 fractions (n=31). Lung nodules were 1.6 cm (0.6–4.5 cm) with a median planning target volume of 19.1 cc (3.7-97.4 cc). Median pre-treatment SUV=4.1 (0-20). Of the 43 patients with post-treatment PETs, median SUV = 2.7(0-7.2) or 53%(0-302%) of the pretreatment SUV. The median follow-up was 18 months with a 3-year survival of 50% for all patients. Local, regional, and distant control rates at 3 years were 91%, 81%, and 78%, respectively. Relative sisease control for pre-treatment SUV ≤4.0 compared to >4.0 is shown in Table 1:

Pre-treatment SUV >4 vs ≤ 4	Hazard Ratio (Confidence Interval)	P Value
Local Failure	5.92 (0.74 – 47.15)	0.08
Regional Failure	6.67 (1.86 – 23.98)	<0.01
Distant Failure	3.28 (1.02 – 10.55)	0.04
Overall Progression	3.62 (1.43 – 9.12)	<0.01

There was no difference in tumor size, location, nodule morphology, or prior cancer/smoking history between patients with pre-treatment SUV ≤ 4 (n=40) and > 4 (n=38). Receiver operating characteristic curve analysis identified optimal SUV cutoff values of 6.0, 3.5, and 4.0 to predict local, regional, and distant failure, respectively. Post-SBRT PET scans with SUV reduction ≥50% demonstrated a 2-year freedom from progression of 89% compared to 57% with SUV reduction <50% (P=0.08). **Conclusion:** Our study demonstrates a strong correlation between initial PET avidity and regional/distant recurrence, and a trend with local recurrence. Perhaps patients with pretreatment SUV>4 warrant a mediastinal evaluation or closer vigilance in follow-up, though this warrants prospective investigation.

Keywords: PET, SBRT, NSCLC

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-21 POST-TREATMENT SURVIVAL DIFFERENCE BETWEEN LOBECTOMY AND STEREOTACTIC ABLATIVE RADIOTHERAPY IN STAGE 1 NON-SMALL CELL LUNG CANCER IN ENGLAND

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Background: Non-small cell lung cancer (NSCLC) accounts for almost 85% of all lung cancer cases diagnosed in England. Stage 1 lung cancer represents around 15-20% of all NSCLC cases, and while surgical resection (the current standard of care) offers the best chance to improve survival and is the standard of care in early lung cancer, not all patients undergo surgical treatment due to their advanced age and/or multiple comorbidities, while others may refuse surgery. Stereotactic ablative radiotherapy (SABR), a non-invasive external beam radiotherapy, has become an established treatment option for such patients. The aim was to compare survival at 90 days, 6 months, one year and overall for patients who received either lobectomy or SABR for NSCLC stage IA and IB. **Method:** We used data from the 2015 National Lung Cancer Audit (NLCA) database that were collected by Public Health England (PHE) and linked with Hospital Episode Statistics (HES) and the Radiotherapy Dataset (RTDS) to identify patients with NSCLC stage IA-IB and performance status 0-2 who underwent surgery or SABR treatment. We looked at survival risk difference at 90 days, 6 months, 1 year and 1 year between the two patient groups using propensity score derived using a logistic regression model with covariates that were predictive of treatment including age, sex, performance status and stage. **Result:** We identified 2373 patients in our cohort, 476 of whom had SABR. The median difference between date of diagnosis and date of treatment for surgery patients was 17 days while for SABR patients it was 73 days. Increasing age and worsening performance status were associated with having SABR rather than surgery. Patients who had SABR had 1.4% better survival at 90-days; however, this survival benefit dropped at 6 months

after treatment started and patients who had surgery had 14% better overall survival. **Conclusion:** Our analysis suggests that, while patients who underwent SABR have better short-term survival, patients who have surgery have better overall survival. However, the time to the start of treatment with SABR was 8 weeks longer than for surgery. Thus early survival may be underestimated for SABR although other (conflicting) factors may be at play including stage-shift (more in SABR group) and length time (potentially more indolent tumours in the SABR group).

Keywords: Surgery, Lung neoplasm, survival

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P2.16-22 COMPARING TWO COMMON RADIOTHERAPY REGIMENS IN NON-SMALL CELL LUNG CANCER - A RETROSPECTIVE STUDY

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Background: In patients with inoperable non-small cell lung cancer (NSCLC), a variety of radiotherapy regimens are used as potentially curative treatments. At the Beatson West of Scotland Cancer Centre (BWoSCC), continuous hyperfractionated accelerated radiotherapy (CHART: 54 Gy in 36 fractions over 12 days) and hypofractionated radiotherapy (55 Gy in 20 fractions over 4 weeks) are the standard fractionations. The aim of this study was to review the clinical outcomes. **Method:** A retrospective study was performed assessing clinical and dosimetric records of all radically treated NSCLC patients at the BWoSCC in 2010 and 2015. We excluded all patients who had received chemotherapy sequentially or concurrently. Patient demographics, tumour characteristics, radiotherapy and survival data were collected and analysed. **Result:** A total of 254 patients received radical radiotherapy: 113 were treated in 2010 (52 CHART and 61 with 55/20); 141 were treated in 2015 (43 CHART and 98 with 55/20). Median age for CHART patients was 76 IQR (70-81), and for 55/20 patients 74 (68-79). Overall, CHART patients had poorer performance status (PS). 32% of CHART patients had a PS 2/3 compared to 19.5% of 55/20 patients ($p<0.01$). In 2010, 68% of CHART patients were PS 0/1 and 32% were PS 2/3. In 2015, 53% were PS 0/1 and 47% were PS 2 ($p<0.01$). In 2010, more CHART patients had unknown staging compared with the 55/20 patients (28% versus 4%). By 2015, there was no statistically significant difference. The max planning target volumes (PTV) were on average larger in 2015 than 2010. The PTV of CHART patients increased by 19.8%. The PTV of the 55/20 patients increased by 3.4%. Median progression free survival (progression or death) was 14.3 months 95%CI (11.0 to 18.0) for 55/20 patients and 14.6 months 95%CI (11.0 to 18.7) for CHART patients. Median overall survival was 23.2 months 95%CI (16.2 to 30.2) for 55/20 patients and 22.2 months 95%CI (14.5 to 29.2) for CHART patients. **Conclusion:** In this single centre study, we present a series of patients treated with 2 different radical radiotherapy regimens. Despite PTV volumes on average increasing from 2010 to 2015, the median survival has decreased for CHART. In our centre we introduced Stereotactic ablative radiotherapy as a new option for patients with stage I and II disease. Many patients who previously received CHART or 55/20 will now be eligible for SABR. It may be that this has changed selection criteria, with more advanced patients being put forward for CHART.

Keywords: CHART, non small cell lung cancer, 55Gy in 20 fractions

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P2.16-23 FOCAL THERAPY FOR SMALL LUNG CANCER WITH ETHANOL RELEASE HEAT-GENERATING POLYMER

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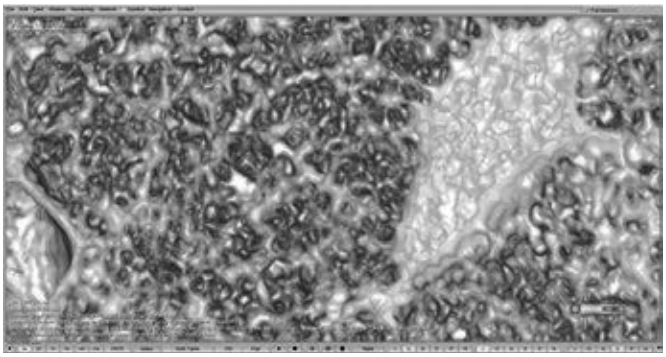
Background: As opportunities to take high resolution CT images of lungs by lung cancer screening increase, the lung cancer lesions of small GGO lesions are increasingly found. Such an elderly person who found a small cancer lesion reveals low durability for surgery and sometimes has many medical complications around chronic diseases. In this study, we have synthesized "Ethanol Release Heat-Generating Polymer", for focal therapy of micro lung cancer. **Method:** We have synthesized low viscosity silicon material which absorb a trace amount of water, generates heats and indurate in a few minutes under industry-academia collaboration. We have adjusted the concentration of titanium catalyzer, and a fine image can be visualized under CT imaging equipment. We perfumed rat experiments that 0.03 mL of injected viscous liquid resin was injected into rat lungs under micro surgery. Histological images of alveolar epithelial cells inside and around the resin injection area were examined by HE staining. Also, in order to analyze three-dimensionally whether the target site is surrounded without cracks, we used the micro CT apparatus of Shimadzu Corporation. Rat lungs are divided in 1 micron unit CT imaging, the indurated conditions of thermosetting resin in the lungs was analyzed as 3D DICOM image data. **Result:** Alveolar cells close to the resin were denatured. According to the 3D micro CT views of the indurated resin in the rat lung (Fig), it was was hardened three-dimensionally without cracks, the surrounding cells were damaged. The CT value of the resin itself was high, and it was distinguished as white induration from the cell components of the lung.



Conclusion: We have succeeded in synthesizing "Ethanol Release Heat-Generating Polymer" for focal therapy of micro lung cancers. This work was PCT patent pending JP2017/025044 and supported by JSPS KAKENHI Grant Number JP15K15517.

Keywords: thermosetting resin, Focal therapy, ethanol release

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P2.16-24 RACIAL DIFFERENCES IN TREATMENT AND SURVIVAL OF STAGE I NSCLC: A COMPARISON OF VETERANS AFFAIRS (VA) AND SEER-MEDICARE POPULATIONS

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Background: Disparities in treatment and survival continue to persist in early-stage non-small cell lung cancer (NSCLC), yet they vary among different patient populations. The objective of this study is to compare racial differences in demographic, clinical, treatment, and survival characteristics among veteran and non-veteran patients with stage I NSCLC. **Method:** Patients with stage I NSCLC diagnosed 2001-2009 were identified in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database and Veterans Affairs (VA) cancer registry. In both cohorts, analyses were restricted to Black and White males aged ≥65 years. Descriptive statistics were used to compare racial differences in demographic and clinical factors. Multivariate logistic regression models estimated odds ratios (OR) and 95% confidence intervals (95% CI) for the association between race and receipt of treatment. Cox proportional hazards models were used to assess 5-year survival. **Result:** Among patients in VA (N=7895) and SEER (N=8744), the proportion of Black patients was 13% and 7%, respectively. In VA, 50% of both Black and White patients were diagnosed at ages 65-74 years ($p=0.60$); in SEER, Black patients were younger than Whites (60% vs 50%, $p<0.0001$). The predominant histology was squamous cell in Blacks (47%) and adenocarcinoma in Whites (42%) in SEER; 40% of both Blacks and Whites in VA had squamous cell histology. In SEER, 11% of Whites and 14% of Blacks had a comorbidity score ≥3 ($p=0.003$); corresponding proportions in VA were 29% and 28% ($p=0.10$). While 84% of SEER patients and 77% of VA patients received treatment, after adjusting for covariates, Blacks were less likely than Whites to get any treatment (OR_{adj}: 0.66, 95% CI 0.57-0.77 in VA; OR_{adj}: 0.56, 95% CI 0.47-0.68 in SEER), and to receive surgery alone when treated (OR_{adj}: 0.73, 95% CI 0.62-0.86 in VA; OR_{adj}: 0.57, 95% CI 0.47-0.70 in SEER). Among treated patients, there was no significant difference in overall survival for Blacks and Whites, after adjusting for type of treatment (HR_{adj}: 0.99, 95% CI 0.91-1.09 in VA; HR_{adj}: 1.00 95% CI 0.89-1.13 in SEER). **Conclusion:** Among older stage I NSCLC patients, the proportion of Blacks in VA was nearly twice that in SEER, and Blacks and Whites were more similar in VA than in SEER. Despite population differences, similar racial differences in receipt of treatment

were noted in both veteran and non-veteran cohorts. No significant racial difference in survival was observed in either cohort when type of treatment is accounted for.

Keywords: treatment, survival, disparities

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P2.16-25 LOWER HILIAR LYMPH NODE UPSTAGING IN EARLY NSCLC VATS SURGERY IS RELATED TO TUMOR LOCATION AND DOES NOT AFECT SURVIVAL

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Background: Nodal upstaging after early stage lung cancer surgery is not only inevitable, but it is also considered a quality marker for surgical lymphadenectomy. Underdiagnosis of pN1 has important significance and leads to undertreatment. Lymphadenectomy has been questioned in video thoracoscopic surgery (VATS) since its description. Recently some authors published lower pN1 upstaging incidence after VATS resection compared to open thoracotomy. We want to evaluate the rate of upstaging in our centre after starting a VATS program. **Method:** All patient who required an anatomical resection for non-small cell lung cancer (NSCL) in our department have been retrospectively reviewed. Patients were divided in two groups in relation of the performed surgical approach, thoracotomy (THO) and VATS. Both groups were compared in terms of gender, age, smoking history, comorbidities, lung function, histology, clinical stage and tumour location. Rate of hilar lymph node upstaging (pN1) and mediastinal lymph node upstaging (pN2) were compared between both groups. Univariate and multivariate analysis was performed to identify independent risk factors for pN1 upstaging. Overall survival was compared between both techniques in pN0 patients. **Result:** Between January 2011 and October 2017, 1.081 lung resections were carried out in our centre. 323 of those were anatomical resections for early stage (≤ IIB) non-small cell lung cancer (NSCLC). There were no differences among groups except for FEV1, previous history of Diabetes Mellitus, tumour size and location (p<0.05). pN1 ratio was 20,5% in THO vs. 8,6% in VATS (p < 0,05) when performed accesses was compared. No differences were observed regarding pN2 upstaging (6% in THO and 6,5% in VATS; p>0,05). Only gender and centrality were identified as independent risk factors for hiliar lymph node upstaging in a multivariate analysis. For those patient with no upstaging (pN0) there were no survival differences comparing open and VATS approaches. **Conclusion:** In our series pN1 upstaging is less frequent in VATS than in open surgery. When analysed, tumour centrality has shown to be an independent risk factor for hilar upstaging. Additionally central tumours were much more prevalent in open surgery group. In conclusion, lower incidence of unnoticed pN1 in VATS surgery could be related to a selection bias, because thoracotomy was preferred when tumour considered central. Furthermore, the fact that no differences on survival in pN0 patients were detected suggests that no patients have been underdiagnosed and in consequence undertreated.

Keywords: early stage NSCLC, upstaging, VATS

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P2.16-26 LUNG CANCER RESECTION IN PATIENTS WITH CRITERIA FOR LUNG CANCER SCREENING PROVIDES SATISFACTORY SHORT TERM RESULTS

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Background: Criteria for lung cancer screening (LCS) include age 55-74 years old, a smoking history ≥ 30 pack-years with < 15 years smoking cessation. The lack of data regarding the operative risk for lung cancer resection (LCR) in patients with LCS criteria is a limit for national reimbursement of LCS in France. We aimed to determine whether the operative risk for LCR is increased in patients with LCS criteria. **Method:** We performed a retrospective analysis of consecutive LCR operated between October 2015 and October 2016 in a high volume tertiary center with routine minimally invasive thoracic surgery (videothoracoscopy). Among 241 patients who underwent a LCR, the study population were the 169 patients aged 55-74 years old. We compared the perioperative characteristics of patients with and without LCS criteria. **Result:** LCS criteria were present in 92 patients out of 169. Preoperative and operative/postoperative data were reported in Tables 1 and 2, respectively. Despite an increased preoperative cardiovascular risk and a poorer respiratory function, patients with LCS criteria presented a similar postoperative morbidity, mortality and hospital readmission compared with patients without LCS criteria.

Table 1: preoperative characteristics of patient aged 55-74 years old undergoing lung cancer resection. Comparison between patients with and without lung cancer screening (LCS) criteria. M: male; F: female; BMI: body mass index; CV: cardiovascular; EA: endarterectomy; ENT: ear nose and throat; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein; FEV1: forced expiratory volume in 1 second. Quantitative data are expressed as mean ± standard deviation; qualitative data are expressed as n and %.

	All (n=169)	With LCS criteria (n=92)	Without LCS criteria (n=77)	P
Age (years)	64.7 ± 5.1	64.1 ± 4.5	65.4 ± 5.6	NS
Sex (M/F)	100 / 69	65 / 27	35 / 42	0.002
BMI (kg/m^2)	25.0 ± 4.8	24.3 ± 4.3	26.0 ± 5.2	0.023
Smoke habit				
Pack years	35.3 ± 22.0	48.0 ± 15.6	16.7 ± 15.7	<0.0001
CV events history	47 (27.8%)	34 (37.0%)	13 (16.9%)	0.006
Cardiac event	31 (18.3%)	22 (23.9%)	9 (11.7%)	NS
PAD	18 (10.7%)	15 (16.3%)	3 (3.9%)	0.019
Carotid EA	4 (2.4%)	4 (4.3%)	1 (1.3%)	NS
stroke	11 (6.5%)	5 (5.4%)	6 (7.8%)	NS
Aortic surgery	10 (5.9%)	8 (8.7%)	2 (2.6%)	NS
Cancer history	60 (35.5%)	35 (38.0%)	25 (32.5%)	NS
ENT	14 (8.3%)	12 (13.0%)	2 (2.6%)	0.022
Bladder	8 (4.7%)	8 (8.7%)	0 (0%)	0.008
Digestive tract	8 (4.7%)	4 (4.3%)	4 (5.2%)	NS
Breast	5 (3.0%)	2 (2.2%)	3 (3.9%)	NS
Lung	9 (5.3%)	4 (4.3%)	5 (6.5%)	NS
Other	25 (14.8%)	14 (15.2%)	11 (14.3%)	NS
Inflammation				
NLR	3.25 ± 2.27	3.41 ± 1.74	3.05 ± 2.78	NS
CRP > 10	32 (18.9%)	20 (21.7%)	12 (15.6%)	NS
FEV1	87.5 ± 19.9	83.1 ± 20.4	92.9 ± 17.9	0.001

Table 2: postoperative characteristics of patient aged 55-74 years old undergoing lung cancer resection. SSC: squamous cell carcinoma. Quantitative data are expressed as mean ± standard deviation but when specified; qualitative data are expressed as n and %.

	All (n=169)	With LCS criteria (n=92)	Without LCS criteria (n=77)	P
Infra lobar resection	19 (11.2%)	13 (14.1%)	6 (7.8%)	NS
Wedge resection	14	9	5	
Segmentectomy	5	4	1	
Minimally invasive	13	9	4	
Lobectomy	130 (76.9%)	72 (78.3%)	58 (75.3%)	
Minimally invasive	79	46	34	
Bilobectomy	8 (4.7%)	1 (1.1%)	7 (9.1%)	
Totalisation pneumonectomy	2 (1.2%)	1 (1.1%)	1 (1.3%)	

	All (n=169)	With LCS criteria (n=92)	Without LCS criteria (n=77)	P
Pneumonectomy	10 (5.9%)	5 (5.4%)	5 (6.5%)	
Pathology				NS
adenocarcinoma	113 (66.9%)	63 (68.5%)	50 (64.9%)	
SCC	38 (22.5%)	23 (25.0%)	15 (19.5%)	
others	18 (10.1%)	6 (6.5%)	12 (15.6%)	
Stage				NS
Stage I	85 (50.3%)	44 (47.8%)	41 (53.2%)	
Stage II	38 (22.5%)	25 (27.2%)	13 (16.9%)	
Stage III	41 (22.3%)	20 (21.7%)	21 (27.3%)	
Stage IV	5 (3.0%)	3 (3.3%)	2 (2.6%)	
30-day Morbidity				
No morbidity	84 (49.7%)	42 (45.7%)	42 (54.5%)	NS
Medically treated	49 (29.0%)	28 (30.4%)	21 (27.3%)	
Clavien-Dindo I	1	1	0	
Clavien-Dindo II	48	27	21	
Requiring intervention	15 (8.9%)	14 (15.2%)	11 (14.1%)	
Clavien-Dindo IIIa	16	7	9	
Clavien-Dindo IIIb	9	7	2	
Requiring ICU	11 (6.5%)	8 (8.7%)	3 (3.9%)	
Clavien-Dindo IVa	8	6	2	
Clavien-Dindo IVb	3	2	1	
30 –days mortality	0 (0%)	0 (0%)	0 (0%)	
Clavien-Dindo V	0	0	0	
Hospital stay duration (days) median (IQR)	7 (5 ; 11)	7 (5 ; 11)	6 (5 ; 10)	NS
90-days hospital re-admission	4 (2.4%)	2 (2.2%)	2 (2.6%)	NS

Conclusion: LCS program would allow us to achieve similar operative outcomes than patients without LCS criteria despite poorer respiratory function and increased cardiovascular risk.

Keywords: lung cancer, Screening, Surgery

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-27 INDOCYANINE GREEN VIRTUAL ASSISTED LUNG MAPPING (ICG-VAL-MAP): ANYONE CAN PERFORM A VISIBLE PREOPERATIVE MARKING SUCCESSFULLY

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Background: As a preoperative marking of small pulmonary nodules, we developed Virtual Assisted Lung Mapping (VAL-MAP), which is consisted of preoperative simulation using three-dimensional CT images and transbronchial dye marking using indigocarmine (IC). Between 2012 and 2016, we performed VAL-MAP in more than 200 cases in a single institution; however, we sometimes came across a situation, in which an identification of marked IC was difficult at post-marking CT and/or during surgery. Herein, we have developed a new VAL-MAP (ICG-VAL-MAP) using indocyanine green (ICG) and contrast agent. The purpose of this study was to prospectively evaluate the visibility of newly-developed ICG-VAL-MAP in an identification of ICG at post-marking CT and during surgery. **Method:** Since January in 2017, we have performed ICG-VAL-MAP, using ICG and contrast agent in addition to IC as a marker, in 48 patients. During surgery, fluorescence endoscope system was used for identification of marked ICG. **Result:** Targeted lesions were 61 nodules with the diameter ranging from 2 to 38 mm (median 8 mm). The depth from the pleural surface ranged from 0 to 35 mm (median 8 mm). Total marked numbers were 122 (IC: 37, ICG: 85). At post-marked CT, IC was easily identified in 28 markings (76%), difficult to be identified in 5 (13%), unable to be identified in 4 (11%). On the other hand, ICG was easily identified in all markings. During surgery, IC was easily identified in 29 markings (78%), slightly identified in 4 (11%), unable to be identified in 4 (11%). On the other hand, ICG was easily identified in 84 markings (99%). Only in 1 case, ICG marking was accidentally placed far from a pleural surface, but ICG was slightly identified in a collapsed lung during surgery. There were no severe complications related to ICG-VAL-MAP. All nodules were diagnosed intraoperatively and an appropriate sublobar resection was performed in each patient. In all cases, surgeons were very much satisfied with ICG-VAL-MAP. In details, ICG-VAL-MAP was indispensable for resection of the targeted lesions in 17 cases (35%), and it was helpful for resecting the targeted lesion confidently in 30 cases (63%). However, only in 1 case, ICG-VL-MAP was thought to be unnecessary (2%). **Conclusion:** We confirmed that ICG-VAL-MAP was a novel and promising technique with better visibility for the complete resection of small pulmonary nodules.

Keywords: 3D-CT simulation, Indocyanine green, Preoperative marking

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-28 COMPARISON OF OUTCOMES OF VATS SEGMENTECTOMY VERSUS LOBECTOMY FOR NON-SMALL CELL LUNG CANCER USING A PROPENSITY SCORE MATCHING ANALYSIS

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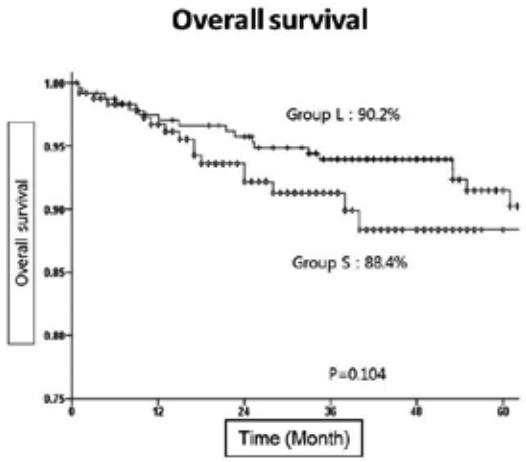
Background: The aim of this study was to compare surgical and oncologic outcomes between thoracoscopic segmentectomy and lobectomy for the patients with non-small cell lung cancer (NSCLC). **Method:** Between 2009 and 2016, 250 thoracoscopic segmentectomies (Group S) and 1,550 thoracoscopic lobectomies (Group L) were performed in patients with NSCLC in our institute. Indications for segmentectomy were peripherally located tumor with smaller than 2 cm size, or the patients with limited pulmonary reserve and multiple comorbidities. Propensity score matching was conducted using preoperative clinical parameters and 240 patients in each Group S and L were included in the study. **Result:** Most commonly performed segmentectomies were left upper lobar upper division segmentectomy (26.7%) and right lower lobar superior segmentectomy (17.1%). Operation time and length of hospital stay were comparable between the groups (162.9 ± 52.8 min and 5.7 days in group S vs. 163.2 ± 40.1 min and 8.7 days in group L; P=0.97 and P=0.13, respectively). Although postoperative mortality rates were not different between the two groups (0.8% vs. 0.8%, p=1.0), post-operative complication rate was significantly lower in the group S (11.2% vs. 19.2%, P=0.02). Especially, pulmonary complication rate including pneumonia, ARDS, and prolonged air leakage was significantly lower in the group S (2.5% vs. 8.3%, p<0.01). Postoperative decrease of diffusion capacity (DLco) was significantly lower in the group S (13.1% ± 16.4 vs. 18.2% ± 19.7, P=0.02). Recurrence-free survival (RFS) and overall survival (OS) were not significantly different between patients who underwent lobectomy (5-year RFS, 84.0%; 5-year OS, 90.2%) and segmentectomy (5-year RFS, 89.0%; 5-year OS 88.4%). (Figure 1)



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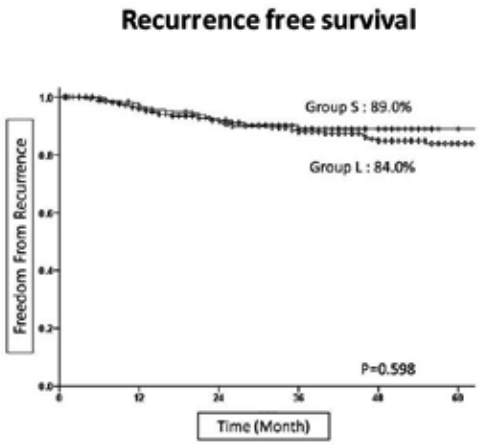

Conclusion: Thoracoscopic segmentectomy could achieve excellent early surgical outcomes with lower complication rates and preserved pulmonary function compared to lobectomy without jeopardizing long-term oncologic outcomes.

Keywords: lung cancer, segmentectomy, lobectomy

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P2.16-29 CLINICAL OUTCOMES OF SURGICALLY RESECTED EXTRAABDOMINAL CHEST WALL DESMOID TUMORS

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Background: Extraabdominal chest wall desmoid tumors are uncommon soft tissue tumors. This study was performed to examine the outcomes of patients with extraabdominal chest wall desmoid tumors and adjacent structures treated with surgery. **Method:** A detailed retrospective clinicopathological study was performed in 17 patients (8 men and 9 women) treated in our institution for extraabdominal desmoid tumors of the chest wall between March 2001 and June 2017. The patients had a median age of 44 years (range, 17-62 years), and the mean pathological diameter of the resected tumors was 92.1mm. **Result:** Complete resection was performed in 13 of the 17 patients (76.5%). One patient had positive microscopic margin and three had gross residual disease. Chest wall reconstruction surgery was necessary in five patients (29%), synthetic patches were used in two patients, muscle flaps in two patients, and a metal plate in one patient. Complications were found in one patient, and there were no cases of operative mortality. Five patients (29%) received postoperative adjuvant therapy (only radiotherapy in three, radiotherapy and chemotherapy in two). Follow-up was complete in all patients and ranged from 9 to 202 months (median 76 months). One of the three patients with gross residual disease showed no change in tumor size during the 114 month follow-up period. Recurrences were found in five patients (29%), four of whom were treated by surgery. Second or more operations were performed in three of these patients. All sites of recurrence were around structures the first resected tumors. The mean recurrence time was 20.8 months after surgery. **Conclusion:** Desmoid tumors of the chest wall are locally aggressive tumors with a high recurrence rate. Surgical treatment requires wide radical resection. Multicentric and long-term investigations would be helpful for management of desmoid tumors because of the low prevalence rate of this disease.

Keywords: Surgery, desmoid tumor, chest wall

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-30 SURGICAL STRATEGY FOR CLINICAL STAGE IA NON-SMALL CELL LUNG CANCER PATIENTS WITH RISK FACTORS OF PATHOLOGICAL INVASION AND/OR METASTASIS

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Background: Because pathological metastasis and involvement are thought to be associated with postoperative recurrence and poor outcomes in non-small cell lung cancer (NSCLC) patients, limited resection for high risk patients of pathological metastasis and involvement is controversial. The aim of this study was to examine a postoperative locoregional control in these patients. **Method:** We retrospectively reviewed completely resected clinical stage IA NSCLC patients on the 8th edition of the TNM classification (solid tumor component size of ≤3 cm on computed tomography; CT). The pathological metastasis and/or involvement was defined that pleural involvement, pulmonary metastasis, lymph node metastasis, and/or lymphovascular involvement were identified on pathological examination. To identify predictors for the pathological metastasis and/or involvement, demographic and clinical factors were analyzed by a univariate analysis and multivariate logistic regression analysis. For the significant factors, optimal cutoff points were determined with a receiver operating characteristic analysis. Locoregional recurrence-free probabilities were calculated using the Kaplan-Meier method in patients with/without the identified predictors, and were compared between patients who underwent limited resection and lobectomy by the log-rank test. **Result:** Of the 286 eligible patients, pleural involvement, pulmonary metastasis, lymph node metastasis, lymphatic permeation, and vascular invasion were identified in 43 (15%), 5 (2%), 11 (4%), 15 (5%), and 32 patients (11%), respectively, and in total, 73 patients (26%) developed the pathological metastasis and/or involvement. Univariate and multivariate logistic regression analysis revealed solid tumor component size on CT (OR: 1.090) and consolidation/tumor ratio on CT (CTR; OR: 1.043) as significant predictors. The optimal cutoff points were determined as 1.7 cm and 86% for solid component size and CTR, respectively, and 47 of the 97 patients (48%) with >1.7 cm of solid component size and >86% of CTR developed the pathological metastasis and/or involvement. In the 97 patients, the 3-year locoregional recurrence-free probabilities were 70% versus 84% in patients who underwent limited resection (n = 21) and lobectomy (n = 76), respectively (p = 0.0963), whereas in 104 patients with ≤1.7 cm of solid component size and ≤86% of CTR, the 3-year locoregional recurrence-free probabilities were 95% versus 97% in patients who underwent limited resection (n = 52) and lobectomy (n = 52), respectively (p = 0.8622). **Conclusion:** An indication for limited resection may be decided with caution in clinical stage IA patients with the predictors of the pathological metastasis and/or involvement because of relatively higher incidence of postoperative locoregional recurrence after limited resection when compared with lobectomy.

Keywords: non-small cell lung cancer, limited resection, sublobar resection

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P2.16-31 EXAMINATION OF THE INTERSEGMENTAL ISOLATION METHOD IN THE SEGMENTAL RESECTION CONSIDERING RESPIRATORY FUNCTION PRESERVATION

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Background: Segmental resection is often performed as limited operation for early lung cancer because it is usually considered the procedure to preserve respiratory function. There are two methods to isolate the intersegmental line. One is the method to isolate along intersegmental plane exactly with electric knife or ultrasonic scalpel and another is to cut the approximate intersegmental border while noting surgical margin with automatic suture instruments. The superiority of the respiratory function preservation effect among two is not known. So we examined which is better method in the respiratory function preservation. **Method:** We targeted the cases respiratory function test were performed one year after operation among all patients which we underwent segmental resection for primary lung cancer between November in 2000 and March in 2017. We compared the recovery rate of postoperative vital capacity for preoperative vital capacity (=RR_{VC}) and the one of postoperative forced expiratory volume in one second for preoperative forced expiratory volume in one second (=RR_{FEV1}) between the group with the method to isolate along intersegmental plane exactly (=ISPG) and the group with the method to cut with automatic suture instruments (=ASCG). **Result:** 175 cases satisfied above detail. There were 119 cases in ISPG and 56 cases in ASCG. RR_{VC} was 94% in ISPG and 88% in ASCG. RR_{FEV1} was 94% in ISPG and 90% in ASCG. The significant difference was shown in both RR_{VC} (p=0.005) and RR_{FEV1} (p=0.03). The procedure which has enough numbers to be compared was the segmental resection of right S2 and either S6. Almost all other simple and complicated segmental resections were in ISPG. RR_{VC} in the segmental resection of right S2 was 100% in ISPG and 85% in ASCG. RR_{FEV1} in the segmental resection of right

S2 was 98% in ISPG and 84% in ASCG. RR_{VC} in the segmental resection of right or left S6 was 88% in ISPG and 88% in ASCG. RR_{FEV1} in the segmental resection of S6 was 93% in ISPG and 91% in ASCG. The significant difference was shown in RR_{VC} of the segmental resection of right S2 (p=0.04). **Conclusion:** We consider the isolation along intersegmental plane exactly is superior to the method with automatic suture instruments from the viewpoint of respiratory function preservation while the difference may depend on the resected segment. We guess it is expected that the difference of the respiratory function preservation effect between the two groups grows big as much as the intersegmental plane is large.

Keywords: respiratory function preservation, segmental resection, isolation of the intersegment plane

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-32 SURVIVAL IMPLICATIONS AND FACTORS ASSOCIATED WITH THE ANATOMIC LEVEL OF INCOMPLETE NON-SMALL-CELL LUNG CANCER (NSCLC) RESECTION

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Background: Incomplete resection impairs NSCLC survival, but the relative significance of specific anatomic levels of margin involvement is uncertain. We examined the survival implications of the anatomic level of margin positivity. **Method:** We analyzed curative-intent primary NSCLC resections from 11 hospitals in 4 contiguous Dartmouth Hospital Referral Regions in West Tennessee, East Arkansas, and North Mississippi from 2009-2018. Overall survival (OS) was evaluated with Kaplan-Meier estimates and hazard ratios (HR) from Cox models. **Result:** Of 3097 resections, 137 (4.4%) had positive margins. The anatomic sites of margin positivity were: mainstem bronchus 28%; peribronchial margin 24%; chest wall margin 21%; lung tissue margin 12%; great vessels 1%; mediastinum 2%; bronchial carcinoma in-situ 1%; not reported 11%. Compared to patients with negative margins, positive margins were more likely in patients who were male (66% v 51%, p=0.0003), had poorly/undifferentiated tumor grade (45% v 34%, p=0.0143), squamous NSCLC (46% v 33%, p=0.0111), or multi-lobar tumors (15% v 5%, p<.0001). Higher pT (p<.0001) and pN (p<.0001), larger tumor size (4.2cm v 3.0cm, p<.0001), a pneumonectomy (16% v 6%, p<.0001), and an open thoracotomy (77% v 60%, p=0.0004) were also associated with margin positive resections. 5-year OS varied by the anatomic site of the margin: mainstem bronchus 35%; peribronchial margin 44%; chest wall margin 22%; lung tissue margin 23%. On unadjusted regression, positive margins at mainstem bronchial (HR=1.98, p=0.0041), chest wall (HR=2.82, p<.0001), or lung tissue (HR=2.92, p=0.0007) had a negative prognostic impact. Positive margins at chest wall (aHR=1.66, 0.0310) and lung tissue margins (aHR=2.24, p=0.0137) had the most significant prognostic impact after controlling for age, sex, race, histology, primary site, tumor grade, cT, cN, and adjuvant chemo/radiation (Table).

	Unadjusted HR (95%CI)	p-value	Adjusted* HR (95%CI)	p-value
Anatomic site of margin				
Negative margin	1		1	
Mainstem Bronchial	1.98 (1.24-3.16)	*0.0041*	1.23 (0.77-1.99)	0.3909
Peribronchial	1.66 (1.00-2.77)	0.0513	1.29 (0.76-2.19)	0.3437
Chest wall	2.82 (1.81-4.39)	*<.0001*	1.66 (1.05-2.62)	*0.0310*
Lung tissue	2.92 (1.57-5.45)	*0.0007*	2.24 (1.18-4.25)	*0.0137*
Other	0.91 (0.38-2.19)	0.8353	0.73 (0.30-1.76)	0.4804
Age	1.02 (1.02-1.03)	<.0001	1.03 (1.02-1.03)	<.0001
Sex				
Female	1		1	
Male	1.62 (1.42-1.84)	<.0001	1.40 (1.23-1.60)	<.0001
Race				
White	1		1	
Hispanic	0.30 (0.04-2.11)	0.2254	0.28 (0.04-1.96)	0.1971
Black or AA	0.91 (0.77-1.06)	0.2096	0.95 (0.81-1.12)	0.5317
Other	1.03 (0.54-1.99)	0.9219	1.22 (0.63-2.38)	0.5515
Histology				
Adenocarcinoma	1		1	
Squamous	1.63 (1.43-1.86)	<.0001	134 (1.16-1.54)	<.0001
Large Cell	1.40 (1.02-1.92)	0.0357	1.04 (0.75-1.45)	0.7959
Other	0.96 (0.74-1.24)	0.7420	1.01 (0.77-1.32)	0.9554
Clinical T category				
T1	1		1	
T2	1.58 (1.38-1.80)	<.0001	1.31 (1.14-1.50)	0.0002
T3	1.35 (1.08-1.68)	0.0078	1.09 (0.87-1.37)	0.4704
T4	1.22 (0.81-1.82)	0.3411	1.06 (0.70-1.60)	0.7821
Unknown	0.69 (0.10-4.89)	0.7107	0.79 (0.11-5.65)	0.8149
Clinical N category				
N0	1		1	
N1	1.44 (1.17-1.78)	0.0008	1.22 (0.98-1.52)	0.0752
N2	1.88 (1.53-2.31)	<.0001	1.63 (1.31-2.02)	<.0001
N3	0.77 (0.32-1.86)	0.5669	0.74 (0.31-1.79)	0.5046
Tumor Location				
Upper lobe	1		1	
Middle lobe	0.86 (0.64-1.15)	0.3063	0.90 (0.67-1.21)	0.4847
Lower lobe	0.92 (0.80-1.05)	0.2153	0.97 (0.84-1.12)	0.6516
Overlapping lesion	1.55 (1.23-1.96)	0.0002	1.20 (0.92-1.55)	0.1761
Tumor Grade				
Well/Moderate differentiated	1		1	
Poorly/undifferentiated	1.43 (1.25-1.64)	<.0001	1.30 (1.13-1.50)	0.0002
Unknown	1.00 (0.82-1.22)	0.9768	1.10 (0.90-1.35)	0.3609
Post-Op Chemotherapy				
No	1		1	
Yes	1.35 (1.16-1.58)	0.0002	1.08 (0.91-1.29)	0.3882
Post-Op Radiation Therapy				
No	1		1	
Yes	2.40 (1.93-2.98)	<.0001	2.23 (1.75-2.85)	<.0001

Conclusion: Incomplete NSCLC resection at the chest wall or the lung tissue margins connotes worse survival than other anatomic sites of margin involvement.

Keywords: NSCLC, Surgical resection, Positive margins

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P2.16-33 ADENOSQUAMOUS CARCINOMA OF THE LUNG: COMPARISON OF SURGICAL OUTCOMES WITH SQUAMOUS CELL AND ADENOCARCINOMA

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Background: Lung adenosquamous carcinoma (ASC) is a rare subtype of lung cancer that contains squamous cell carcinoma (SCC) and adenocarcinoma (AC) components. Clinical and prognostic features have not been fully established. The aim of the study is to compare the clinical characteristics and survival outcomes of ASC, AC and SCC. **Method:** In our clinic, the data of 1076 patients who underwent segmentectomy, lobectomy, or pneumonectomy due to non-small cell lung cancer between 1996-2016 was recorded prospectively and reviewed retrospectively. Patients with histologically proven tumor cell type ASC (n = 25, 2,32%), AC (n = 350, 32,52%) and SCC (n = 740, 50,18%) were included in the study. Univariate and multivariate analysis were performed to determine prognostic factors. The Kaplan-Meier method was used for survival analysis. **Result:** Our study group consisted of 915 patients (834 (91.15%) male, mean age 60.87 ± 9.02 (30-87) years). 65 (7,1%) patient underwent segmentectomy, 711 (77,7%) lobectomy and 139 (15,2%) pneumonectomies were performed as lung resections. Morbidity was seen in 326 patients (35.6%). Postoperative 90-day mortality rate was 2.95% (n = 27). When the demographic data was analyzed between the three groups, female gender was 18% in AC and 4% and 3.1% in ASC and SCC, respectively (p <0.001). In the preoperative positron emission tomography, the maximum standard uptake median value was 13,47 in SCC and 11,73 and 9,40 in ASC and AC, respectively (p <0.001). Pneumonectomy rate was 20.74% in SCC and 16% and 6.57% in ASC and

AC, respectively (p <0.001). Early stage (stage 1) patients were 41.4% in the AC group and 28% and 35.7% in ASC and SCC respectively. While the presence of lymphatic metastasis was 36% in the ASK group; the rates were 31.7% and 29.6% in AC and SCC, respectively (p = 0.675). There was no statistically significant difference between the groups in terms of survival (p = 0.659, graph 1) after weighted Log-Rank test using Propensity score weights calculated for each cell type in case of more than two groups. **Conclusion:** ASCs are rare, malignant tumors that includes features of SCC and AC cell types, and frequently involves lymphatic metastases. However, there was no difference in survival when compared with AC and SCC.

Keywords: Adenosquamous Carcinoma, Squamous Cell carcinoma, Adenocarcinoma

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P2.16-34 VISCERAL PLEURAL INVASION IS CLOSELY ASSOCIATED WITH NODAL SPREAD IN CSTAGE IA LUNG ADENOCARCINOMA

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Background: Survival outcomes of patients with clinical Stage IA (cIA) lung adenocarcinoma (LAD) are favorable after resections. In this decade, limited resection without lymphnodes dissections have been indicated for selected cases based on the radiological findings and intraoperative hilar explorations, while we sometimes experience occult lymphnodes metastases among them. These facts refer that limited resections could potentially induce underestimation of the disease, local failure and worsened patients' prognoses. In the present study, we retrospectively investigate the clinicopathological and oncogenic factors in association with the occult nodal spread and skip metastases, and aim to identify population for standard resection in cIA LAD. **Method:** We retrospectively investigated 287 patients with cIA LAD who underwent standard pulmonary resections with mediastinal dissections from January 2013 through December 2017. Clinicopathological factors including location of the tumor, radiological pleural invasion and oncogenic status (EGFR/KRAS/ALK/Triple Negative) were reviewed for outcomes of occult nodal spread and skip metastasis. According to the ROC curves analyses, cutoff values of total diameter (TD), solid diameter (SD), mediastinal window diameter (MD) in CT image and pathological invasive size (IS) were settled to diagnose nodal metastases and skip pN2, respectively. **Result:** Among 287 patients with cIA LAD, 34 (11.8%) with lymph node metastases and 8 (2.8%) with pN2 without hilar metastases (skip pN2) were identified. Univariate analyses revealed that high serum CEA level, TD, MD, SUVmax, IS and pathological pleural invasion (pl) were predictive for nodal metastases. And multivariate analysis showed that pl was closely associated with nodal metastases (Odds Ratio: 3.3, p=0.007). Furthermore, multivariate analysis following the univariate analyses also showed that presence of pl was the factor closely associated with skip N2 metastases (Odds Ratio: 5.7, p=0.029), whereas radiological findings nor oncogenic status were not so. In the clinical valuables, serum CEA level, SD, MD, SUVmax were significantly associated with pl. **Conclusion:** In resected cIA LAD, pathological pleural invasion was closely associated with both occult nodal spread and skip pN2, while any other preoperative factors and oncogenic status were not. New diagnostic modalities for pl may provide the candidates for standard resections in cIA LAD.

Keywords: cIA lung adenocarcinoma, occult nodal spread, visceral pleural invasion

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-35 ANALYSIS OF PRE AND INTRA OPERATIVE FACTORS RELATED TO THE OPERATION TIME OF LOBECTOMY IN VATS: IS THE SHAPE OF THORACIC CAVITY A PREDICTIVE FACTOR?

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Background: Video-assisted thoracoscopic surgery (VATS) to treat lung cancer is less invasive than thoracotomy. However, prolongation of the operation time can make VATS more invasive. An understanding of the preoperative factors of patients scheduled to undergo VATS may help us decide the operative approach and select patients for training young surgeons. We investigated preoperative and intraoperative factors related to prolongation of the operation time required to thoracoscopically perform lobectomy with mediastinal lymph node dissection for lung cancer. **Method:** We reviewed all 166 patients who had undergone VATS lobectomy with mediastinal lymph node dissection for lung cancer between April 2013 and September 2016 in our hospital. The depth and width of the thoracic cavity was measured on preoperative computed tomographic scans. Preoperative and intraoperative factors were entered in multiple regression analysis to identify independent predictors of a prolonged operation time. We analyzed the relation between the numbers of factors related to a prolonged operation time and the operation time by one-way ANOVA. **Result:** The average operation time was 175 minutes. On univariate analysis, the shape of the thoracic cavity was not associated with operation time. On multivariate analysis, smoking index (>600), location of the resected lobe (right middle and left upper lobes), clinical lymph-node metastasis, massive adhesion in thoracic cavity, and the number of autosutures for lobe division (3 or more) were independent factors related to a prolonged operation time. The presence of more factors was related to a longer operation time (p<0.001; no factor: 153 min, one factor: 163 min, two factors: 194 min, three factors: 219 min, and four factors: 222 min). **Conclusion:** The shape of the thoracic cavity was not associated with operation time. We identified 5 predictors of a prolonged operation time. Our findings may be useful for deciding the operative approach and selecting patients suitable for training of surgeons.

Keywords: thoracic cavity, operation time, VATS

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-36 ADJUVANT CHEMOTHERAPY IS EFFECTIVE FOR COMPLETELY RESECTED STAGE IB NON-SMALL CELL LUNG CANCER

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Background: The efficacy of adjuvant chemotherapy for completely resected stage IB non-small cell lung cancer (NSCLC) still remains controversial. The Cancer and Leukemia Group B (CALGB) 9633 trial reported that the adjuvant chemotherapy with paclitaxel and carboplatin showed a significant survival advantage in a subset of patients with tumors larger than 4cm in diameter. In Japan, uracil-tegaful (UFT) has been recommended for stage IB NSCLC. The purpose of this study is to compare the efficacy of platinum-based regimens with UFT as the adjuvant chemotherapy for stage IB NSCLC. **Method:** Patients who underwent complete resection with systemic nodal dissection for stage IB NSCLC between January 2008 and December 2017 in our hospital were retrospectively studied. Disease stage was defined according to the 6th edition of UICC TNM classification. Patients who underwent sublobar resection or any induction therapy prior to surgery were excluded from this study. This study was conducted with the approval of the Ethics Committee of Kawasaki Medical School. **Result:** There were 135 eligible patients consisting of 91 male and 44 female, with mean age of 72.1 years (range, 43-87 years). Of 135 patients, 59 patients (43.7%) underwent adjuvant chemotherapy (platinum-based 15, UFT 44). Median follow-up period was 37.9 months (range 1.1-107.3 months). Overall survival of patients undergoing adjuvant chemotherapy was significantly better compared with that of patients with surgery alone (p=0.032). There were no differences in recurrence-free survival between the two groups (p=0.470). Patients who underwent adjuvant chemotherapy with platinum-based regimens survived significantly longer than patients who underwent surgery alone (p=0.029). Overall survival of patients with platinum-based regimens tended to be better than that of patients with UFT. In a multivariate analysis including sex, age, histologic type, and tumor size, adjuvant chemotherapy was an independent prognostic factor for overall survival (p=0.037). **Conclusion:** Adjuvant chemotherapy, especially with platinum-based regimen, provided a significant survival advantage for completely resected stage IB NSCLC.

Keywords: non-small cell lung cancer, Surgery, adjuvant chemotherapy

P2.16-37 THE INTRODUCTION OF ROBOTIC LOBECTOMY FOR NON-SMALL CELL LUNG CANCER IN SOUTH EAST ASIA: A 5-YEAR SINGLE CENTRE STUDY

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Background: Over the past decade, minimally invasive robotic-assisted thoracic surgery has gradually evolved into the preferred platform for oncological thoracic resection, demonstrating respectable perioperative and long-term outcomes. The aim of this study is to evaluate the feasibility of completely portal robotic lobectomy (CPRL4) for non-small cell lung cancer (NCSLC) at a geographical region that has yet to assimilate this relatively new platform. **Method:** This is a 5-year retrospective review of consecutive patients with NCSLC who underwent CPRL4 by a single surgeon at our institution from January 2013 – October 2017. **Result:** A total of 80 patients (female 55%, median age 67 years) underwent elective completely portal robotic lobectomy CPRL4 for NCSLC. 67.5% were non-smokers. The top 3 co-morbidities were hypertension (60%), hyperlipidaemia (55%) and diabetes (21.3%). 17.5% had previous non-lung related malignancies. Median operative time was 202 mins (range 80 – 335 mins). Conversion rate was 12.5%, the vast majority were due to non-progression of the case. Median ICU/HDU stay, chest tube duration and length of hospital stay were 1 day (range 0 – 4 days), 3 days (range 1 – 34 days) and 4 days (range 2 – 30 days) respectively. There was no perioperative (30-day) mortality in this study. The two commonest complications were prolonged chest tube duration (11.3%) and atrial fibrillation (3.75%). Median tumour size on histology was 2.3cm (range 0.9 – 7cm). Most were adenocarcinomas (85%), followed by squamous cell carcinoma (7.5%), adeno-squamous cell carcinomas (2.5%) and other rare tumours. Final pathological staging distribution was 68.8% stage 1, 15.8% stage 2, 9.2% stage 3A and 5.3% stage 4. 25% were upstaged after pathological staging. Median follow up was 2 years (range 0.2-5.33 years). All lung cancer related mortality at the end of follow-up was 7.8%. **Conclusion:** The perioperative and early to mid-term oncologic results of CRPL4 for NSCLC are promising. With the surge of big data supporting this platform of oncologic surgery, we are confident that CPRL4 will be the preferred choice for minimally invasive surgery in lung cancer patients. However, to establish this body of evidence, further prospective randomised controlled trials will be necessary.

Keywords: Completely portal robotic lobectomy, non-small cell lung cancer, Surgery

P2.16-38 CHARACTERISTICS OF PREOPERATIVE N STAGING IN PATIENTS WITH OPTIMAL PATHOLOGIC N STAGING OF NON SMALL CELL LUNG CANCER(NSCLC)

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Background: Despite its prognostic value, the thoroughness of clinical and pathologic nodal staging varies significantly. We compared anatomic preoperative nodal sampling details to anatomic surgical lymphadenectomy details in resections meeting National Comprehensive Cancer Network (NCCN) quality criteria. **Method:** Patients had curative-intent NSCLC resections between 2009-2018 in 12 hospitals in 4 contiguous Dartmouth Hospital Referral Regions in the mid-Southern USA. Univariate statistics were calculated to summarize characteristics. **Result:** 1,346 of 3,297 resections (40.8%), met all 4 NCCN criteria (anatomic resection, negative margins, examination of >0 N1 nodes and ≥3 mediastinal stations). Of these 1,346, 1,114 (83%) received PET/CT scans and 148 (11%) received invasive nodal staging (all had EBUS/EUS/TBNA; 10 [16%] also had mediastinoscopy). Among 148 invasively staged patients, 72% were histologically node-negative, 19% were node-positive; 34 (23%) were down-staged and 20 (13.5%) were up-staged after surgery. Stations 4 (70.3%), 7 (73.6%), and 10 (33.8) were most frequently sampled preoperatively, 4, 7 and 9 intraoperatively (Table 2). Except for station 7, there was little overlap in anatomic station examination between invasive clinical and pathologic nodal staging.

Table 1. Preoperative characteristics among those patient with NCCN quality resections.

Variables	NCCN Met N (%)
N	1346 (40.8)
PET/CT scan	1114 (83)
Invasive staging	148 (11)
EBUS/EUS/TBNA	148 (100)
Mediastinoscopy	10 (16)
Results of invasive staging (n=148)	
Conclusive, benign	106 (72)
Conclusive, malignant	28 (19)
Inconclusive/Results not found	14 (9)
Clinical* to pathologic N category change among those receiving invasive staging (n=148)	
Up-stage	20 (13.5)
No Change	94 (63.5)
Down-stage	34 (23)

*Clinical stage includes findings on PET/CT scan

Table 2. Sampling information during invasive staging and surgical resections.

	Sampled during invasive staging N=148 (100%)	Sampled during surgery N=148 (100%)	Stations Resampled N (%)	Stations not Resampled N (%)
Stations Sampled				
Station 2L	5 (3.4)	5 (3.4)	2 (1.4)	6 (4.1)
Station 2R	14 (9.5)	57 (38.5)	9 (6.1)	53 (35.8)
Station 3a	4 (2.7)	3 (2)	3 (2)	1 (0.7)
Station 3p	1 (0.7)	2 (1.4)	1 (0.7)	1 (0.7)
Station 4L	66 (44.6)	52 (35.1)	38 (25.7)	42 (28.4)
Station 4R	91 (61.5)	90 (60.8)	66 (44.6)	49 (33.1)
Station 5	7 (4.7)	59 (39.9)	7 (4.7)	52 (35.1)
Station 6	2 (1.4)	43 (29.1)	2 (1.4)	41 (27.7)
Station 7	113 (76.4)	140 (94.6)	109 (73.6)	35 (23.6)
Station 8	3 (2)	94 (63.5)	2 (1.4)	93 (62.8)
Station 9	6 (4.1)	108 (73)	5 (3.4)	104 (70.3)
Station 10R	39 (26.4)	57 (38.5)	20 (13.5)	41 (27.7)
Station 10L	24 (16.2)	81 (54.7)	30 (20.3)	60 (40.5)
N2-NOS	1 (0.7)	24 (16.2)	0 (0)	25 (16.9)
Station 11L	18 (12.2)	7 (4.7)	1 (0.7)	23 (15.5)
Station 11R	21 (14.2)	14 (9.5)	5 (3.4)	25 (16.9)
Station 12L	0 (0)	5 (3.4)	0 (0)	5 (3.4)

Station 12R	1 (0.7)	2 (1.4)	0 (0)	3 (2)
Station 13R	0 (0)	4 (2.7)	0 (0)	4 (2.7)
N1-NOS	0 (0)	103 (69.6)	0 (0)	103 (69.6)

Conclusion: In a pathologic well-staged cohort of NSCLC recipients, invasive clinical nodal staging was infrequently and less-than-thoroughly used.

Keywords: NSCLC, NCCN, Staging

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-39 THE APPLICATION OF 3D MEDICAL IMAGE ANALYZER AND A FLUORESCENCE GUIDED SURGERY FOR PULMONARY SUBLOBAR RESECTION

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Background: The confirmation of an appropriate resection margin from the tumor is crucial for reducing the risk of local recurrence after sublobar resection for lung cancer. Furthermore, the precise anatomical sublobar resection is also important for preserving pulmonary function. We developed the novel operation method for pulmonary sublobar resection. **Method:** From Aug. 2014 to April 2018, 43 primary lung cancers were enrolled. Active limited resection was done in 29 and passive limited resection was done in 14. Preoperatively, each patient underwent computed tomography for creating several virtual sublobar resections by using Volume Analyzer Synapse VINCENT (Fujifilm, Tokyo, Japan). We measured the shortest distance from the tumor to the resection margin in each simulated resection and selected the most appropriate area of sublobar resection based on the adequate resection margin of approximately 2 cm from the tumor. After the simulation, we performed sublobar resection by using an infrared thoracoscopy with transbronchial ICG instillation. Before operation, 10ml of 10-fold diluted ICG with autologous blood and 400ml of air were instilled into each associated subsegmental bronchus. sublobar resection was performed under ICG visualization. **Result:** The types of sublobar resection were subsegmental resection in 3, simple segmentectomy which was defined a simple plane cut surface of pulmonary division in 13, complex segmentectomy which was defined multiple plane cut surfaces of pulmonary division in 10 and extended segmentectomy which was defined segmentectomy with adjacent subsegmental resection in 14 and super deep extended wedge resection in 3. Average number of simulation was 4.3+/-1.5. The shortest distances from the tumor to the resection margin by simulation and an actual measurement were 23.6+/-11.6 mm and 24.6+/-8.6 mm, respectively (p=0.647). Postoperative recurrence was found in 5 cases (distant in 3 and mediastinal or supra-clavicular lymph node in 2) who all underwent passive limited resection. No ipsilateral lung recurrence was found. **Conclusion:** The advantages of this method are applicable to any type of sublobar resection, initial determination of resection area at operation, possible super deep wedge resection without broncho-vascular transection with enough margin, long identification of fluorescence, and indication in case of COPD, IP, reoperation and adhesion. On the other hand, the drawbacks are the necessity of a near infrared thoracoscopy and 3D medical image analyzer, knowledge of precise bronchial anatomy and advanced manipulation skills of bronchoscopy, ununiformity of ICG distribution and distribution of ICG into the adjacent area with the passage of time.

Keywords: fluorescence imaging, three dimension image analysis, sublobar resection

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-40 IMPACT OF PREOPERATIVE PECTORALIS MUSCLE QUANTITY AND DENSITY ON OUTCOME AFTER COMPLETE RESECTION OF NON-SMALL CELL LUNG CANCER

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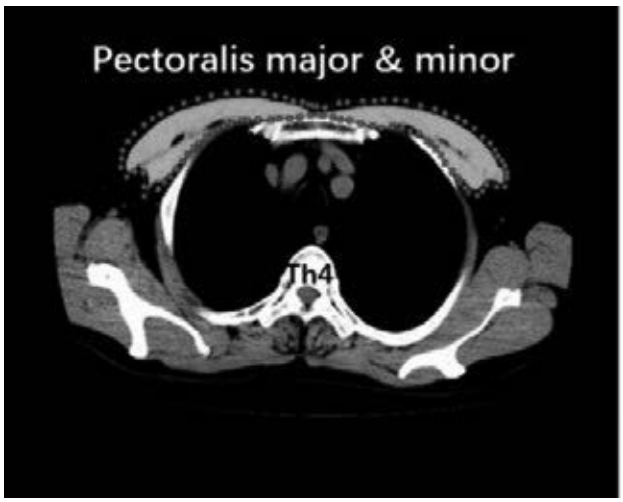
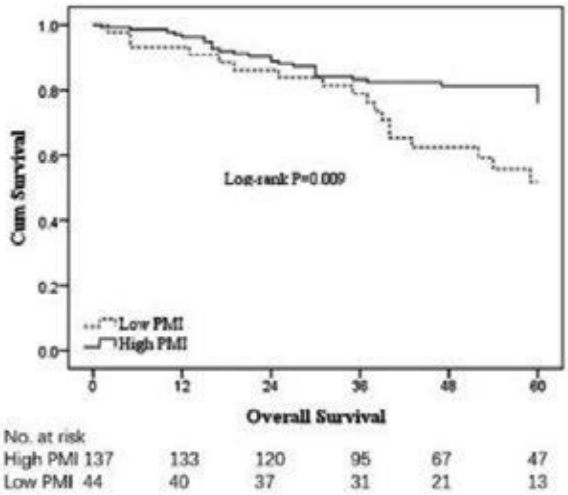
Background: Body composition measures may predict outcomes of cancer surgery. In this study we evaluated the prognostic significance of pectoralis muscle quantity and density in patients with surgical non-small cell lung cancer. **Method:** Preoperative pectoralis muscle quantity and density were retrospectively assessed in 181 patients undergoing lobectomy and lymph node dissection for non-small cell lung cancer from 2009 to 2013. The pectoralis muscle index (cross-sectional area/height^2) and density (average Hounsfield unit, HU) at the fourth thoracic vertebra level were measured and calculated on preoperative plain computed tomography. Overall survival was analyzed between the lowest gender-specific quartile of the pectoralis muscle index and density and the other quartiles. **Result:** Positive correlations between pectoralis muscle index and density and body mass index (BMI) were identified in the cohort (Pearson's r=0.349, p <0.001; r=0.206, p=0.005, respectively). The gender-specific lowest quartile cut-off values of the pectoralis muscle index and density was 10.14cm^2/m^2 and 28.97HU for males, 7.86cm^2/m^2 and 21.23HU for females, respectively. The cumulative five-year overall survival rates were significantly shorter in patients with low pectoralis muscle index (51.7% vs. 76.0%, p=0.009), while for low pectoralis density (66.0% vs. 70.7%, p=0.391). The multivariate analysis including age, smoke index, BMI, c-reactive protein, carcinoembryonic antigen and pathologic stage revealed that the pectoralis muscle index, not the pectoralis density or BMI, was an adverse independent risk factor for overall survival (p=0.002, hazard ratio: 2.815, 95% confidence interval: 1.473–5.377).





Conclusion: A low preoperative pectoralis muscle index was associated with a poor postoperative outcome in surgical patients with non-small cell lung cancer. Pectoralis muscle quantity which is more predictive than density and BMI as a convenient measure, may be included in the preoperative assessment when surgical intervention is considered for non-small cell lung cancer.

Keywords: pectoralis muscle, non-small cell lung cancer, prognostic factor

P2.16-41 INTRAOPERATIVE COMPUTED TOMOGRAPHY AFTER TUMOR MARKING WITH METAL CLIPS FOR NON-PALPABLE LUNG TUMORS

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Background: Locating small, non-palpable lung tumors during video-assisted thoracoscopic surgery (VATS) is difficult. We report a simple method to identify such tumors during VATS, using intraoperative computed tomography (IO-CT). **Method:** From 2015 to 2017, we performed IO-CT scans for patients who preoperatively seemed to have non-palpable lung tumors. We initially tried to locate these tumors by finger palpation through the thoracoscopic ports. IO-CT scans were performed after marking tumors with metal clips. For difficult-to-palpate tumors, tumor marking was based on the anatomical position as follows. First, we estimated the intercostal muscle that could best be used as a marker from preoperative CT. A needle was inserted along the caudal side of the intercostal muscle to make a slight "pin-point" depression in the parietal pleura. Next, under bilateral lung ventilation, the surface of the visceral pleura touching the parietal pleural needle depression was marked by a modern electrosurgical unit in SOFT COAG mode. Under unilateral lung ventilation again, metal clips were used to indicate the SOFT COAG marking. Intraoperative CT scans under bilateral lung ventilation and 3D-CT imaging allowed us to locate the tumor by reference to the clips. We performed wedge resections during VATS, based on the marking clips, using surgical staplers. **Result:** We employed this procedure for a total of 20 tumors in 17 patients, whose mean age was 63.5 years (range: 34–78 years). Of the 20 tumors, 11 were in the right lung and 9 in the left lung; 8 were non-palpable and 12 were palpable; in preoperative CT, 7 were seen as pure ground-glass nodule (GGN) type, 2 were part-solid type, and 11 were pure solid type; pathologically, 10 were primary lung cancers, 7 were metastatic lung cancers and 3 were benign tumors. Mean tumor size was 7.1 mm and mean distance from the pleura was 7.2 mm. All tumors were identified intraoperatively by using IO-CT scans. All tumors were completely resected during VATS, with no intra-postoperative complications. **Conclusion:** IO-CT scans after tumor marking with metal clips during VATS can accurately locate non-palpable small sized lung tumors.

Keywords: Intraoperative CT, Metal clip marking, Non-palpable lung tumors

P2.16-42 STANDARD MEDIASTINOSCOPY VERSUS VIDEO-ASSISTED MEDIASTINOSCOPIC LYMPHADECTOMY IN CLINICAL N1 NON-SMALL CELL LUNG CANCER

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Background: A considerable number of patients with clinical N1 (cN1) non-small cell lung cancer (NSCLC) based on positron emission tomography–computed tomography (PET-CT) imaging have occult mediastinal nodal involvement (N2 disease). We aimed to compare the role of video-assisted mediastinoscopy lymphadenectomy(VAMLA) and standard mediastinoscopy in pre-resectional mediastinal staging in patients with cN1 disease. **Method:** A total of 821 patients with potentially resectable NSCLC seen between January 2004 and November 2016 were included in the study. The preoperative mediastinal staging was accomplished by standard cervical mediastinoscopy or VAMLA in all patients except those with peripheral cT1N0 tumors. Resection via thoracotomy or video-assisted thoracoscopic surgery was performed in patients with no mediastinal lymph node metastasis. A systematic lymph node sampling or systematic lymph node dissection was performed during resectional surgery. Surgical-pathological results were compared with the pathological findings. Primary aim was to compare the sensitivities and accuracies to detect N2 by two methods. **Result:** Out of 85 patients with cN1 on PET-CT, a mediastinal metastasis was disclosed in 29 patients (34.1%). Of 56 patients who underwent VAMLA 24(42.9%) were found to have N2/3 disease, whereas standard mediastinoscopy revealed N2/N3 disease in 7 patients(24.1%)(p=0.029) VAMLA and standard mediastinoscopy had both sensitivities of 85.7% to detect N2 disease(p=1). The NPVs were 87.5% and 85.7% by VAMLA and standard mediastinoscopy respectively(p=0.821). **Conclusion:** VAMLA is more accurate to detect mediastinal nodal disease in operable cN1 lung cancer, and could be used in patients with cN1 NSCLC patients since it discloses N2 disease in an important fraction of patients.

Keywords: Non-small cell lung cancer, resection, N1, VAMLA, mediastinoscopy

P2.16-43 DIABETES IS A NEGATIVE PROGNOSTIC FACTOR IN NON-SMALL CELL LUNG CANCER PATIENTS UNDERGOING RESECTIONAL SURGERY

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Background: During the last decades, lung cancer has been a major health problem as it is one of the leading causes of cancer death among both genders all over the world other than subsaharan Africa. Diabetes mellitus(DM) can also be a possible prognostic factor because it effects similar age groups with non small cell lung cancer(NSCLC). **Method:** A total of 634 patients with resected NSCLC seen between January 2004 and June 2017 were included in the study. The preoperative mediastinal staging was performed by video-assisted cervical mediastinoscopy or video-assisted mediastinoscopic lymphadenectomy in all patients except those with peripheral cT1N0 non-adenocarcinoma tumors. Possible prognostic factors such as presence of diabetes mellitus(DM), gender, age, smoking history, clinical stage, histology and laboratory parameters were recorded. **Result:** A total of 84 patients (13.2%) were found to have DM. The median survival time of patients with or without DM were 33.0 months(95% confidence interval: 26.5-39.5 months) and 127.0 months respectively(p<0.001). T and N factors were found to be prognostic parameters (p<0.001, p=0.01 respectively). When we analyzed only male patients(n=544), DM was found to be highly significantly associated with worse survival (p<0.001). Multivariate Cox analysis showed that absence of DM(p<0.001), absence of nodal metastasis(p=0.007), and lower T factor (p=0.04) were independently good prognostic elements in resected patients. **Conclusion:** We concluded that, presence DM was independently associated with worse survival in lung cancer patients who underwent resectional surgery.

Keywords: Non-small cell lung cancer, resection, older patient, prognosis, diabetes mellitus

P2.16-44 LONG-TERM OUTCOME OF PULMONARY SEGMENTECTOMY FOR C-IA NON-SMALL CELL LUNG CANCER

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Background: Pulmonary segmentectomy is being accepted as a favorable treatment option for small peripheral non-small cell lung cancer (NSCLC) although lobectomy is the standard surgical procedure. The long-term outcome and related issues in remote phase after pulmonary segmentectomy needs to be investigated. **Method:** We retrospectively reviewed 135 and 313 patients with clinical (c-) stage IA NSCLC who underwent segmentectomy (S) or lobectomy (L) from January 2008 to December 2015. Patient characteristics, prognosis, recurrence sites, and occurrence of second primary lung cancer were reviewed and compared between the 2 groups. Segmentectomy was intentionally selected when a target tumor was less than 3cm in diameter and ground-glass predominant. Solid part predominant tumors were also eligible for segmentectomy if its diameter was 2cm or less. Segmentectomy was reluctantly selected instead of lobectomy if patients presented insufficient vital organ function or have other pulmonary lesions which needed to be removed. **Result:** In segmentectomy group, the average age was 68.1± 9.1 and 74 males were included. The solid tumor diameter and consolidation-tumor ratio in the S group were statistically smaller than those in the L group. There were no statistical differences in 5-year overall survival (S: 92.0% vs L: 91.5%) and relapse-free survival (5y-RFS) (S: 87.9% vs L: 84.4%) between the 2groups. The 5-year RFS stratified by clinical T factors in 8th edition showed no statistical differences between the 2 groups. Tumor recurrence occurred in 14 patients (10.4%), including loco-regional in 11 (8.1%) and distant metastasis in 3 (2.2%) patients. Recurrence on the intersegmental plane was developed in 2 patients. Loco-regional recurrence rates were similar in the 2 groups; however, loco-regional recurrence after segmentectomy tended to arise later than

those after lobectomy (median of loco-regional recurrence free survival: 1094 and 512 days). Multi-variate analysis showed that a risk factor for loco-regional recurrence was solid tumor diameter, not segmentectomy. Second primary lung cancer occurred in 7 and 12 patients after segmentectomy and lobectomy, respectively. Additional lung resection including completion lobectomy was applied and showed better outcome than non-surgical treatment. **Conclusion:** The long-term outcome of segmentectomy for selected patients is equivalent to those of lobectomy. However, careful follow-up is mandatory as recurrence and second primary lung cancer can occur in the same lobe after segmentectomy which is avoidable by lobectomy.

Keywords: segmentectomy, lung cancer

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-45 SHOULD PATIENTS WITH STAGE IB NON-SMALL CELL LUNG CANCER RECEIVE ADJUVANT CHEMOTHERAPY?

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Background: There're much controversy over the necessity of adjuvant chemotherapy to stage IB non-small cell lung cancer (NSCLC) . The aim of this study is to compare the efficacy of platinum-based adjuvant chemotherapy for patients with stage IB NSCLC according to the 8th and 7th editions of the TNM staging system who underwent complete surgical resection and systemic mediastinal lymph node dissection. **Method:** Subjects were 569 patients who underwent pulmonary resection for primary NSCLC. Survival characteristics were compared using the 8th and 7th editions of the TNM classification. **Result:** For patients in the observation and adjuvant groups, 5-year overall survival was 76.9% and 83.5%, respectively (p=0.044). In univariate analysis, lymphovascular invasion, TNM stage and performance status (PS) were risk factors for overall survival. In multivariate analysis, TNM stage (hazard ratio=5.808, 95% confidence interval 3.980-8.475, p<0.001), PS (hazard ratio=4.804, 95% confidence interval 3.113-7.413, p<0.001) and adjuvant chemotherapy (hazard ratio=1.565, 95% confidence interval 1.069-2.291, p=0.021) were risk factors for overall survival. Subset analysis showed that for patients with stage IB NSCLC, 5-year overall survival was 87.6% in the observation group (n=265) and 82.4% in the adjuvant group (p=0.021). For patients with stage IIA NSCLC, 5-year overall survival was 48.1% in the observation group and 87.7% in the adjuvant group (p<0.001). For patients with Eastern Cooperative Oncology Group (ECOG) 0, 5-year overall survival was 79.3% in the observation group and 91.6% in the adjuvant group(p=0.001). For patients with ECOG 1, 5-year overall survival was 58.6% in the observation group and 17.2% in the adjuvant group (p=0.021). **Conclusion:** For NSCLC patients with surgically treated, platinum-based adjuvant chemotherapy might result in worse survival than observation alone to stage IB but improve survival to stage IIA. Moreover, patients with good PS (ECOG 0) benefit fromadjuvant chemotherapy.

Keywords: NSCLC, adjuvant chemotherapy, the 8th TNM classification

P2.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.16-46 CLINICAL OUTCOMES AND TREATMENT STRATEGIES OF SARCOMATOID CARCINOMA OF THE LUNG

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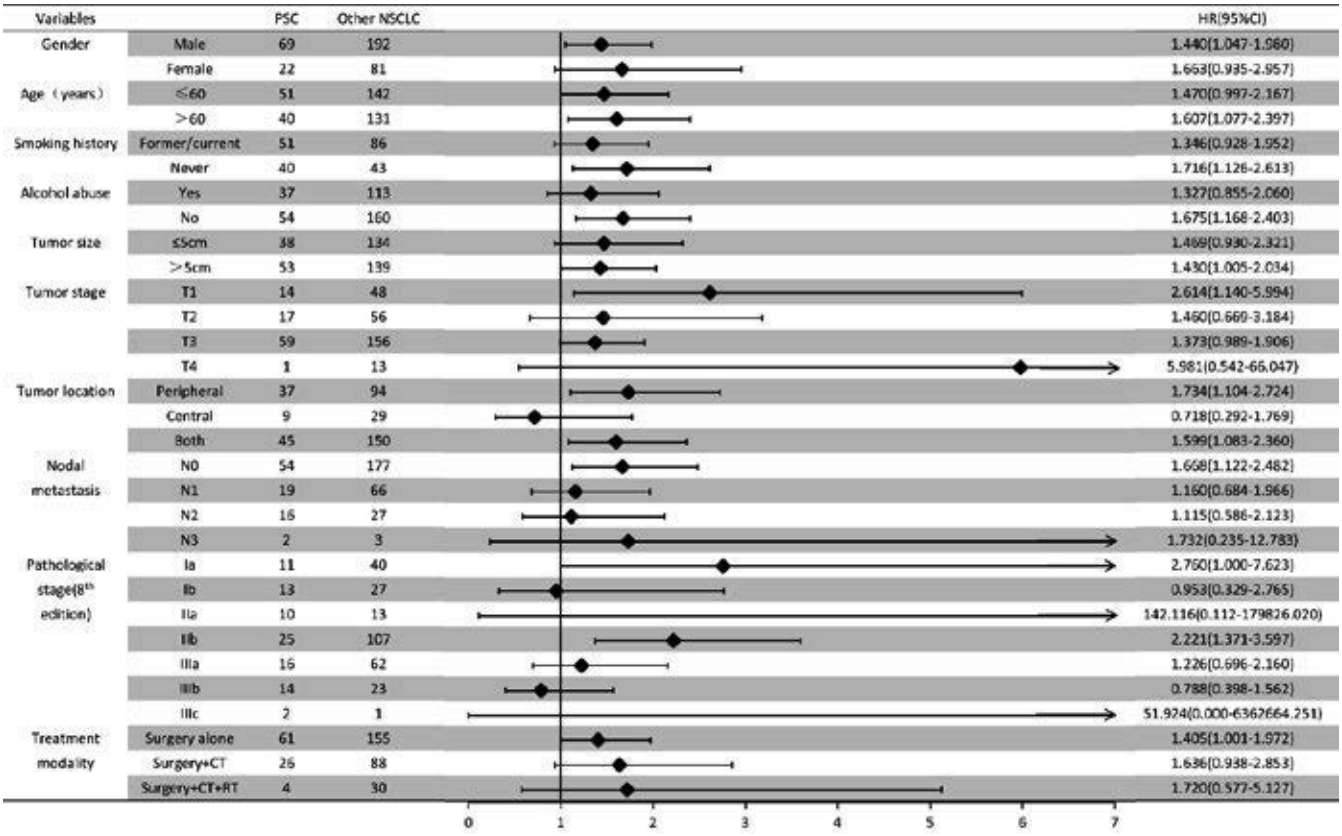
Background: Sarcomatoid carcinoma of the lung is characterized by worse prognosis, and generally felt to be chemo-refractory compared with other non-small cell lung cancer. We conduct this retrospective study to investigate the clinical characteristics of patients with sarcomatoid carcinoma of the lung and determine the optimal treatment strategies. **Method:** We reviewed the medical records of 8176 patients with resected lung cancer in a single high-volume institution between 2008 and 2015. All patients with pathologically diagnosed sarcomatoid carcinoma were evaluated. Clinicopathologic data were analyzed using Kaplan-Meier analysis and Cox regression analysis. Subgroups stratified by pathological stage were analysed to determine the optimal treatment modality. We also conducted subgroup analysis of overall survival among pulmonary sarcomatoid carcinoma and other NSCLC patients. **Result:** Kaplan-Meier and Cox regression analyses showed pathological stage(8th edition)*is the independent prognostic factor(P=0.001, HR=2.601, 95%CI(1.447-4.675)) for pulmonary sarcomatoid carcinoma. Overall survival favored other NSCLC over PSC across subgroups.*



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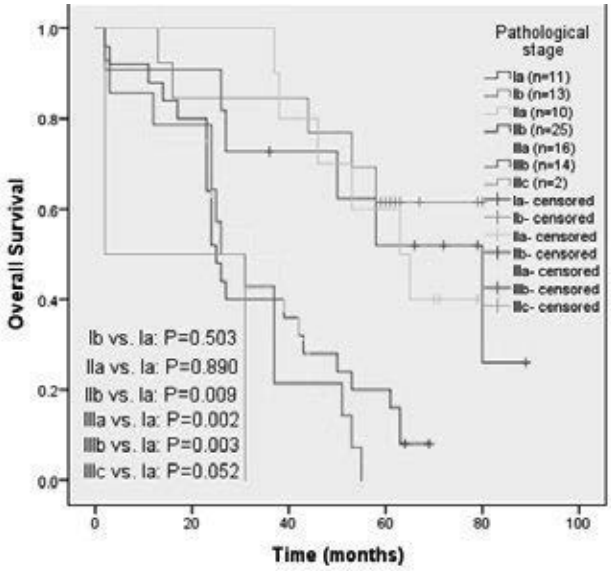
TUESDAY, SEPTEMBER 25, 2018



Conclusion: Pathological stage(8th edition)is independent prognostic factor for sarcomatoid carcinoma of the lung. Surgery followed by adjuvant chemotherapy should be considered for stage I pulmonary sarcomatoid carcinoma. Further prospective studies are needed to confirm these results.

Keywords: Sarcomatoid Carcinoma of the lung, treatment, Prognosis

P2.16-47 "IMPROVED ABVA METHOD" AND "ANTERIOR VAB METHOD" RESULT IN ANALOGOUS SURVIVAL BENEFITS DURING RIGHT UPPER LOBECTOMY

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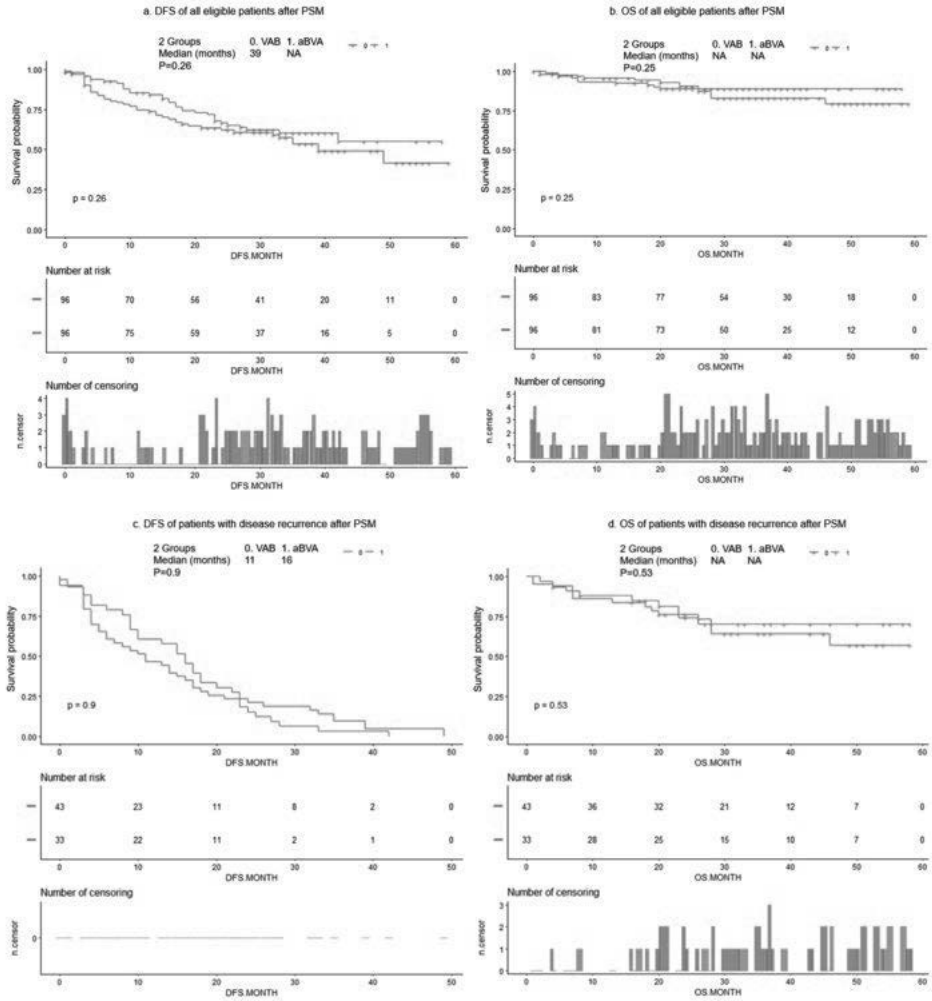
Background: As concluded in recent research, compared with "Anterior VAB Method" (dissecting pulmonary vessels first, followed by the bronchus), "Improved aBVA Method" (dissecting the posterior ascending arterial branch first, followed by the bronchus and vessels) during RUL would promote surgical feasibility and postoperative recovery for lung cancer patients. This study compared their long-term survival benefits basing on propensity score matching (PSM). **Method:** Consecutive lung cancer patients undergoing RUL were grouped into aBVA and VAB groups. PSM was conducted to reduce confounding bias between groups. After PSM, DFS and OS were estimated using the Kaplan–Meier method. **Result:** 397 patients were selected (167 in the aBVA group, and 230 in the VAB group). Before PSM, the histological subtypes, the mean number of dissected lymph node stations, operation time, amount of blood loss, number of used staplers, and the rate of conversion to thoracotomy during the operation, and the rate of pneumothorax and pneumonia, the mean duration of postoperative chest drainage after the operation were not balanced (P<0.05) between two groups. After PSM (caliper=0.02), 96 pairs of patients were successfully matched, and these 9 characters were all balanced (P>0.05) among the two groups. DFS and OS of the two groups were not significantly different (both P > 0.05). The median DFS and OS were comparable for all patients in the two groups (not arrived vs. 39 months, P > 0.05; both not arrived, P > 0.05). DFS and OS among patients with disease recurrence were not significantly different (both P > 0.05). The median DFS and OS were still similar in the two groups (16 vs. 11 months, P > 0.05; both not arrived, P > 0.05).

Conclusion: "aBVA Method" and "VAB Method" result in analogous survival benefits during RUL for lung cancer patients basing on PSM.



POSTER SESSION 2
TUESDAY, SEPTEMBER 25, 2018

P2.16-48 OUTCOMES OF STAGE I LUNG CANCER PATIENTS TREATED WITH SEGMENTECTOMY VIA THREE-DIMENSIONAL UNIPORTAL VATS VERSUS TWO-DIMENSIONAL APPROACH

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Background: Three dimensional uniportal Video-assisted Thoracic Surgery (3D-VATS) segmentectomy is an emerging technique for the surgical resection of early stage lung cancer. There were few reports on its benefits over two dimensional uniportal Video-assisted Thoracic Surgery (2D-VATS) procedure. This study aimed to compare the operative and perioperative data between 2D and 3D-VATS anatomic segmentectomy and to identify the actual role of 3D-VATS in thoracic surgery. **Method:** Between August 2016 and March 2018, a total of 125 consecutive stage I Non-small cell lung cancer (NSCLC) patients who underwent uniportal VATS anatomic segmentectomy in the Department of Thoracic Surgery, Shenyang Chest Hospital, were retrospectively reviewed. Incorporating preoperative clinical features were used to compare the perioperative outcomes and analyze the safety and efficacy of 3D-VATS and 2D-VATS anatomic segmentectomies for stage I NSCLCs. **Result:** There were 64 patients in the 3D-VATS group and 61 patients in the 2D-VATS group from August 2016 and March 2018. During the operation, the anatomic segmentectomy took less time in the 3D-VATS than in the 2D-VATS (81.5±36.7 min vs 105.7±39.4 min, $P< 0.05$) group. The total operation duration, the volume of estimated blood loss (36.5 ± 12.5 ml vs 41.5 ± 18.4 ml, $P= 0.24$), and the length of postoperative hospital stay (4.5 ± 1.6 days vs 5.1 ± 1.9 days, $P= 0.07$) were similar between the two groups. Postoperatively, 3D-VATS and 2D-VATS groups showed similar results in terms of morbidity and mortality. **Conclusion:** In the surgical resection of early-stage non-small cell lung cancer, 3D uniportal VATS anatomic segmentectomy is a safe and effective alternative to the 2D-VATS procedure. Nevertheless, further studies are necessary to better comprehend the role of 3D-VATS in modern thoracic surgery.

Keywords: Three-dimensional, Uniportal Video Assisted Thoracic Surgery, Anatomic segmentectomy

P2.16-49 WHICH NOMOGRAM IS MORE RELIABLE TO PREDICT RECURRENCE OF PATHOLOGICAL STAGE IA LUNG ADENOCARCINOMA TREATED BY SURGERY?

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Background: Previous recurrence risk models offered individualized prediction using a more diverse set of factors than traditional staging measures American Joint Committee on Cancer Tumor Node Metastasis (AJCC TNM) Staging System. Several studies have demonstrated gene mutation as a new prognostic factor, such as EGFR, KRAS and so on. This study aimed to analyze a comprehensive and reliable Nomogram prognostic model to predict recurrence in stage IA lung adenocarcinoma (ADC) with radical resection. **Method:** This was a retrospective, single-center and case-control study. Clinicopathologic, genetic, therapeutic features and survival status were collected. Univariate and multivariate Cox proportional hazards model was conducted. The nomogram for recurrence prediction was developed using Cox proportional hazards regression. Three nomograms were established based on a) AJCC 8th TNM Staging, b) multivariate analysis results and c) risk factors recorded in published references. The higher concordance index (C-index) of model identified better performance of nomogram. **Result:** 1499 patients with pathological stage IA ADC from Cancer Hospital, Chinese Academy of Medical Sciences from October 2012 to December 2015 were enrolled in this study. The recurrence rate was 3.5% (53/1499). No recurrence of 180 patients randomly selected and analyzed in this study. Median DFS was not reached. The C-index of AJCC 8th TNM staging and the nomogram based on multivariate analysis was 0.598 (95% CI 0.538-0.659) and 0.696 (95% CI 0.629- 0.764), respectively. The nomogram established on prognostic factors in previous studies, which included gene mutation such as EGFR, KRAS and ALK, showed higher discrimination with C-index 0.833 (95% CI 0.786-0.880). **Conclusion:** This was the first individualized nomogram combining clinicopathologic features with genetic information to predict recurrence in ADC. The nomogram added with gene mutation status demonstrated superior predictive capability comparing to other nomograms based on traditional AJCC T staging and multivariate analysis. Our nomogram was more reliable to guide prognostic factors and recurrence rate in stage IA ADC patients.

Keywords: stage IA, lung adenocarcinoma, Nomogram

P2.16-50 DO PATIENTS HAVE PRECONCEIVED IDEAS ON VARIOUS SURGICAL APPROACHES? PATIENT PERSPECTIVE: OPEN VS. MINIMALLY INVASIVE SURGERY (PROMIS) SURVEY.

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Background: Patient perspectives on minimally invasive (MIS) versus open surgical approaches have not been well studied. Health care workers often presume that patients prefer MIS. The aim of this survey was to objectively document patient viewpoints on pain, complication risks, cosmesis, travel burden, and functional outcomes throughout the course of treatment. **Method:** From 2012-2017, of the 206 consented patients, 184 lung and esophageal surgical patients were prospectively enrolled in this observational cohort study. Participants were asked to complete a RAND36 short form health survey (SF-36), which measures functional outcomes. They also completed the PROMIS questionnaire, which measures expectations regarding travel burden, pain, complications, and cosmesis on a continuous visual analog scale (VAS). The PROMIS questions were also classified into three anatomic regions (neck, chest, and abdomen). Patients were surveyed pre-operatively, at 1 month and at 6 months. McNemar's test, and paired and independent t-test were used as appropriate. **Result:** Of 206 patients, 184 (89%) completed the survey at least once. SF-36 showed physical functioning, role limitations due to physical health, energy level, pain, and social functioning worsened significantly at 1 month. All indices recovered to baseline at 6 months. Recovery of indices was similar in both MIS and open surgery patients. Patients indicated that pain after surgery (mean VAS = 7.3; 95% CI 6.9-7.6) was more important than size of incision (mean VAS = 4.5; 95% CI 3.9-5.1, $p < 0.001$) and travel burden (mean VAS = 4.0; 95% CI 3.4-4.5, $p < 0.001$). The risk of complications (mean VAS = 7.5; 95% CI 7.2-7.9) was more important than size of incision (mean VAS = 4.5; 95% CI 3.9-5.1, $p < 0.001$) and travel burden (mean VAS = 4.0; 95% CI 3.4-4.5, $p < 0.001$). These findings were similar at each time point and across each body regions. The MIS group perceived pain following surgery (mean VAS = 7.12; 95% CI 6.35-7.89) was more important than the open group though it was not statistically different (mean VAS = 6.02; 95% CI 5.25-6.79, $p = 0.07$). **Conclusion:** Early postoperative deterioration followed by 6-month recovery in functional outcomes was reported by all patients regardless of surgical approach (MIS vs. open). Complication risk and pain after surgery were perceived as more important than size of incisions and distance traveled for treatment. Patients maybe more open-minded to participation in trials comparing MIS to open surgery than expected.

Keywords: minimally invasive vs open surgery, patient perceptions, functional outcome, risks, travel burden, importance

P2.16-51 NATIONWIDE TRENDS IN SURGICAL TREATMENT OF LUNG CANCER IN ESTONIA, 2000-2015

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Background: In last decades several changes have been observed in lung cancer incidence, morphology, diagnostic and treatment options. However, only a few studies have focused on these changes among surgically treated patients. The aim of the current study was to analyse changes in lung cancer surgical treatment, comparing surgically treated patients with all lung cancer patients. **Method:** Data on all surgically treated lung cancer patients in Estonia from January 2000 to December 2015 were obtained from hospitals' medical records. Data on all patients diagnosed with lung cancer in the same period were obtained from the

Estonian Cancer Registry. For analysis the study period was divided into 4-year time periods. **Result:** During the study period 2075 patients (1582 male, 493 female) with mean age 65 (range 10–89) years had been treated surgically in Estonia. The number of patients diagnosed with lung cancer did not change in the 16 years, but proportion of patients treated surgically increased from 13% to 19%. Among surgically treated patients the proportion of women increased from 18% to 31%; while this change among all lung cancer patients was from 20% to 27%. The proportion of younger patients (<60 years) among those treated surgically decreased from 34% to 28%, while the proportion of patients in the oldest age category (>79 years) quadrupled from 2% to 8%; the respective changes among all lung cancer patients were less pronounced. Adenocarcinoma became the most frequent morphological type of surgically treated lung cancer (replacing squamous cell carcinoma), with an increase from 23% to 43%. The proportion of adenocarcinoma was constantly higher among female (compared to male) surgical patients, but the proportion of adenocarcinoma increased among males in all the age groups except >79 years, yet remained stable among females. Lobectomy has been the most common type of lung resection, with an increase from 53% to 76% over the study years. The proportion of pneumonectomy decreased from 28% to 8%. VATS lobectomy was introduced in 2006 and has been applied in an increasing number of cases. In 2015, the VATS approach accounted for 56% of lung resections. **Conclusion:** Although the number lung cancer cases diagnosed in Estonia each year has not changed since 2000, the proportion of patients treated surgically has increased. Among surgical patients, the proportion of women and elderly has increased. Adenocarcinoma has become the most common morphological type of lung cancer. Most importantly, thoracotomy has been gradually replaced by VATS.

Keywords: lung cancer, Surgery, Trends

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-02 CARDIOPULMONARY EXERCISE TESTS IN LUNG CANCER PATIENTS TREATED RADICAL RADIOTHERAPY AND CHEMOTHERAPY – FEASIBILITY STUDY

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Background: Cardiopulmonary exercise testing (CPET) is based on the principle that system failure can be detected when the system is under stress. CPET allows measurement of peak oxygen consumption (peak VO_2), the gold standard measure of exercise performance, and can identify the causes of exercise limitation. Variables measured at CPET can predict mortality in various disease states and is used to assess fitness for surgery. Lung cancer patients often have pre-existing cardiopulmonary disease, however there is limited data on the role of CPET in patients treated with radical radiotherapy (RRT). Recent RTOG 0617 study reported worse survival with RRT dose escalation, which was attributed to cardiopulmonary toxicity. This study aimed to investigate the feasibility of using CPET to study the effects of RRT on exercise capacity and to assess its cardiac and pulmonary components. **Method:** During the period 2003 – 2009, NSCLC patients undergoing RRT consented to participate in this prospective study. Alongside standard incremental CPETs, patients were assessed with pulmonary function tests and standardized measure of activity of daily living, the London Chest Activity of Daily Living scale (LCADL) at four different time points: pre-RRT and at 6 weeks, 6 months and 12 months post RRT. **Result:** Thirty-eight patients participated. Median age was 66 years, and Karnofsky Performance Status >70. Using TNM 5th Edition, staging was T1-2/T3-4 = 50%/50%, N0-X/N1-2 = 50%/50% and M0/1 = 92%/8%. Planned RRT was completed by 34 pts. Over the 12 months the peak VO_2 (l/min) decreased ($p_{overall}$ = 0.009) from a median 0.83 by a maximum of 0.12 at 6 m, thus demonstrating a decline in exercise performance. The V_E/CO_{2AT} increased ($p_{overall}$ = 0.005) post RT from a median 40, most clearly at 3 months (5, p=.028). Furthermore peak alveolar-arterial (A-a) gradient increased ($p_{overall}$ =.001) from a baseline median value of 38.5 at 6w (3.15, p=.046) and 3m (5.75, p=.013) respectively. These results indicate a decline in ventilatory efficiency following RRT. No significant changes were seen in oxygen pulse, a surrogate measure of cardiac function. LCADL completion reduced after 6w. The median baseline score was 22 and a statistically significant difference could not be detected over time ($p_{overall}$ = 0.502) **Conclusion:** The results indicate that CPET is able to detect a decline in exercise performance after RRT and that in this study the decline appears to be driven by a reduction in respiratory function. These results require confirmation in a larger study.

Keywords: chemo-radiation, Cardiopulmonary toxicity, Cardiopulmonary Exercise Test

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-03 A PROPENSITY-MATCHED ANALYSIS OF NEOADJUVANT CHEMORADIOTHERAPY AND ADJUVANT CHEMORADIOTHERAPY FOR IIIA(N2) NON-SMALL CELL LUNG CANCER

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Background: Multidisciplinary treatment is the preferred treatment for patients with IIIA(N2) non-small cell lung cancer (NSCLC). A subset of patients with potentially resectable of this disease are managed with trimodality therapy (surgery combined with chemoradiotherapy). However, little data exist to guide which one is better between neoadjuvant chemoradiation followed by surgery and surgery followed by adjuvant chemoradiotherapy. Given that prospective comparative data on these two managements are limited, we compared the two treatments with a propensity-matched analysis. **Method:** All patients undergoing treatment with trimodality therapy for clinical IIIA(N2) NSCLC between January 2012 and December 2016 were reviewed. Patients received individual chemotherapy (regimens depending on the different pathological types: squamous cell carcinoma: Docetaxel 30mg/m^2 d1,d8, Cisplatines 25mg/m^2 d1-3, repeated every 3 weeks for 2 cycles; non-squamous cell carcinoma: Pemetrexed 500mg/m^2 d1, Cisplatin 25mg/

m² d1-3, repeated every 3 weeks for 2 cycles) plus radiotherapy (46-50 Gy/23-25 fractions) at preoperation or postoperation. Age, gender, tumor characteristics, pathological types, pulmonary function, disease-free survival (DFS), overall survival (OS) data were collected. A propensity-matched analysis was performed. **Result:** *A total of 31 patients underwent neoadjuvant chemoradiation followed by surgery, and 82 received surgery followed by adjuvant chemoradiotherapy. Median follow-up was 27 months. For the entire cohort, the median OS and DFS in neoadjuvant chemoradiation followed by surgery group was 24.0 months (95%CI*: 17.1~29.2) and 16.6 months (95%CI: 10.9~21.5), which is shorter than 30.6 months (95%CI: 20.9~39.5) and 19.3months (95%CI: *11.4~25.7) in surgery followed by adjuvant chemoradiotherapy group (P=0.048 and P=0.037). A propensity matched comparison in a blinded manner (1:1 ratio, caliper distance=0.005) based on age, gender, WHO performance status, pulmonary function (forced expiratory volume in 1 second [FEV1] % and FEV1), pathological types, number of mediastinal lymph nodes and T stage resulted in 22 matched pairs. There were no significant differences between neoadjuvant chemoradiation followed by surgery and surgery followed by adjuvant chemoradiotherapy groups in the median OS (25.3 Vs. 25.0 months, P=0.747) and DFS (16.9 Vs. 17.4 months, P=0.941) respectively. Toxicities associated with chemoradiotherapy and death related with treatments were similar in both groups.* **Conclusion:** *This propensity-matched analysis found multidisciplinary treatment remains a suitable option for a subset of patients with IIIA(N2) disease. Upfront surgery without invasive staging, followed by adjuvant chemoradiotherapy, appears reasonable in resectable N2 disease, simplifying patient care and reducing cost. Participation in clinical trials is essential to define the indications and efficacy in a selected population.*

Keywords: IIIA(N2) non-small cell lung cancer, adjuvant chemoradiotherapy, neoadjuvant chemoradiotherapy

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-04 IMIQUIMOD ATTENUATES RADIATION-INDUCED PULMONARY FIBROSIS

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Background: Radiation-induced lung injury (RILI) is a major dose limiting factor during thoracic irradiation. Imiquimod (I) stimulates the innate and adaptive immune pathways and induces cytokine production.We aimed to evaluate the impact of I RILI. **Method:** Sixty rats were divided into 6 groups: Group (G) 1 control, G2 radiotherapy (RT) only, G3 and G4 5 and 10 mg/kg I; G5 and G6 RT plus 5 and 10 mg/kg I groups respectively. A single dose of 15 Gy RT was given to lungs. I was applied intraperitoneally with daily doses, until animals were sacrificed 6 and 16 weeks after RT. Lung tissues were dissected for light and electron microscopy. **Result:** The inflammation, fibrosis and transforming growth factor (TGF)-β scores of study groups were significantly different at 6th and 16th week of RT (p< 0.001 for all). At 6th week of RT, pair-wise comparisons revealed that inflammation, fibrosis and TGF- β scores of did not different in both RT and non-RT groups. By 16th week of RT inflammation, fibrosis and TGF- β scores were significantly different between G2 and G5 (p values were 0.033, 0.041, and <0.001 respectively), and G2 and G6 (p values were 0.043, 0.002, and <0.001 respectively). By 16th week, there were vacuoles in alveolar epithelial cells and inter/pericellular edema in all RT groups. The vacuoles were larger and the intercellular edema was more prominent in G2 than both G5 and G6; however there weren't any difference between G5 and G6. **Conclusion:** Although I did not improve pneumonitis phase, I attenuated radiation-induced lung fibrosis.

Keywords: Imiquimod, Fibrosis, Radiotherapy

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-05 CONSOLIDATION CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER AFTER CONCURRENT CHEMORADIOTHERAPY

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Background: The effect of consolidation chemotherapy after concurrent chemoradiotherapy (CRT) is controversial in patients with locally advanced non-small cell lung cancer (NSCLC). In this study we aimed to compare the impact of consolidation chemotherapy after concurrent CRT and concurrent CRT alone on survival outcome and safety in patients with locally advanced NSCLC. **Method:** We retrospectively analyzed 136 patients with unresected locally advanced NSCLC that received consolidation chemotherapy after concurrent CRT and concurrent CRT alone between October 2009 and March 2018, in a single center. The groups were compared regarding overall survival (os), progression-free survival (pfs) and toxicities. **Result:** In our study, 120 patients were (88.2%) male and the median age was 63 (42-82). The most seen histologic types of tumor was squamous cell cancer (SCC- 63.2%). Among 136 patients; 77 patients (56.6%) received consolidation chemotherapy after concurrent CRT, 59 (43.4%) patients received concurrent CRT alone. The median PFS was 12.8 months and the median OS was 25.2 months for all patients. The median PFS was 12.8 months and 12.3 months for consolidation group and concurrent CRT group, respectively (p=0.80). The median OS was 23.6 months and 27 months for consolidation group and concurrent CRT group, respectively (p=0.84). There was no significant difference between two groups regarding PFS or OS. Considering all the patients, there was no grade 3-4 toxicities excluding cytopenia. We reported the toxicities that nausea (77.2%), vomiting (76.5%), fatique (81.6%), mucositis (28.7%), stomatitis (18.1%), neuropathy (27.2%), neutropenia (39.7%), trombocytopenia (% 9.6), anemia (24.3%), febrile neutropenia (5.9%), When we compare two groups regarding treatment-related toxicities, there was no significant difference between two goups. **Conclusion:** In the present study, our results revealed that the patients treated with consolidation chemotherapy after concurrent CRT had no better outcomes than treated with concurrent CRT alone.

Keywords: locally advanced, non-small cell lung cancer, consolidation chemotherapy

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-06 FUNCTIONAL LUNG IMAGING IN RADIOTHERAPY FOR LUNG CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Advanced imaging techniques allow functional lung information to be derived and integrated into treatment planning. A prospectively registered systematic review was conducted to: i) assess pre-treatment functional dose metrics as predictors of radiation pneumonitis, ii) evaluate dose response relationships, iii) assess potential utility in radiotherapy treatment planning. **Method:** A structured search was performed for publications including key words for functional imaging, lung cancer and radiotherapy following PRISMA guidelines. Publications were required to have majority of the patients with lung cancer, age over 18, published in a peer reviewed journal and describe a radiotherapy application. Review articles and technical descriptions of functional imaging techniques were excluded. Studies with less than 10 patients were excluded from the meta-analysis. Literature searches were conducted in October 2017 in 3 electronic databases: Ovid Medline, Ovid EMBASE and Cochrane CENTRAL via the Wiley platform. The date of coverage was restricted to 1990 onwards and searches were limited to articles in English only. **Result:** 814 articles were screened against the review criteria: 158 publications were selected for full text review, of these 114 met criteria. The most commonly used investigations were SPECT (64 publications), CT (44), MRI (12) and PET (5). Ten publications evaluated pre-treatment functional lung dose-metrics as a predictor of radiation pneumonitis, 7 of these found that functional V20 and/or functional MLD correlate with the risk of clinically significant radiation pneumonitis. 6 studies comparing differences between functional and

anatomical dose metrics at predicting radiation pneumonitis found higher predictive values using functional dose metrics. Twenty one studies described a dose-response relationship on post-treatment functional lung imaging. Dose-response curves were provided in 5 papers with a majority of these curves exhibiting a sigmoid shape and two curves showing a threshold dose between of 40-50Gy. 9 studies described the phenomenon of reperfusion post radiotherapy. Nineteen planning studies demonstrated the ability of functional lung optimized planning techniques to spare regions of functional lung. Meta-analysis of these studies found that mean (95% CI) functional volume receiving 20Gy was reduced by 4.19% [2.34; 6.04] and mean lung dose by 2.18Gy [1.09; 3.26] when plans were optimized to spare functional lung. **Conclusion:** There is significant heterogeneity identified in imaging techniques, definitions of functional lung and in the reporting of available studies. Whilst the current literature suggests possible correlations with dose to functional lung and clinical toxicity and the utility of functionally adapted radiotherapy delivery, there is a need for prospective interventional trials with clinical endpoints as outcome measures.

Keywords: functional imaging, Systematic review, Radiotherapy

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-07 CONCURRENT CHEMORADIOTHERAPY (CONCRT) USING CISPLATIN-VINORELBINE IN LOCALLY ADVANCED (LA) NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: We adopted ConCRT with cisplatin and vinorelbine as our standard of care for patients with LA NSCLC since 2005. This is an analysis of a register of all patients consecutively assigned ConCRT since 2005 in an intent to treat analysis. **Method:** From Feb 2005 to Dec 2015 we assigned ConCRT for 77 consecutive patients with LA NSCLC, who were deemed unresectable; this included T4/N3/ "bulky" N2 disease or locally recurrent disease after initial surgery. Patients had ECOG performance status 0-2 and were treated with Cisplatin 75mg/m2 d1 and Vinorelbine 30mg/m2 d1-8, 3-weekly during the induction chemotherapy phase (i.e. full doses for the first 1-2 cycles) whilst with the addition of radical RT, Vinorelbine was reduced to 12.5mg/m2 d1-8. After ensuring acceptable toxicity with the first 11 patients treated, subsequent patients received Vinorelbine at 15mg/m2 d1-8 during ConCRT and the number of treatment cycles was escalated to a maximum of 6. Patients received definitive CRT (59.4-64.8 Gy) unless surgery was planned, in which case restaging evaluation for potentially resectable patients was performed at 45-50.4 Gy. PET staging was only available since 2011. **Result:** 77 patients: 69 men and 8 women. Median age was 63 (43-81); PS 0-1 n=69, PS 2 n=8. Radiological stage IIIB n=40 (52%), IIIA n=30 (39%), IIB n=7 (9%). Histology, squamous n=42, adenocarcinoma n=21, other NSCLC n=14. Treatment delivered: median 4 cycles (range 1-6). 71 patients (92%) completed ConCRT. Overall response rate 70% (49 partial and 5 complete responses), stable disease n=7, progressive disease n=8; of the remaining 8 non-evaluable patients, 6 patients did not complete ConCRT, either due to toxicity/death or disease progression. 11 patients who received ConCRT underwent surgery (6 lobectomies, 5 pneumonectomies). 6 of these 11 patients had a complete pathologic response (pCR). Median progression-free survival (PFS) 14.4 months (C.I. 9.0-19.8) and median overall survival (OS) 23.8 months (C.I. 17.2-30.4). Five year OS rate was 28.2%. There were 2 toxic deaths from neutropaenic sepsis during concurrent CRT and one after surgery. The incidence of grade 3-4 oesophagitis or pneumonitis was < 10% and manageable. **Conclusion:** This regimen has produced encouraging results with a 23.8 month median OS in a patient cohort with predominantly IIIB disease and with a significant minority of poor PS=2 patients, with 92% being able to complete the treatment. Finally 8% of patients had pathological pCR, with 28% of patients treated achieving long-term survival.

Keywords: chemoradiation, vinorelbine, Cisplatin

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-08 HEART MOTION IN LUNG RADIOTHERAPY: HOW REPRESENTATIVE ARE DELINEATIONS BASED ON 3DCT, AVERAGE AND MAXIMUM PROJECTION SCANS?

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Background: Evidence is emerging that the heart is more radiosensitive than previously assumed [1-2]. However, only delineations on the average projection or 3D CT scans are used for treatment planning. Therefore the motion of this organ due to respiration and contraction is not accounted for. In this pilot study, we assessed how representative the delineations based on the 3D CT scan, average (AVG) and maximum intensity projections (MIP) are. **Method:** Both 3D and 4D CT scans for 7 lung cancer patients treated by SABR were used in this study. Median delineations, derived from 3 independent observers following a previously agreed protocol, were calculated on the 3D CT, AVG, MIP and 25% exhale scans. Delineations on each 4D phase scan (n=8) were created by propagating the median 25% exhale contours using RayStation v5.99. The volume representing the maximum extent of motion was estimated as the union of all 4D phase delineations (U4D). Surface distances from the U4D to 3D, AVG, MIP volumes were calculated. Distances in the most extreme surface points (1cm most superior/inferior, 10% most right/left/anterior/posterior) are reported. **Result:** Figure 1 shows the distances for the most extreme surface points, for all patients and for each delineation. Patterns vary widely among patients. From the three delineations, MIP is the 'closest' to the maximum extent of motion, followed by AVG and 3D.

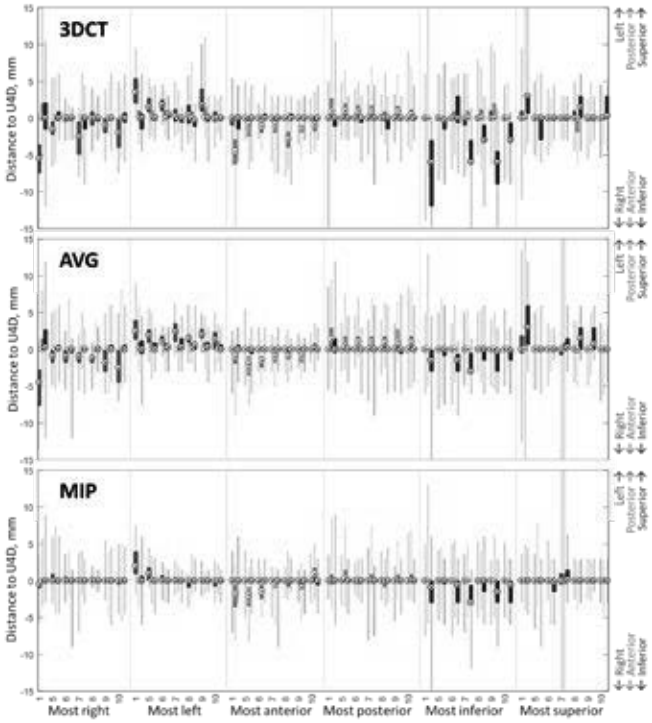

Figure 1. Box plot reporting the distances from the maximum extent of motion volume, U4D, to the 3D/AVG/MIP volumes, discriminated by direction: Right-Left (in red), Anterior-Posterior (in green) and Inferior-Superior (in blue).

Conclusion: None of the delineations represented the heart's maximum extent of motion for all patients, the MIP being the 'most representative' volume. All delineations would require an expansion to include all motion. Research including dosimetry measurements and inter-observer variability is required to determine the relevance of expanding the original delineations, and the corresponding margin magnitudes. [1] Johnson et al. Radiotherapy & Oncology. 2018. Volume 127:S170-1

[2] Wang et al. J Clin Oncol. 2017. 35(13):1387-94.

Keywords: Delineation, Radiotherapy, Heart motion

P2.17-09 EXPLORING THE IMPACT OF AGE ON THE EFFICACY OF ADJUVANT CHEMOTHERAPY AFTER RADICAL RESECTION IN NON-SMALL CELL LUNG CANCER

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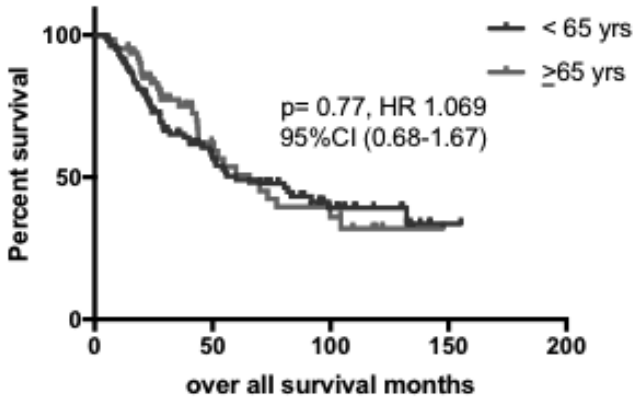
Background: Most adults diagnosed with Non Small Cell Lung Cancer (NSCLC) are over 65 years old. For those with resectable disease postoperative cisplatin-based chemotherapy (PC) has been shown to offer a significant survival advantage. However elderly patients are poorly represented in clinical trial cohorts, here we shall explore our regional experience of treating these patients. **Method:** Patients receiving PC with Vinorelbine 25mg/m^2, D1 & 8/ Cisplatin 75mg/m^2 (VC) following surgery for NSCLC between January 2004 and April 2017 were identified from the electronic computer database. Patients with synchronous tumours or metastatic disease were excluded. **Result:** 165 patients were identified, 63 (38%) ≥65yrs (range 65-77yrs). All were ECOG PS 0-1. 12 patients had Stage 1B disease (7 ≥65yrs), 63 Stage II A (20 ≥65yrs), 40 Stage IIB (21 >65yrs) and 50 Stage IIIA/B disease (17 >65yrs). 53.9% of patients ≥ 65yrs compared to 81% patients < 65yrs completed 4 cycles of PC.19% of patients required dose reductions due to toxicity, 12 were over 65yrs. Grade 3/4 neutropenia occurred in 21.2% of patients (18<65yrs vs. 17 ≥65 yrs) and febrile neutropenia in 9 patients ≥ 65yrs vs. 11<65yrs. No toxic deaths were recorded. Overall 85 (51.5%) patients, 26 ≥65yrs had radiological evidence of disease recurrence. The median time to recurrence was 26.19 months, no significant difference was found in time to relapse based on age (p=0.21). Kaplan Meyer analysis revealed no significant difference in overall survival based on age (p=0.77, HR1.069 95%CI 0.68-1.67). Mortality 6 months post chemotherapy in patients ≥ 65yrs was 1.58% vs. 2.94% inpatients < 65yrs.



Conclusion: This illustrates in routine practice, PC using VC is deliverable in older patients of good PS with resected NSCLC. Though they may experience more toxicity from PC the benefits in terms of disease recurrence and overall survival were equivalent to patients <65yrs.

Keywords: NSCLC, age, adjuvant chemotherapy

P2.17-10 DAILY LOW-DOSE CISPLATIN AND HIGH DOSE RADIOTHERAPY FOR ELDERLY PATIENTS WITH STAGE III NSCLC IS WELL TOLERATED.

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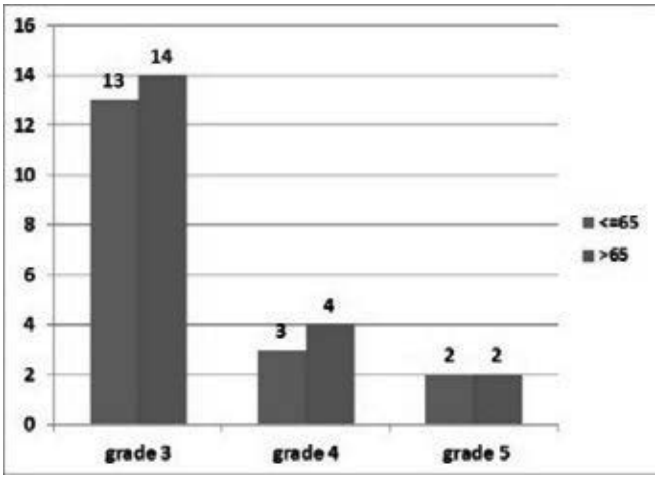
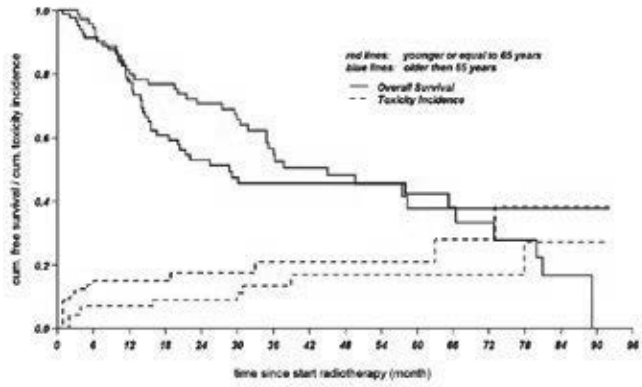
Background: To assess how daily low-dose Cisplatin(6mg/m^2) combined with 66 Gy/24 fractions is tolerated by the elderly patient with stage III NSCLC. **Method:** All patients with stage III NSCLC were selected (2005-2015). The Cox regression model was used to investigate the difference between the younger and elderly patient group concerning toxicity and survival. The Kaplan Meier method was used to show the difference between the dichotomized age factor. **Result:** The crude incidence of severe toxicity (STI) (grade 3-5) was 15% in patients ≤65 years (n=73) and 16% in patients >65 years (n=81)(Fig1). The median time to appearance of STI after treatment was 4 months. Age was a continuous variable in the Cox regression model. The p-value of age was 0.9 (HR=1.002,95%CI:0.968 –1.038) in univariate analysis and 0.4 (HR=1.02,95%CI:0.976–1.063) in multivariate analysis.The univariate analysis with factor age on overall survival showed a p-value of 0.2 (HR=1.01,95%CI:0.99-1.034) and in multivariate analysis a p-value of 0.06 (HR=1.02,95%CI:1.0-1.048) among other prognostic factors. Median follow-up was 31 months for patients ≤65 years and 16 months for patients >65 years(Fig2).





Conclusion: Daily low-dose cisplatin and high dose radiotherapy in stage III NSCLC is as tolerable for both young and older patients resulting in similar toxicity and overall survival.

Keywords: CCRT, NSCLC, elderly

P2.17-11 IMPACT OF QUANTITATIVELY ASSESSED EMPHYSEMA ON CHEST TUBE DRAINAGE AFTER LOBECTOMY FOR NON-SMALL CELL LUNG CANCER

T. Gil[1], Z. Grochowski[1], J. Warmus[1], K. Bederski[1], P. Kocoń[1], J. Włodarczyk[1], Ł. Trybalski[1], T. Smęder[1], K. Żanowska[1], P. Hajder[2], B. Kołodziejczyk[1], W. Cieślak[1], J. Kużdżał[1], R. Banyś[1]

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Background: After pulmonary resections, one or two chest tubes are used, and the choice is based mainly on local habits rather than on evidence. The aim of the study was to evaluate the impact of quantitatively assessed emphysema on chest drainage using one or two tubes in patients with non-small cell lung cancer (NSCLC). **Method:** Single-centre, prospective randomized trial including patients who underwent lobectomy for NSCLC between February 2016 and December 2017. At the end of the operation, patients were randomized in a 1:1 ratio to the single tube group or to the two tubes group. On the day of surgery, controlled suction of -20 cm H2O was used, switched on the 1st postoperative day to -8 cm H2O. Amount and duration of air leak, chest

tube output and differential pleural pressure were recorded using digital chest drainage system. Prolonged air leak was defined as leak lasting >72 h. Chest tubes were removed in the absence of air leak for more than 24 hours, and the chest tube output <250 mL/day. Quantitative analysis of emphysema was performed using the syngo CT. 3D Pulmo software. **Result:** There were 160 patients enrolled, including 100 men, mean age 65.15 years (range: 32-83) and 60 women, mean age 64.58 years (range: 24-81). One chest tube was used in 82 patients, including 52 cases of VATS lobectomy and 108 cases of open lobectomy. Two chest tubes were used in 78 patients, including 22 patients after VATS lobectomy and 56 after open lobectomy. Quantitative assessment of emphysema was performed in a CT study in 160 patients via an assessment evaluation index. In the single chest tube group there was significantly less air leak in first six hours (124.26 vs. 257.1mL/min; p = 0.01),volume of chest tube output (241.08 vs 345.82 mL; p = 0.000015), and differential in first six hours pleural pressure (2.55 vs 3.14 cm H20); p = 0.041. Multivariate regression analysis has shown significant effect of lung volume (dV) (p = 0.007) and mean lung density (dMLD) (p = 0.012) for prolonged air leak in the single chest tube group. In two chest tube group, a significant impact of lung volume (p = 0.002) on the volume of chest tube output was found. **Conclusion:** Emphysema and lung volume affect the prolonged air leak following lung resection.

Keywords: Lung cancer, digital chest drainage system, chest tube, air leak, pulmonary lobectomy, syngo CT. Pu

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
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P2.17-12 ELIMINATING RADIATION RESISTANCE OF NON-SMALL CELL LUNG CANCER BY DHA TROUGH ABROGATING IMMUNITY ESCAPING VIA INHIBITING PD-L1 EXPRESSION

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Background: Lung cancer is a highly immune-suppressing malignancy with numerous methods to evade antitumor immune responses, including deficiencies in antigen processing and presentation, release of immunomodulatory cytokines, and inhibition of T cell activation. Our previous research also demonstrate that radiation can induce a local inflammatory response and simultaneously induce programmed death ligand 1 (PD-L1) expression that attenuate the sensitivity of radiation response in NSCLC. Current data have implicated that the molecular mechanisms by which DHA functions as radiosensitizer are varied, such as inducing apoptosis, extracellular signal-regulated protein kinases 1/2 (Erk1/2) activity, nuclear factor-kappa-B (NF-KB), and so on. However, there is no research about the immunity system alterations after the treatment of DHA plus radiation.In the present study, we demonstrate that combined DHA and radiotherapy synergistically enhances the anti-tumor effect by inhibiting the expression of PD-L1, eradicating the local accumulation of tumor-infiltrating regulatory T cells (iTregs) and myeloid-derived suppressor cells (MDSCs) and stimulating CD8+ T cell infiltration in the tumor microenvironment. Furthermore, DHA may also through inhibiting TGF-β, p-AKT and p-STAT3 pathways, epithelial-mesenchymal transition (EMT) process, facilitating apoptosis, and regulating TRIM21 to induce the synergistic anti-tumor effect. **Method:** Radiation resistance cell lines (A549/X) was induced from A549 by conventionally fractionated radiation. The relationship between PD-L1 expression and the radiation resistance and the immune cell was investigated by immunohistochemistry (IHC) and western blot in vitro and vivo. Apoptosis was evaluated by flow cytometry. The signaling pathway proteins, epithelial-mesenchymal transition (EMT)-related protein were analyzed by western blot. **Result:** PD-L1 was up-regulated after radiation in vivo and vitro. Concomitant with radiation-mediated tumor regression, combined DHA and radiotherapy synergistically enhances the anti-tumor effect by inhibiting the expression of PD-L1. DHA plus radiotherapy also reduced the local accumulation of tumor-infiltrating regulatory T cells (iTregs) and myeloid-derived suppressor cells (MDSCs) and stimulated CD8+ T cell infiltration in the tumor microenvironment. Furthermore, DHA may also through inhibiting TGF-β, p-AKT and p-STAT3 pathways, epithelial-mesenchymal transition (EMT) process, facilitating apoptosis, and regulating TRIM21 to induce the synergistic anti-tumor effect. **Conclusion:** Our study demonstrated a synergistic anti-tumor effect of DHA in combination with radiation trough abrogating immunity escaping via inhibiting PD-L1 expression, which establish a basis for the rational design of combination therapy of DHA plus radiotherapy in NSCLC.

Keywords: tumor microenvironment, dihydroartemisinin, radiation resistance

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-13 GENOME-WIDE COPY NUMBER ALTERATIONS PROFILING PREDICT EFFICACY OF RESECTED STAGE II-IIIA LUNG ADENOCARCINOMA

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Background: The efficacy of platinum-based adjuvant chemotherapy(PBAC) varies for stage II-IIIA resected lung adenocarcinoma(RLUAD) patients, which necessitates the discovery of new potentially prognostic biomarkers. As a major source of genomic variations driving tumor evolution, somatic copy number alterations(CNAs) screening may identify predictive biomarkers. **Method:** The patterns of CNAs were analyzed by Oncoscan MIP array on formalin fixed paraffin embedded(FFPE) tumor specimens collected from 163 consecutive stage II-IIIA RLUAD patients, 145 out of which received PBAC. **Result:** Among the 163 patients, 91(55.8%) relapsed within three years after surgery. The most frequent aberrations identified were 1q, 5p, 5q, 7p, 8q, 14p, 16p, 17q, 20q for copy number gains and 8p, 9p, 13p, 16q , 18q for losses. GISTIC2 analysis generated 45 amplification peaks and 40 deletion peaks, including some significantly mutated genes *TERT, EGFR, MYC, CCND1, CDK4, MDM2, ERBB2, NKX2-1, CCNE1, CDKN2A,* most of which were consistent with TCGA database. It was found that amplifications of 12p12.1(*CMAS, GOLT1B, GYS2, LDHB, RECQL, ETNK1, IAPP, PYROXD1, KRAS*)and *KDM5A* were associated with worse prognosis in our cohort(table), and validated in 506 LUADs from TCGA. 163 patients could be well classified into 4 groups with significantly different clinical outcomes based on thresholded copy number at reoccurring alteration peaks from GISTIC2 analysis. Among the 145 received PBAC patients, focal amplification of *ERBB2* and deletion of 4q34.3 were found to be specific in relapsed patients compared with unrelapsed patients,This result was validated in an independent 183 cases corhort in Imielinski et al, indicating these two CNAs may contribute to RLUAD recurrence.

Amplifications of 12p12.1 and KDM5A associated with overall survival

Characteristics		Univariate analysis (Amp vs Non-Amp)		Multivariate analysis (Amp vs Non-Amp)	
Genes	Location	HR (95% CI)	p	HR (95% CI)	p
CMAS	12p12.1	1.99 (1.22~3.23)	0.006	2.80 (1.60~4.88)	<0.001
GOLT-1B,GYS2, LDHB, RECQL	12p12.1	1.87 (1.14~3.07)	0.014	2.48 (1.41~4.37)	0.002
ETNK1	12p12.1	1.79 (1.10~2.93)	0.020	2.26 (1.60~3.94)	0.004
IAPP,PY-ROXD1	12p12.1	1.78 (1.07~2.94)	0.025	2.30 (1.30~4.07)	0.004
KRAS	12p12.1	1.74 (1.06~2.84)	0.027	2.14 (1.24~3.71)	0.006
KDM5A	12p13.33	1.67 (1.02~2.74)	0.043	1.88 (1.08~3.26)	0.026

Conclusion: This study suggests that CNAs may be a potential prognostic classifier in RLAUD patients, amplifications of 12p12.1 and *KDM5A* might be prognostic biomarkers for RLUAD , and amplification of *ERBB2* and deletion of 4q34.3 predicted early relapse after PBAC. These novel findings may provide implication for better clinical decision making.

Keywords: FFPE, lung adenocarcinoma, copy number alterations

P2.17-14 HOW SHOULD POSITIVE MARGIN FOR BRONCHIAL STUMPS (R1) BE EVALUATED IN PATIENTS UNDERGOING BRONCHOPLASTY FOR LUNG CANCER?

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Background: Bronchoplasty for lung cancer is a surgical procedure aimed at respiratory function preservation and curability. And it may be performed for tumors exposed in the respiratory tract or tumors with lymph node extranodal invasion. "Surgical margin positive for bronchial stump" in bronchoplasty surgery has both out-of-wall and carcinoma in situ (CIS), but the difference is not detailed. In this study, we clarify how to evaluate bronchial stump in bronchoplasty. **Method:** Of 2221 patients of resected lung cancer performed in our hospital from January 2002 to December 2015, 130 patients (5.8%) underwent pulmonary resection with bronchoplasty. The patient's background and its prognostic factors were examined by using Kaplan-Myer method. In addition, we examined details of microscopic residual disease (R1) of bronchial stump. **Result:** There were 101 males and the median age of patients was 67 years old. 19 cases performed sleeve pneumonectomy and 18 cases performed extended sleeve lobectomy. There were 34 cases of pN0, 49 cases of N1 and 49 cases of N2. 30-day mortality was 2.3% (3cases) and 14 cases were R1 resection. 11 of which were positive for bronchial stump. pN2 and incomplete resection cases were significantly poor prognosis (p=0.03, p=0.009). 5 of the 11 microscopic bronchial stump positive cases were due to CIS and 6 were due to out-of-wall positives. However, among these 11 cases, there was only one case of anastomotic recurrence. And there were no statistical differences, but CIS was often found in long-term surviving cases.**Conclusion:** In cases of pulmonary resection with bronchoplasty, pN2 and incomplete resection are poor prognostic factors. Even in bronchial stump positive cases of incomplete resection, there was only one case of local recurrence. And long-term surviving cases were observed. There are some CISs for long-term survival, but there is no statistical difference because of small cases. Further examination is required.

Keywords: bronchoplasty, R1 resection, bronchial stump

P2.17-15 MEDIASTINOSCOPIC ASSESSMENT OF N2 DISEASE AND OPTIMISATION OF SURGICAL TREATMENT OF N2 DISEASE IN NSCLC

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Background: N2 disease in NSCLC carries a dismal prognosis and is usually considered outside the surgical spectrum. N2 disease however is not a homogenous entity. We propose that careful mediastinoscopic assessment of lymph nodes allows better selection of cases for neoadjuvant chemotherapy and potentially surgery, thereby optimising treatment and survival. **Method:** We conducted a retrospective analysis of a prospectively maintained database of patients who underwent cervical mediastinoscopy for NSCLC from Jan 1st 2010 to Dec 31st 2016. Data was retrieved regarding the number of patients diagnosed as N2, number of stations involved, eventual surgical resection, final histopathology and survival. Treatment decisions were based on institutional protocols - initial mediastinoscopic assessment of resectability and histopathology of mediastinal lymph nodes. No invasive restaging was performed after neoadjuvant therapy **Result:** During the study period 127 patients were diagnosed with N2 disease on staging cervical mediastinoscopy. 51 of these patients eventually underwent surgery after neoadjuvant chemotherapy. The remaining patients were excluded for reasons including bulky unresectable disease, progression on chemotherapy and unsuitability for pulmonary resection. 2/51 patients were found unresectable at surgery and the remaining 49 patients were evaluated in this study. The median age was 56 years (SD - 11.1) and the male/female ratio was 35/14. Adjuvant therapy was decided based on the final histopathology and 23/49 patients received postoperative radiotherapy. Patients were followed up for a median of 27 months (Range - 2 to 71 months). The estimated median overall survival of the whole cohort was 43.26 months. Patients with single station nodal involvement(31) on mediastinoscopy fared better than those with multistation involvement(18), 71.7 months vs 32.3 months, but the difference was not statistically significant (p=0.07). Patients with no residual disease(28) in mediastinal lymph nodes in the final histopathology following neoadjuvant chemotherapy survived longer than those with residual disease(21), 71.7 months vs 43.2 months, however the difference was not statistically significant (p=0.17). 23/26 recurrences were systemic and could be salvaged with chemotherapy. There was only one mediastinum only recurrence. **Conclusion:** Cervical mediastinoscopy and assessment of resectability of mediastinal lymph nodes helps in optimising treatment of N2 disease. Surgery has an important role in a carefully selected subset of patients with N2 disease as a part of multimodality management and provides excellent survival. Patients with multistation lymph nodes and residual lymphadenopathy after chemotherapy also have a reasonable prognosis and if completely resectable and should not be denied surgery.

Keywords: N2 disease, Surgery, cervical mediastinoscopy

P2.17-16 RADICAL EN BLOC RESECTION FOR LUNG CANCER INVADING THE SPINE

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Background: About 30% of patients with non-small cell lung cancer(NSCLC) have locally advanced cancer at the time of presentation. The best local control for resectable tumors is obviously achieved by surgical intervention, provided the resection is complete and respectful of oncologic principles.However,locally advanced NSCLC with vertebral invasion have been considered a contraindication to surgical resection for a long time and thus associated with a poor prognosis. In the present study, we review 11 cases in our 16-year experience with en bloc partial and hemi vertebrectomy for lung cancer invading the spine and report outcome and survival. **Method:** Eleven patients with lung cancers involving the spine who underwent en bloc resection. Ten patients underwent radiation therapy(40Gy, in daily fractions of 1.8 Gy, 5 times per week). Preoperative chemotherapy regimens were as follows. Four patients received 2 cycles of cisplatin(80mg/m2 on day1) plus UFT(400-600mg/m2 daily for 14 days), three patients received 2 cycles of cisplatin(80mg/m2 on day1) plus S-1(60-120mg/m2 daily for 14 days), three patients received 2 cycles of carboplatin(AUC5-6) plus paclitaxel(200mg/m2 on day1), one patient with interstitial pneuminitis received no preoperative chemoradiotherapy.The criteria for resection were(1) a histologic diagnosis of NSCLC; (2) a tumor fixed to the vertebral column;(3) absence of mediastinal nodal involvement; and (4) no distant metastasis. Lobectomy was performed in 11 patients. Hemivertebrectomy was performed in 5 patients, and partial vertebrectomy was performed in 6 patients. The number of resected vertebral bodies was 2 or 3 (2,n=4; 3,n=7). Combined resection of the spine and descending aorta was performed in two patients. **Result:** There was no immediate postoperative mortality. Morbidity was observed in 3 patients, including 1 (27%) complications related to the spinal surgery. The median hospital stay was 30 days. Five patients were alive after a mean follow-up of 112 months (range, 89-132 months). The 1- and 5-year survivals are 64% and 45%, respectively. Two local recurrences were observed.Tumor stage was IIIB in 1 patient, IIIA in 10patients. Surgical nodal status was N0 in 10 patients, N2 in 1 patient. Complete macroscopic and microscopic resection was achieved in 9 (82%) patients. **Conclusion:** Our results suggest that en bloc vertebrectomy for non–small cell lung cancers attached to the spine may be performed with low morbidity, and long-term disease-free survival can be achieved even in patients with T4 invasion of the vertebral body. En block vertebral resection with preoperative chemoradiotherapy is a treatment option for highly selected patients with NSCLC invading the spine.

P2.17-17 MULTIMODAL TREATMENT IN PATHOLOGICALLY CONFIRMED SINGLE-STATION RESECTABLE IIIA-N2 NON-SMALL CELL LUNG CANCER: A SINGLE CENTER EXPERIENCE

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Background: The management of patients with resectable stage IIIA-N2 (7th Edition) non-small cell lung cancer (NSCLC) is controversial. Multimodal treatment with neoadjuvant chemotherapy (CT) and radiotherapy (RT) followed by surgery may be recommended for a selected group of patients. **Method:** We have retrospectively analyzed 21 patients with single-station resectable stage IIIA-N2 NSCLC treated in our center from April 2011 to June 2017. N2 was confirmed by EBUS or mediastinoscopy. Patients received CT with cisplatin (70 mg/m2)/ carboplatin (5AUC) + vinorelbine (25 mg/m2 C1, 15 mg/m2 C2-3) concurrent RT with the 2nd cycle of CT with a total dose of 60Gy. PET-CT and mediastinoscopy was performed after induction treatment, and only those patients with mediastinal downstaging disease were proposed for surgery (lobectomy + systematic lymph node dissection). Kaplan-meier analysis was used to evaluate local control (LC), Overall survival (OS), Cause-specific-survival (CSS) and Disease-free-survival (DFS). **Result:** 13 patients were males (62%) and 8 females (38%), median age was 63 (52-75). Histology was: 10(48%) adenocarcinoma, 6(28%) squamous and 5 (24%) NOS NSCLC. Surgery was not performed in 5 patients (24%): 1 presented progressive disease, 2 had persistent mediastinum disease and 2 were excluded due to comorbidities. No severe postoperative complications were observed in patients who underwent surgery. Table 1 shows the results. With a median follow up of 49 (10-84) months, significant differences in terms of OS (p=0,002) and in CSS (p=0,006) were observed between patients with/without surgery, with no difference in LC and DFS. In patients who underwent surgery, there was a trend to a better LC, OS, CSS, DFS when complete pathological response was achieved.

Conclusion: In patients with pathologically confirmed single-station resectable stage IIIA-N2 NSCLC multimodal treatment with high dose radiotherapy is feasible and with a trend to better outcome in patients with complete pathological response.

Keywords: Neoadjuvant treatment, multimodal treatment, stage III-N2

	Overall		CRT + Surgery		CRT			pathological complete response (pCR)		No pCR		
	2 years	5 years	2 years	5 years	2 years	4 years[2]	ns	2 years	5 years	2 years	5 years	ns
Local control (LC)	94%	77%	93%	75%	100%	100%	ns	88%	74%	100%	80%	ns
overall survival (OS)	89%	79%	100%	88%	40%	40%	P=0,002	100%	100%	100%	66%	ns
cause-specific survival (CSS)	94%	83%	100%	88%	50%	50%	P=0,006	100%	100%	100%	66%	ns
disease free survival (DFS)	8%	64%	80%	64%	80%	80%	ns	88%	74%	66%	50%	p=0,08

Table 1. Results. Green, statistically significant differences. Red, p=0.088.
[2] no further data available at the time.

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-18 A PROGNOSTIC SCORE FOR PATIENTS RECEIVING MULTIMODAL TREATMENT FOR LOCALLY-ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Locally-advanced non-small cell lung cancer (LA-NSCLC) represents a heterogeneous entity, distinct regarding patient- and primary tumor features. Introduction of a simple prognostic score can lead to personalized decision-making in clinical routine. The present study aimed to create a prognostic score for LA-NSCLC patients treated with multimodal therapy. *Patients and methods:* Data were collated on a total of 100 patients treated with curative-intent multimodal therapy for LA-NSCLC (UICC stage III) . Several prognostic factors including gender, age, ECOG performance status, comorbidity, tobacco consumption, atelectasis before irradiation, COPD, emphysema and histology were analyzed for impact on overall survival (OS). Factors showing a significant negative association with OS on univariate analysis were included and scored with one point. A prognostic score was defined by the following 4 subgroups: low risk (0-1 points), medium risk (2 points), high risk (3 points) and very high risk (4-5 points). **Result:** Chemoradiotherapy (CRT) was completed by 96 (96%) patients with a total dose range of 50-70Gy. The absolute majority (81%) was treated with a total dose ≥ 60Gy. Intensity-modulated radiotherapy (IMRT) was delivered in 40 (40%) cases. 10 (10%) patients were treated with radiotherapy alone, 11 (11%) with sequential and 79 (79%) patients with concurrent CRT. 13 (13%) patients underwent surgery after completion of radiotherapy. Median OS for the entire cohort was 20.8 months (95% CI: 16.229–25.371). Impact on overall survival was found for age (negative in >60 vs. ≤60 years, p=0.038), gender (negative in male vs. female, p=0.016), pack years (PY) (negative in >21 PY vs. ≤20 PY, p=0.017), presence of atelectasis before irradiation (negative in yes vs. no, p=0.019) and tumor histology (negative in squamous cell carcinoma and NOS vs. adenocarcinoma, p=0.027). Per definition, 11 (11%), 26 (26%), 37 (37%) and 26 (26%) patients were in the low, medium, high and very high risk subgroups, respectively. Median OS was not reached for those with low risk, was 26.4 for medium, 22.0 for high and 13.7 months for patients with very high risk, respectively (p<0.001). **Conclusion:** The simple prognostic score we developed for patients receiving multimodal treatment for stage III NSCLC may aid physicians in making individual therapeutic decisions and personalizing treatment by defining patients with compromised survival outcomes.

Keywords: prognostic score, LA-NSCLC, Chemoradiotherapy (CRT)

P2.17-21 EFFICACY OF CONCURRENT CARBOPLATIN-PACLITAXEL CHEMORADIOTHERAPY WITH 66 GY FOR ELDERLY PATIENTS WITH STAGE III NON-SMALL CELL LUNG CANCER

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Background: The common radiation dose for concurrent chemoradiotherapy for patients with stage III non-small cell lung cancer (NSCLC) is 60 Gy, however, we performed carboplatin-paclitaxel chemo radiotherapy with 66 Gy for elderly patients and examined whether that is feasible and effective. **Method:** One hundred forty-four lung cancer patients underwent radiotherapy in our hospital between 2012 and 2013. In the present study, we analyzed thirty-eight patients with stage III NSCLC out of 144, excluding patients treated with palliative intent in the present study. They were divided into three treatment groups according to age, ECOG performance status (PS) and complications of each patient. Group A patients, who were younger than 70 years old, PS 0 or 1, and without any complications, received the concurrent cisplatin-docetaxel chemoradiotherapy with 60 Gy / 30 fractions. Group B, aged 70 years or older, PS 0 or 1, and without any complications, or younger than 70 and PS 2 or with complications, received the concurrent carboplatin-paclitaxel chemoradiotherapy with 66 Gy / 33 fractions. Group C, aged 70 years or older and PS 2 or over, and with complications, received radiotherapy alone with 70 Gy / 35 fractions. Three-dimensional conformal radiation treatment planning including elective mediastinal nodal irradiation was performed. To evaluate treatment outcomes among the three groups, we estimated overall survival (OS), progression-free survival (PFS) and local progression-free survival (LPFS), and analyzed the differences in these indices statistically by means of EZR (ver1.32). We also evaluated the toxicity among these three groups with NCI-CTCAE ver.4.0. **Result:** The median of OS in Group A, B and C was 37.3 M, 40.4 M and 20.9 M, and that of PFS was 8.8 M, 17.9 M and 8.9 M, and that of LPFS was 25.9 M, 44.3 M and 22.8 M respectively. OS and LPFS were longer in Group A and B than C, and PFS was longer in B than C significantly ($p < 0.05$). There were no significant differences between Group A and B in any indices. In Group A, Radiation pneumonitis and esophagitis were significantly less than Group B or C but blood toxicity was more ($p<0.05$). **Conclusion:** For elderly patients with stage III NSCLC, the concurrent carboplatin-paclitaxel chemoradiotherapy with 66 Gy is suggested to be feasible and effective.

Keywords: carboplatin-paclitaxel, 66Gy, non-small cell lung cancer

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-22 CARDIAC BIOMARKERS IN CART STUDY (CARDIAC TOXICITY IN LUNG CANCER PATIENTS AFTER CHEMO-RADIOTHERAPY).

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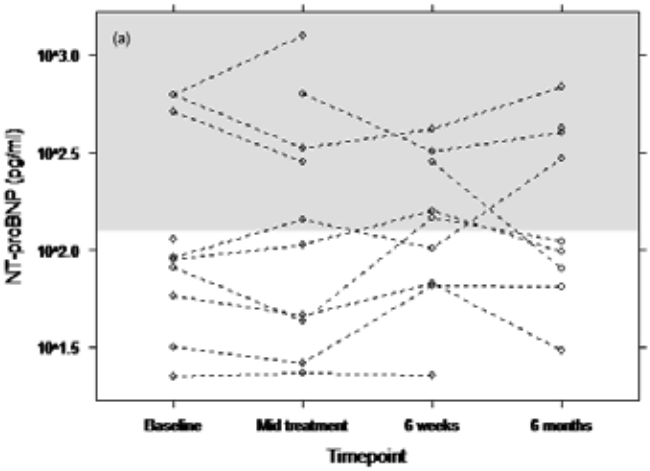
Background: Lung cancer has the highest incidence and mortality. Chemo-radiation (CRT) can achieve curative outcomes, but there is limited knowledge of the associated toxicity. The results of the RTOG 0617 study highlighted the impact of cardiac toxicity. Further investigation of cardiopulmonary toxicity is required. **Method:** This is a single centre, prospective observational study in which NSCLC patients undergoing RRT with or without chemotherapy were invited to participate. Evaluations include clinical assessment, cardiac MRI and ECG. Biomarker results are available for lattermost patients. Evaluations performed at baseline, during treatment, 6 weeks and 6 months after treatment. **Result:** 11 patients underwent translational blood sampling. Key details are given in table 1. Change in biomarker results is shown in figure 1. In this limited sample the change did not reach statistical significance. This study showed that 3/11 patients achieved hsTnT > 14 (suggestive of myocardial damage) during study period. 8/11 patients had NTproBNP > 125 (suggestive of increased heart failure risk) at some point on study. 3/11 demonstrated an NTproBNP levels > 400, a recognised cut off warranting cardiac echo.



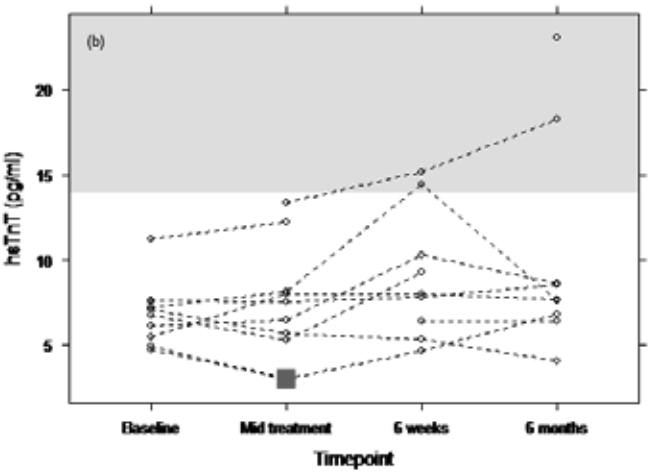


Table 1

Patient	Baseline Co-morbidities	Baseline ECG result	Treatment	Baseline NTproBNP, pg/ml (maximum change post-baseline)	Baseline hsTnT, pg/ml (maximum change post-baseline)	Hospital admission within 6 months (reason)	Status at 6 months
22		Normal	RRT	22 (+ 4%)	6.7 (+38%)	No	Alive
24	IHD, DM, COPD, RA	T-inversion, II, III, aVF	CRT	625 (+101%)	11.2 (+105%)	Yes (COPD, NSTEMI)	Alive
26		Normal	CRT	89 (+79%)	6.2 (+67%)	Yes (Chest pain)	Alive
27	CHOLES, HPT	Normal	RRT	81 (+80%)	5.5 (+47%)	Yes (Unknown)	Alive
28	HPT	Normal	RRT	32 (+106%)	7.1 (-20%)	No	Alive
29	IHD, DM, CHOLES	Sinus Bradycardia, Ist Degree AV Block	RRT	Missing (NA)	Missing (NA)	No	Alive
30	COPD, HEPB	Sinus Bradycardia	CRT	113 (+148%)	7.6 (-16%)	No	Alive
31	AF	Normal	RRT	58 (+15%)	7.2 (+101%)	No	Alive
32	IHD, CHOLES, HPT	Normal	RRT	624 (+10%)	4.9 (+39%)	No	Alive
33	IHD, HPT	Normal	CRT	91 (+220%)	7.6 (+12%)	No	Alive
34		Normal	CRT	509 (-45%)	4.7 (-37%)	Yes (N+V, chest pain)	Dead

Table 1. Listing of comorbidities, treatment, hospital admissions, ECG results and baseline biomarkers. Abbreviations: RRT (radical radiotherapy), CRT (concurrent chemo-radiation), COPD (exacerbation of COPD), NSTEMI (non-elevated ST segment myocardial infraction), N+V (nausea and vomiting), IHD (ischaemic heart disease), DM (diabetes mellitus), HPT (hypertension), CHOLES (hypercholesterolemia), AF (atrial fibrillation), RA (rheumatoid arthritis), HEPB (Hepatitis B), NTproBNP(N-terminal pro-B-type natriuretic peptide), hsTnT (high sensitivity Troponin-T)

Conclusion: Cardiac biomarkers and their changes indicate that further investigation may be required in some to exclude cardiac ischaemia and heart failure risks before or following treatment.

Keywords: Cardiac Biomarkers, chemo-radiation, Cardiac toxicity

P2.17-23 OPTIMAL THERAPY OF STAGE III NSCLC: THE ROLE OF SURGERY IN THE ERA OF IMMUNOTHERAPY

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Background: Curative intent treatment of stage III NSCLC may include surgery, radiotherapy, chemotherapy, or combination therapy. Management is influenced by both patient and disease characteristics. N2 disease is optimally treated with concurrent chemoradiotherapy (CRT) and the role of surgery after CRT remains a subject of debate. The recent PACIFIC study of adjuvant durvalumab after CRT in stage III showed unprecedented improvements in relapse free survival, which further calls into question the role of surgery. We sought to perform a real-world analysis of curative therapies in stage III NSCLC, and explore the impact of known prognostic factors on outcome. **Method:** A retrospective review was completed of all patients referred to BC Cancer from 2005-2012 with stage III NSCLC treated with curative intent including surgery, radiotherapy, chemoradiotherapy, and combined surgery and radiation +/- chemotherapy (S+RT+/-C). Information was collected on known prognostic factors. The primary outcome measure was overall survival. **Result:** 688 patients were included in the study. Baseline characteristics: female 47%, median age 65, ECOG 0-1 65%, weight loss <5% 74%, stage IIIA/IIIB 73%/27%. Treatment: 82 (12%) surgery, 127 (18%) radiotherapy, 423 (62%) chemoradiotherapy, and 56 (8%) combined S+RT+/-C. Median overall survival: surgery 28.6m, chemoradiotherapy 27.6m, radiotherapy alone 18.0m, and S+RT+/-C 55.9m. In a multivariate model incorporating age, sex, weight loss, ECOG, and stage, the survival difference disappeared between the surgery, chemoradiotherapy, and radiotherapy cohorts and persisted in the S+RT+/-C cohort. **Conclusion:** In stage III NSCLC, the performance of surgery, chemoradiotherapy and radiotherapy alone are comparable after controlling for known prognostic factors. Combined S+RT+/-C appears to provide a significant benefit above other modalities in highly selected patients. The role of surgery post-CRT remains controversial, as immunotherapy demonstrates greater promise for improving outcomes for the diverse group of stage III NSCLC.

Keywords: survival, Real-world, curative

Table 1: Univariate and multivariate analysis of the impact of prognostic factors and treatment cohort on survival

Variable		UVA		MVA		
		HR	p-value	HR	95% CI	p-value
Treatment	Surgery Radiotherapy Chemoradio-therapy S+RT+/-C	Ref 1.669 0.993 0.475	0.001 0.625 0.001	Ref 1.241 0.912 0.523	0.873-1.764 0.675-1.234 0.330-0.830	0.229 0.552 0.006
Age		1.018	<0.001	1.009	0.999-1.020	0.076
Sex	Female Male	Ref 1.211	0.028	Ref 1.111	0.923-1.338	0.264
Stage	IIIA IIIB	Ref 1.239	0.025	Ref 1.121	0.910-1.381	0.283
ECOG	0-1 >=2	Ref 2.128	<0.001	Ref 1.844	1.468-2.265	<0.001
Weight loss	<5% 5-10% >10%	Ref 1.382 1.557	0.010 0.001	Ref 1.232 1.268	0.959-1.582 0.958-1.678	0.102 0.097

P2.17-24 DOES THE CHANGE IN BODY MASS INDEX DURING INDUCTION CHEMO/CHEMORADIOTHERAPY AFFECT THE OUTCOME OF SURGERY IN LOCALLY ADVANCED NSCLC?

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Background: In the literature, the affect on prognosis due to changes in Body Mass Index (BMI) for patients diagnosed with cancer have been extensively analyzed. However, there are no studies investigating changes in BMI during induction therapy and its affect on postoperative outcomes. In this study, we aimed to identify how changes in BMI during induction therapy affected morbidity, mortality and long-term survival rates in patients undergoing surgery for locally advanced NSCLC. **Method:** One hundred and seventy one patients with locally advanced NSCLC and undergoing lung resection after induction therapy between 2011 and 2016 were prospectively recorded into the database and retrospectively evaluated. Induction treatment consisted of chemotherapy in 131 (76.6%) and chemoradiation in 40 (23.4%) patients. Body mass index was calculated at the initaition of induction therapy and before surgery. Pathological complete response to induction treatment, morbidity, 90-days mortality, long-term survival and prognostic factors were compared in the light of BMI. **Result:** All but 15 patients were male with a mean age of 59.4 (range 26-76y) years. The median BMI before induction treatment was 25.1 (16-39) and 25.2 (17-38) before surgery. The BMI decreased in 26.3% and remained steady/or increased in 73.7% of the patients during induction treatment. The complete response rate was 27(15.8%) patients [4 (11.8%) in the decreased BMI group and 23 (16.8%) in the BMI steady/increased group, p=0.47]. Morbidity rate was 42.6% (43.8% in decreased BMI and 38% in the BMI steady/increased group, p=0.5). Mortality rate was 4% (5.8% in decreased BMI and 3.6% in BMI steady/increased group, p=0.7). Three years survival rate was 71% (55.6% in the decreased BMI group and 76% in BMI steady/increased group, p=0.029) **Conclusion:** In this study we observed that nutrutional status of the patients undergoing induction therapy and surgery needs clear attention because morbidity, mortality and long term survival rates were negatively impacted in patients with a decline in their BMI during induction treatment.

Keywords: Body Mass Index (BMI), Induction Chemo/Chemoradiotherapy, lung resection

P2.17-25 POST-TREATMENT NEUTROPHIL TO LYMPHOCYTE RATIO IN LOCALLY ADVANCED NSCLC PATIENTS TREATED WITH CONCURRENT CHEMORADIOTHERAPY

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Background: We aimed to investigate the relationship between NLR and prognosis in patients with locally advanced NSCLC who received concurrent chemoradiotherapy as the first line treatment. **Method:** We retrospectively analyzed 62 patients with locally advanced NSCLC treated with definitive CCRT between 2008 and 2016 at Seoul St. Mary's hospital. We excluded patients who received induction chemotherapy to eliminate their influence on NLR. CCRT consisted of weekly chemotherapy using paclitaxel/carboplatin, docetaxel/cisplatin, docetaxel/carboplatin, and etoposide/cisplatin. Radiotherapy was performed with intensity-modulated radiotherapy (IMRT) or three-dimensional conformal RT (3D-CRT). The median radiation dose was 66 Gy in 33 fractions (range, 52 – 70 Gy). The pre-CCRT NLR was calculated from the nearest CBC within 1 week before CCRT and post-CCRT NLR was calculated using CBC 4 weeks after CCRT. Change of NLR before/after CCRT was also analyzed. The maximally selected log rank test was used to acquire the most significant NLR level related with overall survival (OS). **Result:** The pre-, post-CCRT NLR, and NLR change (post-CCRT NLR/pre-CCRT NLR) cut-off levels were 1.9, 3.15, and 1.6, respectively. The median follow up duration was 11 months (range, 2–71 months). The 3-year OS, loco-regional progression free survival (LRPFS), and distant metastasis free survival (DMFS) were 45.4%, 9.3%, and 6.2%, respectively. The post-CCRT NLR and NLR change were significantly associated with OS and LRPFS. The high post-CCRT NLR group (> 3.15) showed significantly worse OS and LRPFS compared to the low post-CCRT NLR group (≤ 3.15) (3-year OS: 21.2% vs. 46.9%, p=0.005; median LRPFS: 7.7 months vs. 11.3 months, p=0.04). The high NLR change group (> 1.6) had significantly worse OS and LRPFS than the low NLR change group (≤ 1.6) (3-year OS: 32.7% vs. 36.9%, p=0.026; median LRPFS 7.7 months vs. 10.4 months, p=0.025). The pre-CCRT NLR showed a marginally significant difference in OS (3-year OS: 29.1% vs. 56.9%, p=0.062). There was no correlation between NLR and DMFS. **Conclusion:** The pre-, post-CCRT high NLR and increased NLR after CCRT are associated with poor prognosis of survival in patients for locally advanced NSCLC. An elevated NLR after CCRT might be an indicator of an increased risk of loco-regional failure. Further studies are needed to confirm the predictive value of NLR and the treatment strategies using NLR.

Keywords: NLR, CCRT, NSCLC

P2.17-26 QUANTIFYING THE INTERFRACTIONAL MOTION OF THE ESOPHAGUS DURING RADIATION THERAPY FOR LOCALLY ADVANCED NON SMALL CELL LUNG CANCER

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Background: To quantify the interfractional motion of the esophagus during radiation therapy for locally advanced non small cell lung cancer using daily cone beam CT. **Method:** The analysis of interfractional esophagus motion was performed on treatment planning 4DCT scans and daily CBCT acquired from 35 patients with stage IIIA/B NSCLC. The simulation CT and CBCT were fused using bone registries and adjusted to the carina. Interfractional motion of the esophagus in the right-left (RL) and anterior-posterior (AP) directions at levels of sternal notch (A), carina (B), 2.5 cm below the carina (C) and the left lower pulmonary vein (D) was recorded and analyzed respectively. **Result:** A total of 612 CBCT image sets were obtained. The mean interfractional RL motion at level A, B, C and D was 0.5±2.9mm, -0.2±3.7mm, -0.5±3.9mm and -1.3±4.8mm, with the mean absolute value of 2.1±2.0mm, 2.7±2.6mm, 2.9±2.6mm and 3.4±3.6mm, respectively. The mean AP motion at level A, B, C and D was -0.3±2.0mm, 1.0±2.0mm, 1.3±2.2mm and 2.2±2.4mm, with the mean absolute value of 1.6±1.3mm, 1.7±1.6mm, 2.6±1.9mm and 3.4±3.6mm, respectively. Coverage of 95% of esophageal mobility requires 4.9 mm left, 4.4mm right, 3.1mm posterior and 3.7mm anterior margins at level A; 5.3 mm left, 6.5mm right, 4.5mm posterior and 1.9mm anterior margins at level B; 5.5 mm left, 7.2mm right, 4.8mm posterior, and 2.0mm anterior margins at level C; and 4.9 mm left, 7.9mm right, 6.3mm posterior, and 1.6mm anterior margins at level D.

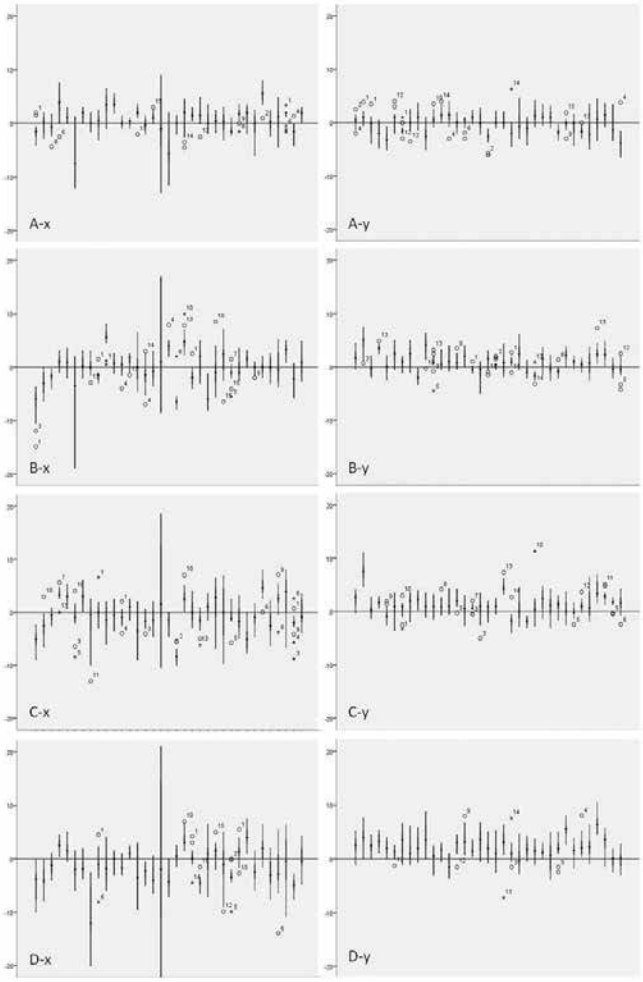

Figure 1: The interfractional motion for each patient in the RL (x) and AP (y) directions at levels of sternal notch (A), carina (B), 2.5 cm below the carina (C), and the left lower pulmonary vein (D).

Conclusion: In RL and AP directions, the average of the absolute interfractional motion of the esophagus was 3.4mm or less at all the four levels. The interfractional motion was greatest at the level of left lower pulmonary vein. The absolute RL motion was greater than AP motion. These data helps to set margin for ITV for future IMRT trials to account for esophageal motion.

Keywords: Radiotherapy, Interfractional motion of esophagus, Locally advanced non small cell lung cancer

P2.17-27 IMPOWER030: PHASE III STUDY EVALUATING NEOADJUVANT TREATMENT OF RESECTABLE STAGE II-IIIB NSCLC WITH ATEZOLIZUMAB + CHEMOTHERAPY

N. Rizvi[1], D. Gandara[2], B. Solomon[3], A. Kim[4], A. Brunelli[5], S. Sun[6], B. Gitlitz[6], K. Tajima[6], W. Lin[6], A. Sandler[6], S. Peters[7]

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Background: A standard of care for resectable early-stage non-small cell lung cancer (NSCLC) is surgery alone or in combination with adjuvant or neoadjuvant platinum-based doublet chemotherapy (PT-DC). Nevertheless, 30%-70% of patients develop recurrence and die due to

disease progression, highlighting the unmet need for more efficacious treatment regimens. Atezolizumab, an anti–programmed death-ligand 1 (anti–PD-L1) antibody that reinvigorates the anti-cancer immune response, has shown efficacy as monotherapy and in combination with chemotherapy in advanced NSCLC. On the basis of this activity, it is thought that the combination of atezolizumab and PT-DC may provide clinical benefit in the neoadjuvant setting by enhancing cancer cell killing and eradicating micro-metastases prior to surgery, thereby reducing the risk of disease recurrence. The objective of IMpower030 (NCT03456063) is to evaluate the efficacy and safety of atezolizumab in combination with PT-DC as neoadjuvant treatment for patients with resectable early-stage NSCLC. **Method:** IMpower030 is a global, Phase III, multicenter, double-blind, randomized study in patients with histologically or cytologically confirmed, resectable stage II, IIIA, or select IIIB (T3N2) NSCLC (per AJCC/UICC, 8th ed). Study inclusion requires measurable disease per RECIST v1.1, ECOG PS of 0/1, and eligibility for R0 resection with curative intent and PT-DC. Patients who have received prior therapy for lung cancer or who present with non-squamous NSCLC with activating *EGFR* mutations or *ALK* translocation are excluded. Approximately 302 patients will be randomized to receive 4 cycles of neoadjuvant atezolizumab (1200 mg Q3W, Arm A) or placebo (Arm B) in combination with an investigator-selected PT-DC regimen. Following surgical resection and pathology response assessment, treatment assignment will be unblinded; patients in Arm A will receive adjuvant treatment with atezolizumab for up to 16 cycles or until disease recurrence or unacceptable toxicity, whereas patients in Arm B will receive best supportive care and scheduled observational follow-up. The primary efficacy endpoint is major pathological response, defined as ≤ 10% residual viable tumor tissue at time of resection as assessed by an independent central pathology laboratory. Secondary efficacy endpoints include OS, ORR, investigator-assessed event-free survival and disease-free survival per RECIST v1.1, pathological complete response and patient-reported outcomes. Exploratory biomarkers will also be evaluated. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: atezolizumab, NSCLC, neoadjuvant

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-28 REAL-WORLD DATA: SURVIVAL OUTCOMES OF CHEMOTHERAPY REGIMENS GIVEN CONCURRENTLY WITH RADIOTHERAPY FOR LOCALLY ADVANCED NSCLC

D.C.C. Tsui[1], C. Butts[2], S. Ghosh[3], R. Sangha[3]

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Background: Initial management for inoperable Stage III non-small cell lung cancer (NSCLC) treated for curative intent is platinum-based chemotherapy with concurrent thoracic radiotherapy (TRT). However, a lack of consensus on the optimal chemotherapy regimen administered with TRT remains. In Alberta, Canada, cisplatin/etoposide (EP), given Days 1-5 + 8 of a 28-day cycle, and cisplatin/vinorelbine (VP), given Days 1 +8 of a 21-day cycle, have been the two regimens used preferentially. Weekly carboplatin/paclitaxel (CP) has historically been used as an alternative in patients (pts) with borderline performance status or contraindication to cisplatin. Here, we retrospectively compare survival outcomes of these chemotherapy regimens. **Method:** The Alberta Cancer Registry identified pts diagnosed with locally advanced NSCLC between 2010 and 2015 and treated with EP, VP or CP chemotherapy with concurrent TRT. Patient and tumour characteristics were collected along with treatment parameters. Progression-free survival (PFS) and overal survival (OS) was determined for each chemotherapy regimen. Survival outcomes were compared using Kaplan-Meier analysis and Cox proportional hazard regression models adjusting for age, gender, tumour histological subtype (squamous vs. non-squamous NSCLC) and 7th edition TNM Stage (IIIA vs. IIIB). **Result:** Of 148 pts reviewed, 44, 79, and 25 pts were treated with EP, VP, and CP, respectively, with median ages of 63, 62, and 68 years. Gender, tumour histological subtype, distribution of Stage IIIA vs. IIIB, and use of PET imaging for staging were balanced between regimens. Median PFS (EP 9.5 mo; VP 12.9 mo; CP 11.2 mo; p=0.875) and OS (EP 17.8 mo; VP 25.3 mo; CP 33.2 mo; p=0.509) were not significantly affected. Non-squamous median OS (EP 33.4 mo; VP 31.0 mo; CP 33.2 mo; p=0.997) and squamous median OS (EP 13.4 mo; VP 22.3 mo; CP not reached (N=11); p=0.406) also did not differ by regimen. Multivariate Cox regression analysis demonstrated Stage (IIIA vs. IIIB) as the only parameter that significantly altered PFS and OS. **Conclusion:** This retrospective analysis of real-word data from 2010 to 2015, in the absence of consolidation durvalumab, shows that PFS and OS in locally advanced NSCLC pts treated with concurrent chemoradiotherapy are similar for the EP, VP or CP regimens. Dose scheduling and respective toxicities will likely determine choice of chemotherapy regimen given with TRT. Further review of the CP regimen, given the small sample size in this study, and the use of next generation chemotherapy regimens such as platinum/pemetrexed for non-squamous NSCLC is warranted.

Keywords: chemotherapy, Localregional NSCLC

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-29 IS COLLAGEN VASCULAR DISEASE-ASSOCIATED INTERSTITIAL LUNG DISEASE A HIGH RISK FOR LUNG CANCER SURGERY?

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Background: Interstitial lung disease (ILD) frequently coexists with collagen vascular disease (CVD), and most of such patients are treated with immunosuppressive agents. Although the prognosis of CVD-ILD is better than that of idiopathic interstitial pneumonias (IIPs), the effect of CVD-ILD on the outcome and postoperative complication, including acute exacerbation (AE), after lung cancer surgery are unknown. **Method:** The subjects of this retrospective study were 2272 patients who underwent surgical resection of lung cancer at our institute between 2009 and 2016. We compared the characteristics, postoperative complication, and outcome of 18 patients with CVD-ILD with those of 201 Patients with IIPs. The pattern of ILD were based on chest computed tomography and classified into usual interstitial pneumonia (UIP) and the others. **Result:** The numbers of UIP patterns were 7 (39%) in CVD-ILD and 77 (38%) in IIPs. Thirteen patients (72%) were taking corticosteroids and 6 patients (33%) were taking immunosuppressive agents in CVD-ILD. Although postoperative AE occurred in 6 (3%) in IIPs, there were no AE events in CVD-ILD. Female (P < 0.01), lower pack-year smoke (P = 0.04), never smoker (P = 0.04), high value of LDH (P < 0.01), and medication of corticosteroids or immunosuppressive agents (P < 0.01) were significantly more common in CVD-ILD. Although there were no significant differences on the incidents of postoperative complications and mortalities, the duration to postoperative onset of IP exacerbation in CVD-ILD were tended to be longer than IIPs (P = 0.07). There were no significant differences on the cause of death between the 2 groups. **Conclusion:** There were no significant differences on the outcome and the incidents of postoperative complication, including AE.

Keywords: Collagen Vascular Disease, interstitial lung disease, lung cancer

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-30 SERUM LIPOPROTEIN(A) CORRELATES WITH THE EFFECT OF ENDOSTAR COMBINED WITH CONCURRENT CHEMORADIOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED LSCC

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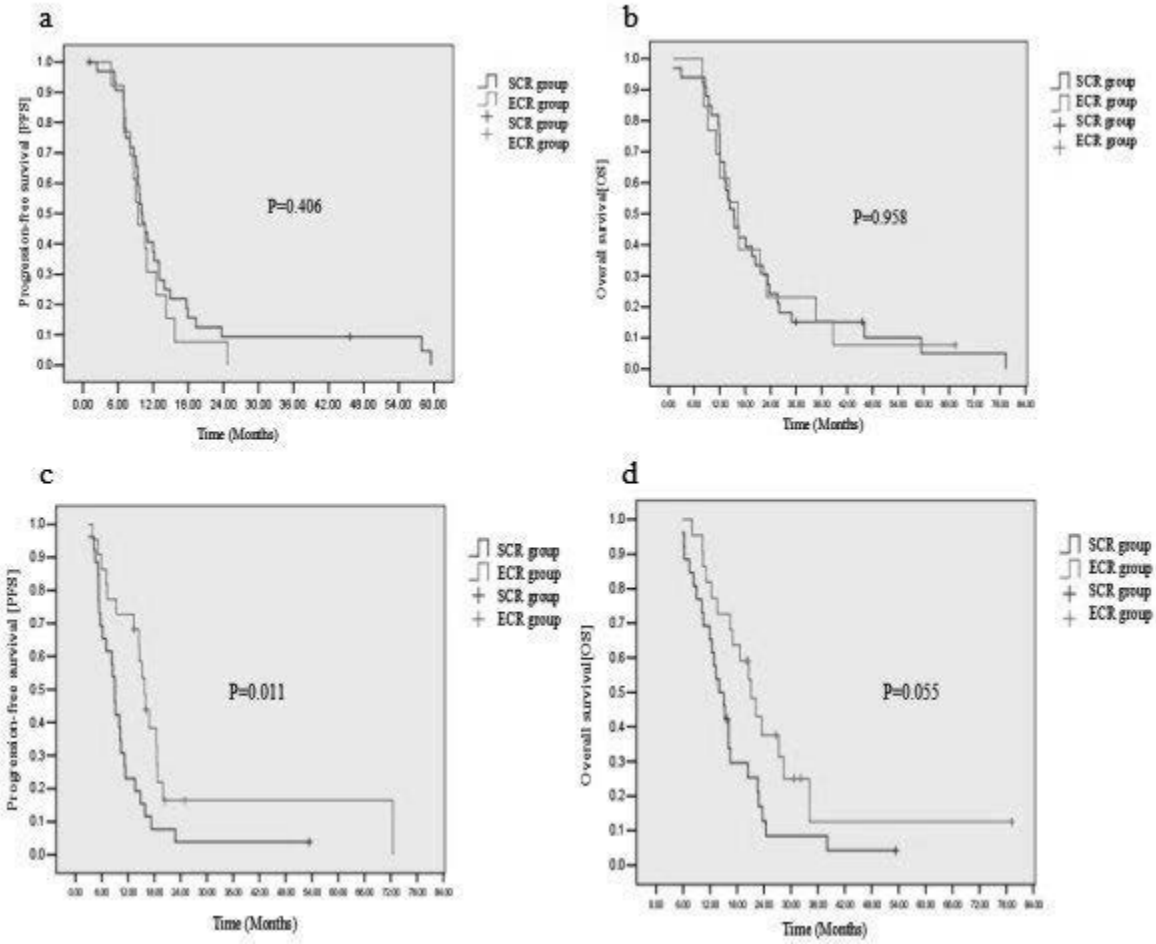
Background: The role of vascular targeting combined with concurrent chemoradiotherapy has produced many inconsistent results in locally advanced non-small cell lung cancer, especially in Lung squamous cell carcinoma [LSCC]. Lipoprotein(a) [Lp(a)] may be critical in development of tumor angiogenesis and its levels are individualized and determined genetically. The study aimed to determine whether Lp(a) is correlated with therapeutic effects of recombinant human endostatin [Endostar] combined with concurrent chemoradiotherapy for locally advanced LSCC. **Method:** Patients with locally advanced LSCC concurrent chemoradiation therapy in our hospital from December 2007 to December 2017 were retrospectively analyzed. Patients were divided into two groups: 1) Chemoradiotherapy group [CRT group] which received weekly vinorelbine (12.5mg/m^2) / carboplatin (AUC=2) concurrently with radiotherapy 60 Gy in 30 daily treatments, and 2) Endostar combination with chemoradiotherapy group (ECRT group) which received Endostar intravenous drip 1-14 days (every three weeks) concurrently with CRT.

Fasting venous blood samples were collected before the treatment for The measurement of serum Lp(a) level in all patients, the effect of Endostar was assessed by stratified analysis. **Result:** 94 patients were recruited in this study. There were 59 cases in CRT group and 35 cases in ECRT group. Overall, the median progression-free survival was 9.6 vs. 14.2 months (P=0.067) with overall survival 15.0 vs 20.6 months (P=0.114), in CRT and ECR groups respectively. The median of Lp(a) was 218mg/l. In patients with serum Lp(a) less than 218mg/l, the median PFS was 10.0 vs. 9.4 months (P=0.406) and OS was 15.4 vs. 16.3 months [P=0.958], in CRT and ECR groups, respectively. However, in patients with serum Lp(a) higher than 218ng/ml, the median PFS was 9.0 vs. 15.2 months [P=0.011] and OS was 14.0 vs. 21.1 months [P=0.055], in CRT and ECR groups, respectively. Patients with Grade 3 and above AE were observed in 32.2% vs. 34.3% (P=0.658) in CRT vs. ECR groups respectively.



Conclusion: The serum concentration of Lp(a) may serve as a biomarker to identify the patients who would benefit from Endostar treatment with concurrent chemoradiotherapy in stage III LSCC. Perspective study is needed to validate this finding.

Keywords: Lung Squamous cell carcinoma, Recombinant human endostatin [Endostar], Lipoprotein(a) [Lp(a)]

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-31 THE EFFECT OF THE EXTENDED BILATERAL MEDIASTINAL LYMPH NODE DISSECTION THROUGH A MEDIAN STERNOTOMY FOR NON-SMALL-CELL CARCINOMA OF THE LEFT LUNG.

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Background: *Whether mediastinal lymph node dissection (MLND) improves survival is controversial. But, lymph node dissection plays important role in oncologic surgery. The removal of the whole regional lymphatic system together with primary tumor is one of the fundamental rules in oncological surgery. For left-side tumors, upper zone lymph nodes are considered inaccessible. Due to anatomical limitations imposed by arch of aorta, it is difficult to perform complete dissection upper zone mediastinal lymph nodes through the left thoracotomy. According to the study of regional lymphatic drainage, we considered reasonable lymphadenectomy contributes the post-operative survival of the NSCLC patients with mediastinal lymph node metastasis. And we had devised Systemic extended bilateral mediastinal dissection and lung resection through a median sternotomy (ND3 operation) for patient with NSCLC of the left lung. This study aimed to investigate the prognostic impact of Extended bilateral mediastinal lymph node dissection for left NSCLC.* **Method:** We retrospectively studied 314 patients [220 male and 94 female, mean ages 61.2 years (range, 37-75)], underwent ND3 operation due to NSCLC, from January 1990 till December 2017. The patients with NSCLC who are estimated to be able to conventional radical operation and aged 75 year-old or less becomes the adaptation of ND3 operation. **Result:** Postoperative survival rates calculated with Kaplan-Meier method. Clinicalpathological data were compared according to the p stage. Overall 5-year survival rate in the 314 patients of left lung primary was 65.5%. Operative mortality in 314 patients was 2.8%. Lymph node metastasis to the mediastinum was confirmed in 95 (30.1%) patients (pN2 was 53 patients,pN3α was 23 patients, pN3β was 2 patients, pN3γ was 16 patients). According to pathological stages, five-year survival rate was 90.5% in stage IA ,75.8% in stage IB, 58.7% in stage IIA, 68.2% in stageIIB, 51.2% in stageIIIA, 38.9% in stageIIIB. And it was 51.5% in pN2 cases, and 53.6% in pN3α cases. Five-year disease free survival rate was was 84.3% in stage IA ,70.3% in stage IB,53.6% in stage IIA, 52.2% in stageIIB, 33.8% in stageIIIA, 15.6% in stageIIIB, 34.0% in pN2 cases, and

20.6% in pN3α cases. **Conclusion:** *In this nonrandomized study, the post-operative survival of left side NSCLC patients with mediastinal lymph node metastasis would be remarkably improved. And better local tumor control by ND3 operation does not increase mortality. When faced with a patient with resectable mediastinal lymph node metastasis, we should consider Extended bilateral mediastinal lymph node dissection through a median sternotomy.*

Keywords: Lymphadenectomy, non small cell lung cancer, Surgery

P2.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
TUESDAY, SEPTEMBER 25, 2018 - 09:45-18:00

P2.17-32 DYNAMIC MONITORING BEFORE AND AFTER NEO-ADJUVANT CRIZOTINIB IN NON-SMALL CELL LUNG CANCER: A BRIEF REPORT

C. Zhang[1], Y. Chen[2], S. Dong[1], Q. Nie[1], J.-. Yang[3], X. Yang[1], X. Zhang[4], Y. Wu[4], W. Zhong[3]

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Background: Neo-adjuvant therapy has been considered as an optional approach for locally advanced non-small-cell lung cancer (NSCLC) patients. While targeted therapy has been widely applied in advanced NSCLC, neo-adjuvant targeted therapy remains poorly explored. **Method:** We describe four ALK-positive patients with pathological confirmed locally advanced NSCLC receiving neo-adjuvant Crizotinib. All patients received Crizotinib at a starting dose of 250mg twice daily for 1-3 months before surgical resection. One patients provided dynamic monitoring before and after neo-adjuvant therapy through next generation sequencing of plasma and tissue. **Result:** Three patients were partial response without apparent adverse event before surgery while one received pathological complete response to neo-adjuvant Crizotinib but suffering from grade 4 hepatic damage. One of them had disease recurrence but achieved long duration of response (PFS=15m) through first-line Crizotinib. Dynamic monitoring with both plasma and tissue indicated simultaneously decrease of sensitive ALK-signaling in a patient with partial response (-51%) and no ALK-dependent resistant variants were captured.

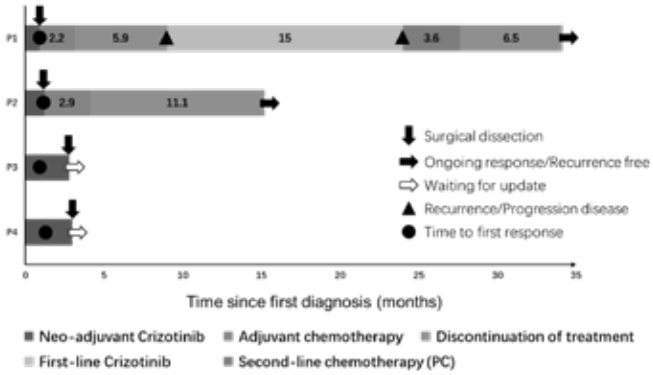

Fig 1. Duration of response in four reported patients.

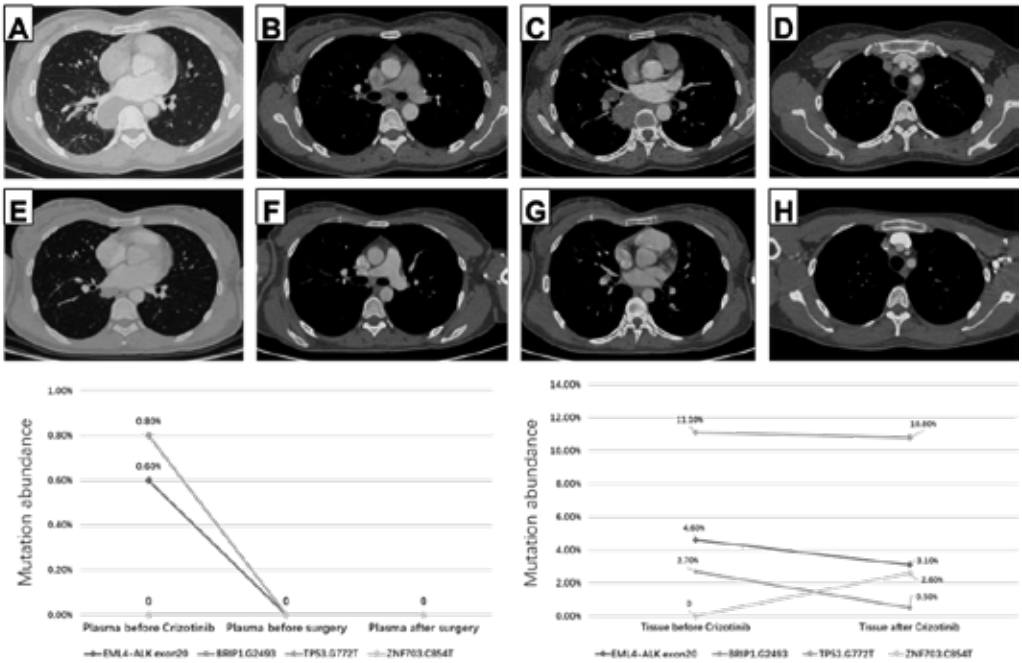

Fig 2. Radiological evaluation before (A-D) and after (E-H) neo-adjuvant Crizotinib. Dynamic monitoring indicated simultaneously decrease of ALK-signaling and no ALK-depend resistant variants were induced.

Conclusion: Neo-adjuvant Crizotinib may be feasible and well-tolerated in locally advanced disease for complete resection. Crizotinib prior to surgery may provide thorough elimination of circulating molecular residual disease and it did not influence the response of reusing Crizotinib in first-line setting.

Keywords: crizotinib, locally adcanced non-small-cell lung cancer, neo-adjuvant therapy

P2.17-33 ROLE OF ADJUVANT THERAPY IN PULMONARY ADENOSQUAMOUS CARCINOMA

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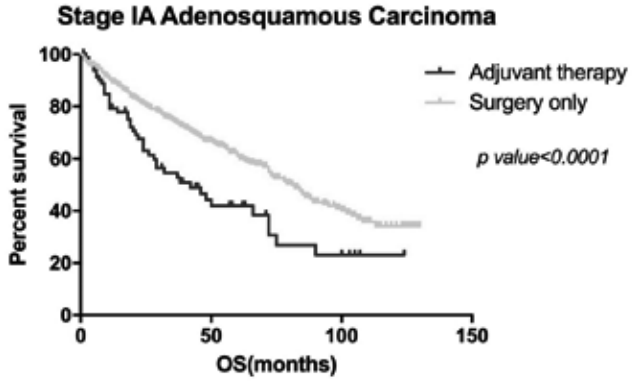
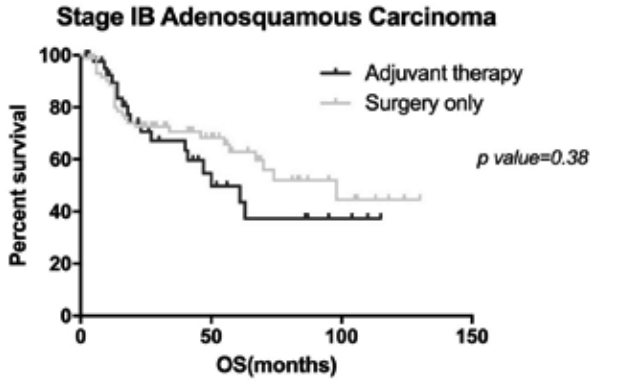
Background: Lacking of the data on the pulmonary adenosquamous carcinoma causes difficulty in choosing therapies. No study reported the role of adjuvant therapy in stage I of this type. This study was performed to elucidate the necessity and effect of adjuvant therapy in patients who received complete resection for Stage I adenosqumaous lung cancer. **Method:** Patients with T1-2N0M0 adenosqumaous lung cancer who underwent complete resection in the SEER database from 2004 to 2014 were identified. The overall survival were evaluated using Kaplan-Meier and Cox regression. Patients with pre-operative treatments were excluded. **Result:** A total of 1152 patients with T1-2N0M0 adenosquamous lung cancer were included. Among them, 607 and 545 patients were diagnosed as IA/IB. 929 patients received surgeries alone whose 1, 5, 10-year survival rate were 92.4%, 73% and 56.8%, while 223 patients received adjuvant chemotherapy whose survival rate were 82.1%, 49.6% and 41.3%, respectively. Patients in IA without adjuvant therapy had better outcomes. No survival benefit was observed in IB. Tumor size, age, sex and grade were significant prognostic factors. **Conclusion:** Adjuvant therapy may not be recommended to the patients with pulmonary adenosquamous carcinoma in stage IA-IB. More cases and clinical data are warranted to verify such findings and elucidate the roles of adjuvant therapy.





Keywords: adenosquamous carcinoma, Adjuvant therapy, Prognosis

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-01 PROSPECTIVE COMPARISON OF FOUR PLASMA TESTING PLATFORMS FOR T790M AND EFFECTIVENESS OF OSIMERTINIB IN CHINESE NSCLC PATIENTS

Y. Wu[1], Y. Chen[2], G. Wu[3], H. Zhang[4], Y. Lu[5], Y. Cheng[6], Y. Hu[7], Z. Liang[8], J. Wang[9], J. Ying[10], W. Liu[11], X. Zhang[1], Z. Liang[12]

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Background: T790M testing provides guidance for treatment decisions in NSCLC patients with acquired resistance to EGFR tyrosine kinase inhibitors (TKIs). However, tissue re-biopsy remains challenging while various detection methods using circulating tumor DNA (ctDNA) lack prospective clinical trial evidence to demonstrate their clinical utility as a stand-alone diagnostics test. This study aims to prospectively evaluate four T790M plasma detection platforms and clinical outcomes with osimertinib. **Method:** In this open-label, multicenter, single-arm study (ADELOS; NCT02997501), Chinese advanced NSCLC patients progressed on previous EGFR-TKI therapy were evaluated by four platforms, including cobas real-time polymerase chain reaction (PCR), super amplification refractory mutation system (Super-ARMS) PCR, capture-based next-generation sequencing (NGS), and QuantStudio3D digital PCR (3D dPCR). Patients genotyped as plasma T790M+ and met treatment eligibility received oral osimertinib 80 mg/day until disease progression. The primary objectives were to evaluate concordance in plasma T790M genotyping between platforms (reported in 2017 WCLC), and PFS (using investigator assessments, per RECIST v1.1) in plasma T790M+ patients receiving osimertinib. **Result:** Of 256 NSCLC patients enrolled, 181 were plasma T790M+ and 167 received osimertinib. The number of events (progression or dead) at data cut-off (April 24th, 2018) for primary PFS analysis was 100/167 (60% maturity). ORR and median PFS for plasma T790M+ patients were 56.9% and 9.7 months, and was consistent between platforms (Table 1, ORR: 61.8%, 63.4%, 54.7%, 62.8%; median PFS: 10.5, 10.5, 9.7, 11.0 months for cobas, Super-ARMS, 3D dPCR, NGS, respectively). OS maturity was not reached yet (27.5% events observed), number of death events was summarized in Table1.

Table 1. Diagnostic and clinical outcomes analysis of T790M genotyping between different platforms

	Cobas PCR (n=89)	Super-ARMS PCR (n=101)	NGS (n=129)	3D dPCR (n=148)	Overall (n=167)
mPFS, months (95% CI)	10.5 (8.4, NR)	10.5 (8.7, 11.7)	11.0 (9.5, 12.0)	9.7 (8.3, 11.1)	9.7 (8.4, 11.1)
ORR %, (95% CI)	61.8 (50.9, 71.9)	63.4 (53.2, 72.7)	62.8 (53.8, 71.1)	54.7 (46.3, 62.9)	56.9 (49.0, 64.5)
No. of death events (%)	25 (28.1%)	26 (25.7%)	31(24.0%)	44 (29.7%)	46 (27.5%)

NR: Not reached. ORR: objective response rate. PFS: progression-free survival, estimated by Kaplan-Meier method.

Conclusion: In this prospective study, the clinical outcomes of osimertinib in plasma T790M+ patients are equivalent to other studies with tissue T790M+ patients. Validated plasma T790M assays could be an alternative choice to provide guidance for second-line treatment decisions.

Keywords: T790M detection, NSCLC

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-02 PATIENTS WITH A SMALLER PRIMARY TUMOR AND FEWER METASTASES COULD BE CURED EVEN IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Various types of immunothrapies have been extensively developed in advanced non-small cell lung cancer (NSCLC). Although median survival times have been getting very long in a certain population, complete remission (CR) is still uncommon. This study aimed to elucidate features of CR cases with advanced NSCLC. **Method:** From our hospital database, 1,699 patients, registered as having lung cancer between August 2004 and April 2011, were examined. Those with stage III or IV histologically or cytologically confirmed NSCLC, whose treatment included chemotherapy, were retrospectively evaluated on Feb 13, 2017. CR, for the purposes of this study, was defined as a sustained CR at the five-year follow-up without treatment for one year, and features of CR patients were compared with those of long-surviving patients whose overall survival time (OS) exceeded 3 years. **Result:** There were 279 stage IV and 164 stage III patients. OS of 51 (18.3%) and 37 (22.6%) patients with stage IV and III were over 3 years, respectively. Five and 12 patients with stage IV and III, respectively, showed CR. The tale effects were observed in Stage III and IV advanced NSCLC mainly by chemotherapies without immunocheckpoint inhibitors. In stage IV, primary tumor diameters in the CR patients were shorter than those in the $3 \leq OS < 5$ patients, and metastatic numbers in the CR patients were fewer than those in the $3 \leq OS < 5$ patients. In stage III, there were no differences in primary tumor diameters and metastatic numbers among the $3 \leq OS < 5$, the $5 \leq OS$ with existence of tumor, and the CR ($5 \leq OS$ without tumor) groups. **Conclusion:** This study demonstrated that CR might be possible in certain patients with small primary tumors and fewer metastases even in advanced NSCLC by employing combinations of various treatment modalities.

Keywords: advanced NSCLC, Complete remission

P3.01 ADVANCED NSCLC
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P3.01-03 THE COST BENEFIT FROM SECOND LINE IMMUNOTHERAPY IN METASTATIC NSCLC: ASCO VALUE FRAMEWORK PROSPECTIVE

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Background: In recent years there has been a major paradigm shift in the management of advanced stage NSCLC with uses of novel immunotherapy. Three immune check point inhibitors were approved as second line in advanced stage NSCLC namely nivolumab, pembrolizumab and atezolizumab. The high cost of these drug making decision for both physicians and patients challenging. ASCO developed a tool for help in decision making based on data obtained from clinical trial **Method:** In this study we used ASCO Value Framework to compare the net health benefit (NHB) of second line immune check point inhibitors approved in metastatic NSCLC **Result:** Nivolumab was approved based on Check mate 17 and check mate 057 which compare nivolumab vs docetaxel in both squamous cell carcinoma and non-squamous NSCLC respectively with statistically significant improvement in overall survival with hazard ratio(0.59; 95% CI, 0.44 to 0.79; P<0.00) and (0.73; 96% CI, 0.59 to 0.89; P = 0.002) for both squamous cell carcinoma and non-squamous respectively. The calculated NHB for nivolumab vs docetaxel were 62.8 and 49.8 in both squamous cell carcinoma and non-squamous NSCLC respectively. Pembrolizumab was approved based on Keynote 010 which compare pembrolizumab vs docetaxel in metastatic NSCLC with statistically significant improvement in overall survival with hazard ratio 0·71, 95% CI 0·58–0·88; p=0·0008.The calculated NHB for pembrolizumab vs docetaxel was 46.1 Atezolizumab was approved based on OAK trial which compare atezolizumab vs docetaxel for metastatic NSCLC with statistically significant improvement in overall survival with hazard ratio 0·73, 95% CI 0·62–0·87, p=0·0003. The calculated NHB for atezolizumab vs docetaxel was 49.8.

(See next page)

	CheckMate 017	CheckMate 057	KEY-NOTE-010	OAK
Clinical Benefit	HR 0.59, P<0.001	HR 0.73; P = 0.002	HR 0·71; p=0·0008	HR 0·73 ; P = 0·0003
(HR death)	9.2 vs. 6.0 months	12.2 vs. 9.4 months	12.7 vs. 8.5 months	13.8 vs. 9.6 months
	+41 points	+27 points	+29 points	+27 points
Toxicity	7% versus 55%, -87%	10% vs. 54%, -79%,	13% vs. 35%, -60%,	15% vs. 43%, -63%,
	+7.2 Ponts	+6.8 Points	-2.9 Points	+6.8 Points
Bonus Points	20 Points	16 Points	20 Points	16 Points
NHB	68.2	49.8	46.1	49.8
Cost	$39,300	$39,300	$39,000	$37,500

Conclusion: For second line immunotherapy for metastatic NSCLC calculated NHB is comparable for both three Immune check points inhibitors with nivolumab has best calculated NBH for metastatic squamous cell carcinoma NSCLC patients.

Keywords: Immunotherapy, NSCLC, NHB

P3.01 ADVANCED NSCLC
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P3.01-04 IMMUNE CHECKPOINT INHIBITORS (ICIS) IN NSCLC: IMMUNE RELATED ADVERSE EVENTS (IRAES) AND OUTCOMES. A CANADIAN SINGLE INSTITUTION EXPERIENCE.

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Background: The ICIs are a major therapeutic advance in NSCLC with recognized toxicity in the form of irAEs. The association between irAEs and clinical benefit remains unclear but promising. The aim of this study was to examine the incidence and nature of of irAEs and correlative outcomes in patients treated with ICIs for advanced/recurrent NSCLC. **Method:** A retrospective chart review of all advanced NSCLC patients treated with immunotherapy between January 2015 to December 2016 was undertaken. Treatment was either on a clinical trial or as a standard of care. Patient demographics, clinical, pathological, and radiological parameters were assessed and an exploratory analysis was conducted to review these factors and outcomes in patients with and without irAEs. The nature and timing of the irAES was also evaluated. **Result:** 47 patients had ICIs: 24 (51%) received either Nivolumab, Pembrolizumab or Durvalumab alone (SAIO), 15 (32%) had dual agent immunotherapy (DAIO), 8 (17%) had chemotherapy plus ICI. 26 pts (55.3%) were female; median age was 65 years (range 50-90), 15 (31%) had squamous NSCLC. Median months (m) of ICI treatment were 5 (1 – 32). 21/47 (45%) were alive at 1 year. IrAEs occurred in 29 patients (61.7%), 13% SAIO, 23% DAIOs and 15% chemotherapy plus ICI. IrAEs were: dermatological (n=13), diarrhea/colitis (n=10/1), thyroid dysfunction (n=9), and pneumonitis (n=8), hypophysitis (n=1) and nephritis (n=1). The earliest irAE was dermatological with a median onset of 6 weeks. In those with irAEs versus (v) no irAEs: RR = 55% v 11%, disease control rate (DCR) 76% v 33%. 13/29 (45%) had an irAE in ≤ 6 weeks: RR = 38%, DCR = 53% and 6 of these (46%) were alive at 1 year. 21 patients were alive at 1 year: 16/21 (76%) had an irAE and of these, 13/16 (81%) had 2 irAES or irAEs ≥ grade (G) 2. Median overall survival (OS) for all patients was 9m (6.3-11.7). Landmark analysis at 3m: median OS for no irAES v irAEs was 15m v 18 m, log rank p=0.76. Median survival of those with no irAE v G1 v ≥ G2 was 2m v 8m v 23m, log rank p= 0.014. Further correlative outcome data will be presented. **Conclusion:** A landmark analysis at 3m did not show a statistically significant correlation between irAEs and survival. This merits further study as does the suggestion of a correlation between number of irAEs and grade with regards to outcome.

Keywords: irAEs, immunotoxicity, Immunotherapy

P3.01 ADVANCED NSCLC
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P3.01-05 MATURE PROGRESSION-FREE SURVIVAL IN STAGE IV NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH PEMETREXED MAINTENANCE THERAPY

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Background: Pemetrexed maintenance therapy is associated with superior survival in stage IV Non-Squamous, Non-small Cell Lung Cancer patients. We have observed long term disease control in real world patients treated with Pemetrexed(Pem)/Platinum(Plat) +/- Bevacizumab(Bev) followed by Pem +/- Bev maintenance therapy. To our knowledge, there is no mature data regarding the tail of the Progression Free Survival (PFS) curve in these patients. The objectives of this retrospective analysis are to determine the frequency of long term disease control on Pem+/- Bev maintenance and to identify parameters associated with absence of disease progression. **Method:** Our study looked at patients with Stage IV nsqNSCLC who received first line Pem/Plat followed by Pem maintenance between May 2010 and December 2017. We identified 241 patients from our database and analyzed their demographics, lab values, dates of therapy, and dates of progression. PFS was estimated by the Kaplan-Meier method and associations with patient characteristics were assessed by log-rank tests and Cox proportional hazards analysis. **Result:** Median age was 66 years, 60% female, and 72% Caucasian. Baseline ECOG performance status (PS) was 0(22%), 1(50%) and ≥ 2(22%). Disease progression was observed in 233 of 241 pts. with median PFS of 6.2 months. Absence of disease progression was observed in 34 pts. (14.2%) at 2 years, 19 pts. (7.9%) at 3 years, and 3 pts. (1.2%) at 5 years. Improved PFS was strongly associated with lower baseline neutrophil: lymphocyte ratio (NLR) when using NLR≤3.5 vs >3.5 (median PFS 9.7 mo vs 5.2 mo, p =0.004) as well as in a continuous scale (HR=1.04, p < 0.001). ECOG PS of 0/1 was also associated with superior PFS (p<.001). **Conclusion:** The similarity in median PFS in our patients (6.2 mo) and clinical trial data suggests that our group of real world patients did not have uniquely favorable baseline characteristics. Although long term absence of progression may have been solely due to favorable natural history of disease, we believe that it was also due to Pem maintenance. As a result, continued development of Pem plus immunotherapy regimens in nsqNSCLC may result in a higher rate of long term disease control.

Keywords: PROGRESSION FREE SURVIVAL, non small cell lung cancer, Premetrexed

P3.01 ADVANCED NSCLC
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P3.01-06 CONCOMITANT PLASMA-GENOTYPED T790M POSITIVITY AND SMALL CELL CARCINOMA TRANSFORMATION IN EGFR-MUTATED NSCLC

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Background: Patients of non-small cell lung cancer (NSCLC) having epidermal growth factor receptor (EGFR) gene mutation, initially show clinical response to EGFR Tyrosine-Kinase Inhibitors (TKI), but develop resistance after some months. However, the type and timing of TKI-resistance cannot be predicted as it is highly variable. Transformation to small cell lung cancer (SCLC) at progression during TKI-therapy and simultaneous acquisition of T790M EGFR-mutation is uncommonly reported. **Method:** Case report: Our patient is a 51 year-male, with stage IV NSCLC of adenocarcinoma subtype (TTF1 positive by IHC). He was initially treated with six cycles of pemetrexed and carboplatin to which he showed good response and was on regular follow up since September 2015. In the meantime, he was detected to have EGFR exon 21-mutation and was treated with Gefitinib for over two years. Patient was doing well and had complete disappearance of the tumour radiologically. After about 26 months of treatment he again became symptomatic. Repeat Computed tomography showed a lobulated mildly enhancing lesion 4.4 × 3 cm in right upper lobe. There were small nodules over bilateral lung fields and subpleural areas in right lower lobe, likely to be metastatic. Lytic lesions were also detected in dorsal (D2) and cervical (C5) vertebral bodies. Liquid biopsy showed T790M EGFR-mutation. Re-biopsy from right upper lobe showed transformation to neuroendocrine carcinoma (SCLC). Gefitinib was stopped and the patient was started on standard platin based doublet regimen for SCLC for the transformation. Patient

has received four cycles of platin based chemotherapy and is doing well. **Result:** "Section not applicable" **Conclusion:** This case report shows the possible underlying relationship between SCLC transformation and the T790M mutation, and that liquid biopsy approach may help overcome the problem of heterogeneity in acquired resistance to EGFR-tyrosine kinase inhibitors. In advanced NSCLC with EGFR-mutation, delayed onset of TKI-resistance can occur during TKI-treatment. Re-biopsies have increased the chance of detecting a T790M mutation and transformation. "Liquid biopsies" may potentially help identify heterogeneous genetic resistance-mechanisms; however, assessment of mechanisms such as SCLC-transformation needs tissue biopsies.

Keywords: liquid biopsy, lung cancer transformation, EGFR mutation

P3.01 ADVANCED NSCLC
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P3.01-07 OUTCOME AND PROGNOSTIC FACTORS IN ALK+VE METASTATIC ADENOCARCINOMA OF LUNG: SINGLE CENTER EXPERIENCE FROM EASTERN INDIA

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Background: Anaplastic lymphoma kinase (ALK) positive metastatic adenocarcinoma of lung constitutes 3-5% of all lung cancers. Outcome of this small sub-group improved substantially over last few years with discovery of many ALK-inhibitors. Indian patients scarcely represented in the registration trials of ALK-inhibitors. Here, we report our experience of clinic-pathological characteristics, treatment outcome & prognostic factors in ALK-positive metastatic adenocarcinoma of lung **Method:** This is a single institutional review of patients treated between Oct'13 and Feb'18. ALK was assessed by Ventana immunohistochemistry and/or fluorescent-in-situ hybridization analysis. Response assessment was done by RECIST v1.1. Patient who received at least one cycle of chemotherapy or one month of ALK-inhibitor was assessed for survival analysis in a modified intent-to-treat analysis **Result:** Seventy-eight patients were registered with median age of 53 years (range: 24-82). Baseline features and treatment details are mentioned in Table 1. After median follow-up of 15 months (range: 1-53), median overall survival (OS) was 52.2 months (95 CI: 37.2 – not reached) and median progression-free survival (PFS) was 17.8 months (95 CI: 13.1-24.2). Median OS was 37.2 months & not reached whereas median PFS was 14.2 months & 22 months in patients treated with upfront chemotherapy (n=24) and with upfront ALK-inhibitor (n=32), respectively. 2ndline PFS was 22.6 months among patients (n=13) treated with 2nd line treatment. On multivariate analysis, gender (p=0.007) and upfront treatment regimen (p=0.001) emerged as independent prognostic factors for PFS whereas performance status (p=0.02) and upfront treatment regimen (p=0.01) showed significance for OS. Table 1: Baseline clinical characteristics & treatment details (n=78)

Characteristics	Number	Percentage (%)	Median (range)
Age (years)			53 (24 – 82)
Sex Male Female	47 31	60 40	
Smoking status (n=74) Never smoker Current smoker Former smoker	45 26 03	61 35 04	
Symptom duration (months)			1.5 (0.2 – 12)
Eastern Cooperative Oncology Group performance status PS 1 PS 2 PS 3 PS 4	36 29 11 02	46 37 14 03	
Tumor size (cm) n=44			4.1 (0.9 – 12.2)
Nodal status (n=63) N1 N2 N3	03 32 28	05 51 44	
No of involved organ metastasis Single Two Three Four Five	19 24 20 11 04	24 31 26 14 05	
Brain metastasis Yes No	20 58	26 74	
Treatment taken Yes No	56 22	72 28	
Upfront treatment type (n=56) Chemotherapy Chemotherapy f/b crizotinib Crizotinib Ceritinib	24 11 18 03	43 20 32 05	
Treatment response (n=44) Ccomplete response Partial response Stable disease Progressive disease	02 23 17 02	4.5 52 39 4.5	
Site of progression (n=21) Brain Lung/pleura Others	10 08 03	48 38 14	
2nd line treatment (n=13) Chemotherapy Crizotinib Ceritinib	02 03 08	15 23 62	

Conclusion: Primary tumor size was small with higher nodal burden and brain metastases in our cohort. Outcome was excellent with use of ALK-inhibitors in our series. Female sex and upfront use of ALK-inhibitors showed superior PFS whereas as good performance status and upfront use of ALK-inhibitors showed superior OS.

Keywords: ALK, adenocarcinoma lung, crizotinib, PFS

P3.01 ADVANCED NSCLC
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P3.01-08 GENDER DIFFERENCES IN LUNG CANCER SURVIVAL

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Background: Lung cancer death rate in women rose in the past years surpassing breast cancer as the main cause of cancer mortality. The rise in lung cancer mortality in women appears to corelate with the increased prevalence of smoking. Adenocarcinoma has become the most frequent histologic subtype in both genders, and women present with adenocarcinoma in a higher proportion than men do. **Method:** Medical records of the patients diagnosed with lung cancer in Clinical hospital center Zagreb, Department for respiratory diseases Jordanovac during the year 2012 were retrospectively collected and reviewed. Baseline data were reported using descriptive statistics. Survival analysis was measured and analyzed using the Kaplan-Meier and log-rank test. **Result:** During the year 2012 there were 661 patients diagnosed with lung cancer in our Department. 482 (73%) were men and 179 (27%) were women. Median age at diagnosis was 64 (37-90). Total lifetime amount smoked varied from 2 to 200 pack/years in the smokers, with median 41 pack/years. The most predominant histological type was adenocarcinoma (287 patients, 43%), followed by squamous cell carcinoma (185; 28%) and microcellular carcinoma (79; 12%). Women had proportionally more adenocarcinoma and less squamous cell carcinoma than men. Cumulative exposure of smoking (as measured by pack-years of cigarettes) is significantly different with 33,6% of men smoking more than 50 pack years compared to 11,7% of women ($p < 0.01$). No significant difference in stage was observed across genders ($p = 0.40$). There were no significant differences in treatment between genders. Median overall survival (mOS) for all diagnosed lung cancer patients was 9 months. 1-year survival for all lung cancer patients is 39%, and 5-year survival is 8.1%. Female patients had significantly better survival rates. 1-year survival for female patients is 46% versus male patients 37%. 5-year survival rate for female patients is 11% versus male patients 7%. **Conclusion:** Male gender has been reported as a significant independent negative prognostic factor for patients with lung cancer in previous studies. Our results are similar to these findings. Over the last 20 years there were changes in the epidemiology of lung cancer between men and women. Characteristics of our patient population reflect the current trends of lung cancer epidemiology. Female patients smoke less but seem more susceptible to develop lung cancer. Although adenocarcinoma is the most common subtype in both genders, women have proportionally more adenocarcinomas than men do. Women have better survival than men.

Keywords: gender, survival, lung cancer

P3.01-09 IMPACT OF URBAN OR RURAL RESIDENCE ON OVERALL SURVIVAL FOR PATIENTS WITH METASTATIC NON-SQUAMOUS NSCLC

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Background: Although data suggests that disparities in ethnicity impact survival outcomes in lung cancer, little is known about whether disparities according to primary residence (rural vs urban) impact survival outcomes in metastatic non-squamous, non-small cell lung cancer (ns-NSCLC). **Method:** This is a retrospective study of 176 patients with stage IV ns-NSCLC treated at our institution from 2014-2016. Patients were classified as urban or rural residents based on zip codes using the RUCA and SAS zip code databases. Socioeconomic factors were derived from the AHRF database. Risk of death and overall survival (OS) were calculated using COX proportional hazards regression. **Result:** Baseline characteristics are in Table 1. Patients from rural zip codes had worse median OS (12.2 mo, 95% CI 5.1-16.0) compared to patients from urban zip codes (15.7 mo, 95% CI 9.6-27.9), with a hazard ratio (HR) of 1.589 (95% CI 1.052-2.401, p=0.0278). When adjusted for age, gender, smoking status, median income, percent in poverty per county, and EGFR mutational status, these results remained significant (HR 1.670, 95% CI 1.016-2.743, p=0.0376). A secondary analysis based on median household income (MHI) showed that those from regions with MHI less than the median of the cohort were 1.931 times more likely to die than those from regions with greater MHI (95% CI 1.038-3.595, p=0.0378).

Table 1. Baseline patient characteristics

Characteristic	Rural	Urban
Total (%)	76 (43.2)	100 (56.8)
Median age in years	65	64
Male gender (%)	36 (47.4)	50 (50)
Race/ethnicity		
White	66 (86.8)	75 (75.0)
Black	9 (11.8)	16 (16.0)
Hispanic	1 (1.3)	2 (2.0)
Other	0	7 (7.0)
Ever-smokers (%)	65 (85.5)	80 (80.0)
Median household income in dollars	52818	63343
Percent persons in poverty	14.4	14.3
EGFR mutation present (%)	14 (18.4)	19 (19.0)

Conclusion: Overall survival for rural patients with metastatic ns-NSCLC was inferior to those living in urban areas. This risk was more pronounced after adjusting for potential confounders. Those from regions with MHI below the median also had increased risk of death compared to those from areas above the median, suggesting that rural financial toxicity may influence lung cancer survival in our area. Further efforts to characterize the socioeconomic determinants of poorer outcomes in rural areas are needed and could support the formation of programs aimed at improving access to care.

Keywords: NSCLC, rural, healthdisparities

P3.01-10 DYSPNEA AS A PROGNOSTIC FACTOR IN HISPANIC PATIENTS WITH NON-SMALL CELL LUNG CANCER COHORT

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Background: Lung cancer is a commonly diagnosed cancer, and the leading cause of cancer death around the world. Over 80% of lung cancer patients in México are diagnosed in advanced stage. Common symptoms include cough, dyspnea, weight loss, and chest pain. Dyspnea is one of the most common symptoms in patients with lung cancer at initial presentation with a prevalence of 55–90%. The intensity of dyspnea is an important and validated factor for assessment of quality of life (QOL) in cancer patients. In addition, improvement of health-related QOL and symptoms, such as dyspnea, are related with the efficacy of chemotherapeutic regimens and favorable outcome in lung cancer. In this study, we investigated the association between the degree of dyspnea and clinical outcomes to identify the prognostic role of dyspnea in hispanic patients with non-small cell lung cancer (NSCLC). **Method:** We retrospectively reviewed lung cancer database of Centro Oncologico Estatal ISSEMYM. From 2013 to 2016 we enrolled patients with diagnosis of advanced NSCLC. Clinicopathological information on age, sex, smoking history, histologic type, stage, Eastern Cooperative Oncology Group (ECOG) performance status, clinical outcomes and evaluation of symptoms of dyspnea at diagnosis using modified Medical Research Council (mMRC) scores from each patient were recorded. **Result:** A total of 120 patients with diagnosis of NSCLC were identified, of these only in 65 patients (54%) the symptom of dyspnea were detected and evaluate using modified Medical Research Council (mMRC) scores at initial diagnosis. The median age was 58 years. Among those patient with dyspnea and mMRC scores available at diagnosis, 29 (45%) patients had an mMRC score ≥ 2, while 36 (55 %) had an mMRC score < 2. In multivariate analysis, poor performance status and an mMRC score ≥2 were found to be significant prognostic factors for patient survival. The overall median survival for all patients was 18 months. The overall survival of patients with dyspnea (mMRC grade 2 or higher) was significantly lower than that for patients without or low grade dyspnea (median survival, 17 months vs. 35 months, p<0.036). **Conclusion:** In conclusion, this study showed that the dyspnea mMRC mMRC grade 2 or higher in Hispanic patient with NSCLC were significantly associated with poor prognosis. Therefore, clinicians should pay more attention to evaluation and management of dyspnea.

Keywords: Hispanic lung cancer patient, lung cancer, dyspnea

P3.01-11 DEPRESSION AND INFLAMMATION IN PATIENTS WITH EGFR-MUTATED NON-SMALL CELL LUNG CANCER

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Background: Although depression appears to be associated with worse survival outcomes in cancer patients, the underlying mechanisms and basis of this association remain unknown. *EGFR* mutations have been associated with improved treatment response and prognosis in advanced non-small lung cancer (NSCLC). However, previous reports have described a positive association between this genotype and depression. This relationship could be at least partially explained by TNFa-mediated inflammation, which activates the hypothalamus-pituitary-adrenocortical (HPA) axis, leading to tryptophan depletion through the stimulation of indoleamine 2,3 dioxygenase. **Method:** 32 patients diagnosed with metastatic NSCLC with an *EGFR* mutation were enrolled and followed monthly. In all cases patients were evaluated using the Self-rating depression scale (SDS) and the Numeric Rating Scale (NRS) in order to obtain a detailed evaluation of the initial symptoms and a qualitative assessment of the state of depression. In parallel we measured TNFa levels in serum/plasma (MaxDiscovery™ Human TNF-α ELISA Test Kit) upon receipt of genotype report, 4 and 12 weeks after initiating the targeted therapy, and at the time of progression. We examined differences between patients with and without depression with respect to the TNFa, as well as impact on various outcomes. **Result:** Mean age was 58.9 years (+/- 12.4), 22 (68.8%) were women and 94% had an ECOG <2. Nineteen patients (59.4%) carried a del19, 8 (25%) had L858R, 2 (6.3%) L858R+T790M, 2 (6.3%) G719S and one patient had a del19+S768I (3.1%). Median follow-up was 15.4 months (95%CI 2.8-32.0), overall survival (OS) was 28.1 months (95%CI 25.5-30.6) and median progression-free survival (PFS) to first-line TKI was 13.1 months (95%CI 9.6-16.6).37.5% (n=12) of patients self-reported depression; in 25, 9.4 and 3.1% the clinical manifestations were mild (SDS 50-59; supportive psychotherapy), moderate (SDS 60-69; requirement of antidepressants) and severe (SDS 70 and above; required hospitalization). Depression was significantly associated with moderate-to-severe basal dyspnea (p=0.043), with brain metastases (p=0.003), and poor performance status (p=0.021). The average TNF at the time of

genotype report was 12.2 pg/mL (SD±4.1), and was significantly higher in those who manifested depression (p=0.03). TNF levels increased 11% at 4 weeks and 75% at 12 weeks. Depression did not influence OS or first-line PFS. **Conclusion:** Mild to moderate depression is prevalent in patients with lung cancer harboring *EGFR* mutations. As previously reported, TNFa levels are elevated in patients with lung cancer and depression, particularly in the first 12 weeks post-treatment, a finding attributable to inflammation.

Keywords: Depression, Inflammation, NSCLC

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P3.01-12 EGFR MUTATION AND TARGETED THERAPIES: DIFFICULTIES AND DISPARITIES IN ACCESS TO NSCLC TREATMENT IN BRAZIL.

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Background: Non-small cell lung cancer (NSCLC) is the most prevalent lung cancer subtype, commonly presenting as advanced disease at diagnosis. Epidermal growth factor mutation (EGFRm) occurs in 10-15% of Western population with advanced NSCLC and its management includes the use of mutation-driver EGFR tyrosine kinase inhibitors (EGFR-TKIs). In Brazil, patients with EGFRm NSCLC may face barriers to access EGFR test and directed-therapy; otherwise, there is a lack of national clinical data addressing this issue. This study intended to evaluate the access to molecular EGFR testing, initial treatment, and its respective response in this patients setting in public and private institutions in Brazil. **Method:** In this retrospective cohort, patients with newly diagnosed advanced NSCLC between January and December 2014 were consecutively included. Data were collected from medical records of 10 Brazilian cancer institutions, and recorded in electronic clinical report form. Demographic data, medical history, tumor staging, pathological characteristics, treatments and outcomes were collected and analyzed. For each patient, maximum follow-up was 36 months. **Result:** 402 patients from 8 different Brazilian states were enrolled, and 391 were included in the analysis, being 236 men (60.4%). Median age was 64 years, 80% have been treated in the public and 20% in private health system; 74.9% (n = 293) were former or current smokers. The most frequent histological subtypes of NSCLC were adenocarcinoma (ADC) with 267 cases (68.3%) and squamous cell carcinoma (SqCC) with 87 cases (22.3%). Among smokers, 66.6% were diagnosed with ADC and 24.6% with SqCC; among never smokers (n = 63), 84.1% had ADC and 9.5% SqCC. Clinical staging (CS) at diagnosis was IV in 251 cases (81.6%) and locally advanced (stage IIIB) in 62 cases (18.4%). From patients diagnosed with ADC, only 52.1% (n = 139) have been tested for EGFR mutation and, of these, 21.6% (n = 30) had an EGFR activating mutation. Only 43.3% (n = 13) of those with EGFRm (n=30) received an EGFR-TKI as initial therapy, while the remaining were treated with cytotoxic chemotherapy. Based on the number of patients with EGFRm, the rate of access of EGFR-TKIs in first-line treatment was 75% in private care, compared to 31.8% in public care. Only 8 of 13 mutated patients (61.5%) treated with EGFR-TKI were evaluable for response, and the disease control rate was 62.5%. **Conclusion:** The frequency of EGFRm in locally advanced or metastatic ADC in Brazil was comparable to previous studies. Access to EGFR test and EGFR-targeted therapies are restricted specially in public health system. In Brazil, public policies to assure a broader access to these technologies must be implemented.

Keywords: advanced NSCLC, Targeted therapy, Health system

P3.01 ADVANCED NSCLC
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P3.01-13 PROGNOSIS OF NON-DRIVER, NEVER SMOKER METASTATIC NON-SMALL LUNG CANCER (NSCLC)

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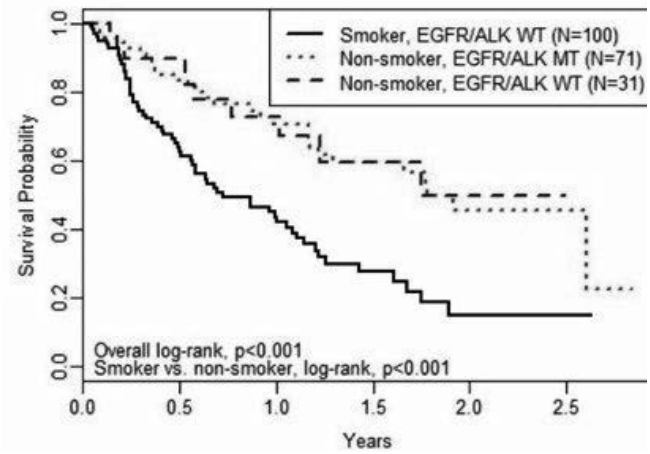
Background: The overwhelming majority of NSCLC does not have an actionable driver mutation, termed wild type (WT). Never smoking (NS) lung cancer has a high frequency of actionable driver mutations relative to smoking (S) related lung cancer. Those with EGFR or ALK mutations who receive appropriate targeted therapy, regardless of smoking status, demonstrate twice the survival of WT NSCLC in the metastatic setting. It is unclear if WT NS behaves more like WT S or EGFR/ALK. **Method:** Electronic medical record data from lung cancer patients treated at Huntsman Cancer Institute was processed by Flatiron Health using technology-enabled abstraction and supplemented with third-party death information. Patients with metastatic NSCLC were categorized according to smoking status (never [NS] or history of smoking[S]) and molecular profile (EGFR, ALK or WT). Kaplan-Meier estimates of survival from advanced/metastatic diagnosis were plotted by category, and survival times compared between groups in the context of Cox proportional hazards models. **Result:** From 2016, 202 patients were identified with smoking data and EGFR/ALK testing in the data set. The respective median ages and median survival in the NS WT, ALK/EGFR, and S WT groups were 68 (N=31), 63 (N=71), and 68 (N=100) years and 1.8, 1.8, and 0.7 years, respectively. Estimated survival curves are shown below. NS WT was the reference population with hazard ratio=1. Hazard ratios for the remaining categories were ALK/EGFR 1.09 (p=0.823) and S WT 2.64 (p=0.005).



Conclusion: Survival times for NS WT are significantly greater than S WT NSCLC and behave more like EGFR/ALK. Clinical history may be more important than molecular biomarkers, but further study is needed.

Keywords: NSCLC, Prognosis, non-smoker

P3.01 ADVANCED NSCLC
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P3.01-14 MTORC1 REGULATES THE RADIOSENSITIVITY OF NSCLC CELLS WITH WILDTYPE PI3KCA AND KRAS GENES BY AFFECTING EMT

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Background: Resistance to radiotherapy has been shown to be a key cause of treatment failure in NSCLC and associates with local recurrence and metastasis. Understanding how NSCLC cells sensitize to radiation is therefore important for developing new treatments and prognostics. It has been shown that mTORC1 can regulate tumor cell radiosensitivity, although the mechanisms that underlie this phenomenon are unclear. It have found that mTORC1 also regulates EMT, important to metastasis and recurrence. We therefore hypothesized that mTORC1 might affect NSCLC cell radiosensitivity by suppressing EMT. **Method:** We analyzed the expression of mTOR protein in NSCLC tissues from patients, in addition to adjacent and normal tissue.These data showed that mTOR protein was elevated in NSCLC tissue. We then evaluated the effect of the mTORC1 inhibitor RAD001 (everolimus) on *in vitro* radiosensitivity, protein levels, and dose-survival curves using NCI-H460 and NCI-H661 NSCLC cell lines. RAD001 inhibited the mTORC1 pathway in both lines and enhanced the radiosensitivity of NCI-H661 cells with wildtype *PIK3CA* and *KRAS*genes. However, there was no evidence of a similar effect in NCI-H460 cells with mutant *PIK3CA* and *KRAS* genes. We also analyzed the expression of various EMT-associated proteins after irradiation in RAD001-treated and control cells. This showed that mTORC1 inhibition led to changes in the expression of several EMT-associated proteins in NCI-H661 cells after irradiation. Finally, we used publicly available expression data to confirm that mTOR and EMT-associated genes were affected by irradiation at the transcript level in NSCLC cells. **Result:** In conclusion, our study has revealed that the mTORC1 signaling pathway is involved in regulating the

radiosensitivity of some non-small cell lung cancer (NSCLC) cells. Our data showed that there was increased expression of mTOR in primary tumors and matched adjacent tissues in patients with NSCLC. We also confirmed that the mTORC1 inhibitor RAD001 had a cytostatic effect on NCI-H661 and NCI-H460 NSCLC cells lines. However, mTORC1 inhibition only increased radiosensitivity and affected mTOR signaling downstream targets in NCI-H661 cells with wildtype *PIK3CA* and *KRAS* genes. RAD001 had only a marginal effect on NCI-H460 cells with mutant *PIK3CA* and *KRAS*genes. Finally, the effect of radiation on EMT-associated markers was also assessed, revealing that mTORC1 inhibition couldalleviate irradiation-specific EMT changesin NCI-H661 cells. **Conclusion:** these data suggest that mTORC1 inhibition in NSCLC may enhance radiosensitivity by affecting the expression of EMT-associated proteins. This suggests targeting mTORC1 may provide a potential new strategy for the treatment of NSCLC with wildtype *PIK3CA* and *KRAS* genes.

Keywords: mTOR, epithelial-mesenchymal transition, KRAS

P3.01 ADVANCED NSCLC
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P3.01-15 EFFICACY OF PACLITAXEL PLUS TS1 AGAINST NON-SMALL CELL LUNG CANCER PREVIOUSLY TREATED

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Background: Salvage chemotherapy is frequently used. However, the efficacy of salvage chemotherapy of paclitaxel plus TS1 (TTS1) is still unknown. **Method:** We retrospectively reviewed the chart records of our non-small cell lung cancer patients who were treated between 2010 and 2013. Clinical characteristics, type of tumor *EGFR* mutation, response to first-line EGFR-TKI treatment or not, and efficacies of TTS1, were collected. **Result:** Total 25 patients were enrolled in this study. No patients archived complete response and six patients had partial response (ORR: 24%). The disease control rate was 60% (15/25). The progression free survival (PFS) was 4.8 months and overall survival (OS) was 12.4 months. Among these 25 patients that received TTS1, 17 of them had driver mutations. Patients with driver mutations had better PFS (4.9 months vs 1.8 months) and OS (15.5 months vs 7.2 months) compared with those without driver mutations. **Conclusion:** TTS1 are effective salvage chemotherapeutic agents, especially in tumor EGFR mutated patients. Paclitaxel plus TS1 is another treatment of choice for NSCLC patients before a more efficient salvage treatment strategy is found.

Keywords: non-small cell lung cancer, S-1, EGFR

P3.01 ADVANCED NSCLC
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P3.01-16 LOW DOSE APATINIB COMBINED WITH EGFR-TKIIN TREATING ADVANCED NSCLC AFTER FIRST-GENERATION EGFR-TKIS TREATMENT FAILURE

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Background: EGFR TKIs have been approved as the first-line therapy for treating advanced non-small-cell lung cancer (NSCLC). However, treatment failures frequently occurred in NSCLC patients with EGFR-sensitizing mutations. Apatinib, a novel small molecule TKI targeted VEGFR2, recommended as third-line treatment for metastatic gastric cancer patients. This retrospective study tried to investigate the efficacy and safety of low dose Apatinib combined with original targeted drugs in treating advanced NSCLC after first-generation EGFR-TKIs treatment failure and trying to explore the underlying mechanisms. **Method:** From March 2016 to November 2016, 11 patients of advanced NSCLC acquired resistance for Erlotinib, gefitinib and Icotinib treated with original targeted drugs plus Apatinib(250 mg, once daily), and CT scan every 4 weeks. Meanwhile observe drug-related adverse events. **Result:** In 11 patients, there were 10 patients available for efficacy and safety evaluation. 2 of 10 patients were progress disease in 12 weeks, 8 of 10 patients were stable disease and still in treatment. The disease control rate (DCR) was 80%. The rate of PFS at 12 weeks was 72.73%. The most frequent treatment-related adverse events were fatigue (20%, 2/10), rash (20%, 2/10), poor appetite (20%, 2/10), respectively. Severe AEs included grade 3 proteinuria (10%, 1/10). **Conclusion:** Low dose Apatinib combined with original targeted drugs is efficacious in treating patients with advanced NSCLC who failed to first-generation EGFR-TKIs treatment, with acceptable toxic effects. The mechanism may be related to Apatinib regulate tumor microenvironment and reverses multidrug resistance.

Keywords: low dose Apatinib; Advanced NSCLC; first generation EGFR-TKIs; tumor microenvironment

P3.01 ADVANCED NSCLC
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P3.01-17 LONG SURVIVORS WITH ADVANCED LUNG CANCER- EFFICACY AND TOLERABILITY OF NIVOLUMAB

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Background: The group of the patients with advanced lung cancer surviving more than two years was limitated, particullary at era of the classic chemotherapy.In our material presented in 2013 on WCLC it made up 11%.The differences in efficacy betweeen Nivolumab and conventional treatment in pretreated patients remains unclear, particullary in the group with good response on chemotherapy with long interval between lines. We analyzed the efficacy and tolerance of Nivolumab in the long surviving group. **Method:** 7 patients characterized by long earlier history of lung cancer were found. Baseline characteristic and historical treatment data are presented in table 1.

(See next page)

age	sex	First diagnosis date	Type of cancer	I line CHT-type, response	I line CHT-period	II line CHT- type	II line period	Date of Nivo start
71	Male former smoker	2014	squamous	Paclitaxel/Carboplatin-partial regression	To AUG 2014-8 cycles	Reinduction Paclitaksel/carboplatin - PR	6 cycles- XII 2015	III line, XI 2016- 2 years from initial diagnosis one year from last CHT
55	Female-never smoking	2012	Adeno, no EGFR, no ALK	Cispaltin/Vinorelbin-stopped due to AE	VII-IX 2012 – 3 cycles	Alimta with maintenance- PR	2013/ 2014-one year	III line ,XI 2016 4 years from initial diagnosis two years from last CHT
60	Female former smoker	2014	Adeno, EGFR mut.	Erlotinib partial regression	2014-2015-one year	Paclitaksel/Carboplatin -PR	2015/ 2016-VI cycles	III line, XII 2016- 2 year from initial diagnosis half year from last CHT
61	Male former smoker	2007	Adeno, no EGFR, no ALK	Cisplatin/Gemcytabin partial regression	IV-VIII 2007-4 cycles	Alimta - PR	2008/2009	III line, XII 2016 9 years from initial diagnosis 7 years from last CHT
63	Male fromer smoker	2010	Adeno no EGFR, no ALK	Paclitaxel/Carboplatin+/-Axitinib partial regression	V 2010-VI2012-with maintenance	Paclitaksel/Carboplatin -PR	2014	fourth line XII 2016 6 years from initial diagnosis one years from last CHT
73	Female former smoker	2014	Squamous	Carboplatin/Vinorelbin partial regression	2014-4 cycles	Docetaxel - PR	2016	III line, I 2017, 3 years from initial diagand one year from last CHT
52	Female active smoker	2012	Adenocarcinoma, no EGFR, no T790M, no ALK	Carboplatin + Gemcytabin- partial regresion	2012-2013 – 8 cycles	Docetaxel-6 cycles-PR	2015	III line, XII 2017, 5 years from initial diagnosis 2 years froma last CHT

Result: Table nr 2 presents the efficacy and tolerability of Nivolumab. The patients obtained 190 injections of drug and only one patient requires 2,5 months break beacuse of typical AE-tyreoiditis G3. Other short breaks were dependent on personal requests ,not from AE. Treatment time is 12-17 months and is plannig to continue .No progression has been noticed. Follow-up is planned.

Patient	Number of cycles	Response	AE	SAE	Continuing/ stopped	Alive/Death
71/M	34	partial	no	no	cont	alive
55/F	24	partial	yes- tyreoiditis G III	no	cont	alive
60/F	28	stabilisation	no	no	cont	alive
61/M	30	complete	no	no	cont	alive
63/M	33	partial	no	no	cont	alive
73/F	29	stabilisation	no	no	cont	alive
52/F	12	partial	no	no	cont	alive

Conclusion: Long surviving patients with significant interval between chemotherapy lines show excellent tolerability and good efficacy of Nivolumab regardless of the type of previous chemotherapy.Efficacy and tolerance of these patients are comparable to described group with better prognosis from trials Checkmate 003 and 153

Keywords: Nivolumab, long survivors, NSCLC

P3.01-18 COMPARISON OF PD-L1 IMMUNOHISTOCHEMICAL ASSAYS AND CLINICAL RESPONSE TO ANTI PD-1 CHECKPOINT INHIBITORS IN PATIENTS WITH LUNG CANCER

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Background: The anti-programmed cell death 1 (PD-1) immune checkpoint inhibitors, nivolumab and pembrolizumab, are currently approved for the treatment of patients with NSCLC. The PD-L1 expression represents the most validated predictive marker of response to PD-1 inhibitors. However, there are several different immunohistochemical assays to assess the PD-L1 expression using different antibodies, platforms, and cutoff values. We compared the PD-L1 expression evaluated by IHC 22C3 PharmDx with that observed by Ventana SP263 and analyzed correlation with response to anti PD-1 inhibitors. **Method:** We retrospectively analyzed 109 patients with lung cancer to be treated with anti PD-1 inhibitors who have PD-L1 expression levels obtained with both the 22C3 and SP263 assays. We reviewed medical records to obtain information about the patient's clinical characteristics, response evaluation and survival data. The relationship between PD-L1 expression levels evaluated by the 22C3 and SP263 assays was calculated using the concordance correlation coefficient, Pearson's precision analysis. **Result:** Most patients were male (70%), smoker (65%), ECOG PS 1 (73%), and histologically adenocarcinoma (55%) or squamous cell carcinoma (29%). 30% of patients had EGFR mutations. Patients were treated with pembrolizumab (n=41, 38%), or nivolumab (n=67, 61%). The median cycle of anti PD-1 checkpoint inhibitor was three (range, 1-25). There was moderate analytical correlation between 22C3 and SP263 PD-L1 levels. At the clinically relevant cutoffs (< 10% vs. ≥10%; and <1% vs. 1-49% vs. ≥50%), the concordance correlation coefficient between 22C3 and SP263 were 0.68 (95%CI: 0.59-0.77) and 0.66 (95%CI: 0.51-0.81), respectively. The overall response rate (ORR) was 25.0% for all patients. The ORR was comparable regardless of the cutoff levels of PD-L1 expression by SP263 assays (ORR 39.6%, 41.7%, and 47.4% respectively for PD-L1 expression by 1%, 10%, 50% cutoff levels). But, the correlation between ORR and PD-L1 expression by 22C3 assays was not statistically significant. At 1% cutoff value, progression free survival was longer in patients with high vs. low tumor PD-L1 expression (2.8 months vs. 1.2 months, HR 0.63, 95%CI: 0.41-0.97, p=0.03) by the 22C3 and (3.1 months vs. 1.3 months, HR 0.61, 95% CI:0.40-0.93, p=0.02) by the SP263, respectively. **Conclusion:** We showed a moderate correlation between PD-L1 expression data obtained with the 22C3 and SP263 assays. These two assays could be used interchangeably and might be helpful for decision with anti PD-1 checkpoint inhibitors. Further analysis will be updated.

Keywords: PD-L1, lung cancer

P3.01-19 SEQUENCING OF RAMUCIRUMAB+DOCETAXEL POST-IMMUNE CHECKPOINT INHIBITORS IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: The Phase III REVEL study demonstrated the efficacy and safety of ramucirumab+docetaxel (ram+doc) in advanced non-small cell lung cancer (aNSCLC) patients who had disease progression on prior platinum-based chemotherapy (chemo). Given recent positive data disclosures supporting the use of chemo+immune checkpoint inhibitor (ICI) combinations in frontline, there is a need for additional data on the sequencing of ram+doc post-ICIs. **Method:** Baseline characteristics and outcomes were assessed for aNSCLC patients identified in the Flatiron Health EHR-derived database, who received ram+doc as 3rd line therapy (3L) between March 2015 - May 2017 in the United States after 1st or 2nd line platinum-based chemotherapy, with ≥ 3 months of potential follow-up. Analyses were conducted for the overall cohort and among the subset of patients who received 3L ram+doc post-ICI. Overall survival (OS) was calculated from start of 1st line therapy. Real-world progression-free survival (rwPFS) and time-to-progression (rwTTP) were measured from start of 3L ram+doc. OS, rwPFS, and rwTTP were estimated using Kaplan-Meier method. **Result:** Among platinum-treated patients who subsequently received ram+doc in 3L overall (N=98), of whom the majority (n=65, 66.3%) received ram+doc post-ICI, the median age was 66 years and the majority were male (54.1%), Caucasian (67.4%), and had nonsquamous histology (81.6%). Of the 61 (62.2%) with available ECOG performance status (PS) data, 72.1% had ECOG PS of 0 or 1. Baseline characteristics were similar between the overall cohort and ram+doc post-ICI patients, as were clinical outcomes between the two groups (Table 1).

Table 1. Clinical Outcomes for 3L Ram+Doc Treated Patients

	3L Ram+Doc (Overall) n=98	3L Ram+Doc (Post-ICI) n= 65
Median OS (95% CI), month	19.1 (16.3 - 23.7)	19.0 (15.7 - 23.7)
Median PFS (95% CI), month	3.6 (3.0 - 4.2)	3.6 (3.0 - 4.6)
Median TTP (95% CI), month	5.5 (4.0 - 7.9)	5.5 (3.6 - 7.9)

Conclusion: In this real-world platinum-treated cohort, most 3L ram+doc usage was post-ICI. Clinical outcomes for ram+doc post-ICI patients were consistent with those for the overall 3L ram+doc cohort. These data may support the use of ram+doc post-ICI among platinum-treated patients with aNSCLC. Further research is needed to evaluate the efficacy and safety of ram+doc following chemo+ICI combinations.

Keywords: NSCLC, ramucirumab, Immunotherapy

P3.01-20 ADVANCED NSCLC TREATMENT AND OUTCOMES AFTER NIVOLUMAB

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Background: Nivolumab is now often used in the second line in non-small cell lung cancer (NSCLC). Fitness for further treatment and outcomes in clinical practice, after discontinuation of nivolumab, are not well documented. **Method:** A single centre retrospective analysis was conducted on all patients who had received and ceased nivolumab between July 2015 and February 2018. 61 patients were identified. Management after nivolumab and survival outcomes were reviewed. **Result:** The median age of patients was 66 years (range 28-82). 31 patients were male (51%). 71% had adenocarcinoma (n=43), 21% had squamous carcinoma (n=13), and 8% other NSCLC (n=5). 33 received nivolumab as second line therapy, 18 as third line, 9 as fourth line, and 1 as fifth line. 79% of patients ceased nivolumab due to progressive disease (n=48) and 16% due to toxicity (n=10). 3 patients discontinued treatment after developing unrelated medical issues. 36% of patients (n=22) underwent further treatment. Next line treatments included pemetrexed (n=10), platinum doublet rechallenge (n=4), docetaxel (n=4), vinorelbine (n=2), weekly gemcitabine (n=1), and crizotinib (n=1). Of those who received further treatment, 9 were alive at censoring and 13 were deceased. In Australia, carboplatin/gemcitabine is more likely to be used in first line treatment of metastatic adenocarcinomas because of Medicare restriction on reimbursement. Nivolumab and pemetrexed are used subsequently after progression. The efficacy of pemetrexed when used after nivolumab is not well documented. In our cohort, 10 patients received pemetrexed after nivolumab, and showed a median survival of 10.6 months after discontinuation of nivolumab. The median duration of pemetrexed therapy was 5.4 months. Median overall survival, from last nivolumab dose, of all patients was 4.4 months (n=61). The median survival in patients who received any treatment after nivolumab was 10.5 months (n=22). Those who received nivolumab as a 2nd line treatment after platinum doublet therapy (n=33) had a median overall survival of 8.0 months. **Conclusion:** In a heavily pre treated heterogeneous population, median survival after nivolumab was 4.4 months. 36% commenced further treatment and this population had an increased median survival of 10.5 months. Pemetrexed has efficacy in the 3rd line setting after platinum doublet and nivolumab therapy.

Keywords: Advanced NSCLC treatment, Treatment after nivolumab, Survival after Nivolumab

P3.01-21 METASTATIC LUNG CARCINOMA —AN INSTITUTIONAL EXPERIENCE FROM EASTERN INDIA

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Background: Carcinoma lung carries poor prognosis and is the leading cause of death among all malignancies.In developing countries like India,two-third of patients present with advanced stage of disease,where survival is dismal.Hence a retrospective study was planned to be conducted to observe the clinicopathological profile of patients presenting with metastatic lung carcinoma and to analyse the treatment response and survival in these cases. **Method:** A retrospective analysis was done from hospital files of patients with metastatic carcinoma lung presenting to our hospital from January 2015 to April 2018. **Result:** Out of 55 patients of metastatic lung carcinoma ,36(65%) were male and 19(35%) were female.Majority of the patients were of elderly age group >60yrs i.e 47%(36patients),followed by 40-60yrs age group i.e 31%(17 patients).Considering laterality of primary malignancy,right lung was more commonly affected than left lung(60% vs 40%).Histopathologically adenocarcinoma was the most common variety encountered(85.45%,47 patients) followed by squamous cell variety(0.9%,5 patients).Among 47 patients of adenocarcinoma variety,20 patients(42.5%)have EGFR mutations,whereas 27 patients(57.5%) were EGFR nonmutated. The pattern of metastases shows single organ metastasis in 19 patients(34.5%) and multiple organ metastases in 36 patients(65.5%). Overall bone was the most common site(25 patients) of metastases whereas brain was the most common single organ metastasis site.The followup period ranged from 2months to 40 months(median followup period-7mnths).One year and two year overall survival was 30% and 10.9% respectively.Subgroup analysis between patients who have received Tyrosine Kinase Inhibitors(TKI)±chemotherapy group and those who have received chemotherapy only group showed median overall survival of 19 months vs 6mnths respectively. **Conclusion:** Inspite of increased awareness,incidence of metastatic lung carcinoma is still high.Adenocarcinoma is the most common histopathological variety. Bone,contralateral lung and brain were the common organs involved by metastases.EGFR mutation status should be assessed in all cases of adenocarcinoma lung.Adding TKI in EGFR mutated cases has shown increased survival in our study.Larger sample size and longer followup period can further validify the results.

Keywords: metastatic, lung, carcinoma

P3.01-22 AN EXPLORATORY ANALYSIS OF PD-L1 EXPRESSION AND SMOKING HISTORY IN A COHORT OF ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Response to PD-1 checkpoint inhibitors in NSCLC is associated with PD-L1 expression. One hypothesis is that high PD-L1 expression may correlate with tumour mutational load, the latter reflecting past tobacco exposure. **Method:** We examined PD-L1 expression by tumour proportion score (TPS) in patients with advanced NSCLC and correlated this with the subjects' smoking history. Number of pack-years was estimated by the same individual during the initial consultation. Demographic characteristics, performance status(PS), stage, histology were obtained from the electronic patient records. PD-L1 testing was performed using the Dako PD-L1 IHC 22C3 pharmDx test in all but 3 cases where the SP263 Roche antibody was used. We compared pack-years and smoking status of subjects with PD-L1 negative(TPS<1%), weakly-positive (TPS1-49%) and strongly positive (TPS≥50%) NSCLC. **Result:** Between 12/2016-3/2018, 54 biopsy specimens from 52 patients with advanced NSCLC were tested for PD-L1 expression at UHB. In 5 biopsies, material was not tested, as unsuitable in 4(<100 tumour cells present) and testing was cancelled in 1 patient who declined treatment. For the remaining 47 biopsies patient characteristics were: Median age 70 (43-82), male/female 26/21, PS 0/1/2/3-4 was 10/26/8/3, stage IIIA/IIIB/IV 3/18/26, histology adenoca/squamous/mixed 33/11/3. Median pack-years in PD-L1 negative 30(0-60), PD-L1 weakly positive 35(0-80), PD-L1 strongly positive 33(0-100); current+former smoker/never smoker numbers: PD-L1 negative 14/3(82.4%/17.6%), PD-L1 weakly positive 11/1(91.7%/8.3%), PD-L1 strongly positive 15/3(83.3%/16.7%). Strong/weak PD-L1 expression was seen in 3/1 never smokers; of these 2 had EGFR mutation. Weak expression was also seen in 1 ALK-positive NSCLC patient, former light smoker (5pack-years).

	PD-L1 neg N=17	PD-L1 pos Weakly +ve N=12 Strongly +ve N=18 N=30	Total N=47
Age	70 (44-82)	71 (43-81)	70 (43-82)
Sex M/F	9/8	17/13	26/21
% M	52%	57%	55%
PS 0-1/2/3-4	11/5/1	25/3/2	36/8/3
% 0-1	65%	83%	77%
Stage IIIA/IIIB/IV	1/5/11	2/13/15	3/18/26
% IIIB-IV	94%	93%	94%
Path Adeno/Sq/Mixed	12/4/1	21/7/2	33/11/3
% Adeno	71%	70%	70%
Pack-years, mean	28	35	33
Median (range)	30† (0-60)	33† (0-100)	30 (0-100)
Smoking status			
Current/Former/Never	6/8/3	12/14/4	18/22/7
Current + Former (%)	14‡ (82%)	26‡ (87%)	85%

†, Mann Whitney U test, p=0.5552; ‡ Fischer's exact test, p=0.6918

Conclusion: In this small retrospective cohort there were no differences in median pack-years of smoking or proportions of current+former/never smokers between PD-L1 negative and positive tumours. Smoking history alone may not be the only factor influencing PD-L1 expression. Never smoking status and EGFR-mutated/ALK-positive NSCLC should not be excluded from PD-L1 testing.

Keywords: PD-L1, smoking, pack-years

P3.01-23 IMAGING MODALITIES FOR SURVEILLANCE AND FOLLOW-UP OF PATIENT WITH LUNG CANCER AFTER ADJUVANT CHEMOTHERAPY

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Background: Non-small cell lung cancer (NSCLC) represents over 80% of lung tumours. If diagnosed early, treatment is surgical with curative intent. The addition of postoperative cisplatin-based chemotherapy has demonstrated a significant survival advantageand is generally accepted as a standard treatment in patients of good performance status. Despite this, risk of relapse remains high and current ESMO (2017) guidance suggests 'NSCLC patients treated with radical intent should be followed for treatment-related complications, detection of treatable relapse or occurrence of second primary lung cancer. Recommendations for surveillance, include regular review, physical exam and imaging. This should be tailored to suitability of individual patients for further intervention. Local practice mandates a chest x-ray (CXR) with CT and/or PET follow-up of anomalies. **Method:** Between January 2004 and May 2017 165 patients underwent surgical resection for Stage 1B-IIIA NSCLC. We identified all patients within this cohort with radiological evidence of thoracic recurrence who had relapsed following postoperative chemotherapy. Electronic patient care records were used for data collection. Patient characteristics, surveillance modalities and overall survival (OS) from date of diagnosis to first relapse were analysed. Imaging modalities detecting recurrence and OS were determined using Kaplan-Meier methodology (SPSS). **Result:** 89 patients were identified, the median age was 62 years (range 42-77 years). Patients underwent surveillance initially every 3 months following completion of postoperative chemotherapy. Median time to relapse was 25.6 months (range 0.53 to 50.9 months). 62 patients (69.7%) had radiological confirmed evidence of disease recurrence. 4 (6.5%) had relapsed with extra-thoracic recurrence. 28 patients (45.2%) had confirmed intra thoracic disease recurrence on CXR despite chest CT imaging

performed at designated time intervals. However, 27 patients (43.5%) that underwent surveillance with CXR had confirmed intra thoracic disease recurrence with chest CT imaging. Median OS for CXR detected recurrence was 27.5 months (range 6.5 – 99.1 months) and 27.45 months (range 5.9 to 104.2 months) for chest CT detected recurrence (p-value 0.46). **Conclusion:** There is a paucity evidence specifically around the follow-up and surveillance modalities aimed at detecting relapse to improve survival after curative intent therapy in NSCLC.Our data demonstrate that 3 monthly CXR is an appropriate surveillance modality for initial detection of intra-thoracic disease recurrence.

Keywords: adjuvant NSCLC, Surveiilence, Disease Recurrence

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-24 THE IMPORTANCE TO SWITCH FROM EGFR-TKI TO CYTOTOXIC CHEMOTHERAPY FOR EGFR MUTATION-POSITIVE ADENOCARCINOMA

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Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have become the first-line treatment for *EGFR*-positive non-small cell lung cancer (NSCLC) patients all over the world. Furthermore, *EGFR*-positive patients who received not only EGFR-TKI but also chemotherapy have good prognosis. However, transition rate from first-line EGFR-TKI to chemotherapy is low. **Method:** A total of 229 consecutive patients with adenocarcinoma were treated with EGFR-TKI from January 2010 to December 2016 at Tokyo Medical University Hospital. Among these, 159 patients were analyzed in the present study. After excluding 70 patients (45 patients undergone first-line treatment, 7 received chemoradiotherapy,and 18 received osimertinib). The prognosis according to treatment sequence and the reasons patients could not switch from first-line EGFR-TKIs to chemotherapy were analyzed. **Result:** The median follow-up period was 22.5 months. Of the total 159 patients, 113 (71%) were female, 114 (72%) were <75 years old, and 86 (54%) showed postoperative recurrence. The most frequent subtypes of *EGFR* were exon 19 deletion in 84 patients (53%) followed by exon 21 L858R in 54 patients (34%). EGFR-TKIs were administered as a first-line therapy in 93 (58%) patients, and chemotherapy was administered in 66 (42%) patients. The most common first administered EGFR-TKI as a first-line was gefitinib in 133 (84%) of 159 patients. Among the 93 patients who were administered EGFR-TKIs as a first-line treatment, 32 (34%) patients transitioned to chemotherapy. The median survival times (MST) of EGFR-TKIs combined with chemotherapy group and EGFR-TKIs alone group were 59.8 months and 22.5 months, respectively ($p < 0.001$), and MST of patients who received EGFR-TKIs first and chemotherapy first were 38.8 months and 66.4 months, respectively ($p = 0.016$). The main reasons patients could not transition to chemotherapy was worsening of performance status followed by the patient's preference. **Conclusion:** EGFR-TKIs and chemotherapy led to good prognosis in *EGFR* mutation-positive adenocarcinoma patients. It is necessary to consider the timing to switch the treatment strategy before PS becomes worse.

Keywords: chemotherapy, EGFR-TKI, NSCLC

P3.01 ADVANCED NSCLC
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P3.01-25 FEASIBILITY OF MODERATE HYPOFRACTIONATED THORACIC IRRADIATION FOR NON-SMALL CELL LUNG CANCER PATIENTS WITH VERY LIMITED LUNG FUNCTION

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Background: To determine the feasibility of moderate hypofractionated image-guided thoracic irradiation (modHypo-IGRT) in locally advanced node-positive non-small cell lung cancer patients with very limited pulmonary function. **Method:** Eight selected patients with highly diminished pulmonary function (FEV1 ≤ 1.0L and/or DLCO ≤ 40% and/or long-term oxygen therapy) were treated with modHypo-IGRT. Planning was based on 18F-FDG-PET/CT and 4D-CT. Gross tumor volume (GTV) included primary tumor and involved lymph nodes. Internal target volume (ITV) was defined through the overlap of GTVs on 10 phases of 4D-CT. An isotropic margin of 5 mm was added to ITV to generate the planning target volume (PTV). modHypo-IGRT was delivered to a total dose of 45 Gy (ICRU) in 15 daily fractions under strict image-guidance. Vital capacity (VC), forced expiratory volume in 1s (FEV1), and single-breath diffusing capacity of the lung for CO (DLCO-SB) were analyzed prior to, 3 and 6 months after modHypo-IGRT. **Result:** Eight patients completed modHypo-IGRT. The median follow-up was 20 months. The median age was 64 years. Two, 4 and 2 patients presented with stage IIIA, IIIB, and IIIC. Seven patients were with performance status ECOG 2 and 1 with ECOG 3. Five patients (63%) were on long-term oxygen. Three patients received chemotherapy prior to modHypo-IGRT. The median PTV was 226.9 cm^3 (range: 100.17 - 379.80). The median overall (OS) and progression-free survival (PFS) for the entire cohort were not reached. The 1- and 2-year OS rates were 100% and 87.5%. The 6- and 12- months PFS rates were 100% and 63%. Three patients developed local failure. Median mean lung dose was 9.4 Gy (range: 5.3 -11.6). V15 and V20 for both lungs were 22% (range: 10-25) and 15% (range: 6-19). Median mean esophageal dose was 12.76 Gy (range: 2.1-26.7). There was no case of radiation pneumonitis. Four patients developed grade 2 radiation esophagitis. Median initial VC, FEV1 and DLCO-SB was 1.69L/64.8% predicted (range: 1.36-2.66/33-80%), 1L/39.4% predicted (range:0.78-1.26/28-60%) and 33.3% (range: 13.3-54), respectively. Median value for VC, FEV1 and DLCO-SB 3 months after modHypo-IGRT was 2.05L/56.35% predicted (range: 1.34-2.33/47-81.5%), 1.08L/47.5% predicted (range: 0.74-1.60/30.8-59.59%) and 38.55% (range: 24-68). At 6 months post-treatment, the median value for VC, FEV1 and DLCO-SB was 1.64L/66% predicted (range: 1.41-2.79/35.5-75.5%), 1.0L/47% predicted (range: 0.65-1.28/24.5-54.10%) and 31% (range: 27-43%). **Conclusion:** modHypo-IGRT can be considered for individual patients with locally advanced node-positive NSCLC patients with very limited pulmonary function hence inadequate for conventional treatment. This protocol is being assessed in an ongoing single-center prospective study.

Keywords: Radiotherapy, survival, NSCLC

P3.01 ADVANCED NSCLC
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P3.01-26 A FRAMEWORK FOR SYSTEMATIC CLINICAL EVALUATION OF TECHNICAL INNOVATIONS IN LUNG CANCER PATIENTS TREATED ON THE MR-LINAC (MRL)

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Background: A recent innovation in radiotherapy is the MRL developed by Elekta and Philips. The MRL combines a 1.5 T MRI with a 7 MV linac. It allows the acquisition of high resolution MR images for on treatment verification, adaption and response monitoring. **Method:** Seven cancer institutions from Europe and North America, are working within the Elekta MR-Linac Consortium to evaluate the MRL within a framework called 'R-IDEAL' (Radiotherapy Idea Development Exploration Assessment Long-term Evaluation) [1]. **Result:** The table below summarizes the ongoing and planned work within the Elekta MR-Linac Consortium.

(See next page)

	Predicate studies Stage 0	Idea Stage 1	Development Stage 2a	Exploration Stage 2b	Assessment Stage 3
Purpose	Technical preparatory studies	First time use of the innovation for treatment delivery in men	Technical optimization of the innovation for treatment delivery	Investigate early clinical effectiveness and safety of the innovation	Formal comparison of innovation against standard treatment
Ongoing and planned work	Development of MR lung sequences Development of a consensus atlas for MR guided lung radiotherapy Comparison of quality of the pre-beam cone beam CT (CBCT) to MR image guidance	Investigation of the feasibility of conventionally fractionated RT on the MRL and scope for RT adaptation	Small prospective cohort study demonstrating improved accuracy	Investigation of differentiated dose escalation in locally advanced NSCLC	Randomised controlled trial: standard of care vs. dose escalated RT

Progress to date:

Stage 0: We defined in 80 patients the optimal MRI sequences suitable for GTV and organ at risk (OAR) contouring: T2 Turbo Spin Echo (TSE), T2 TSE with fat sat, T1 radial gradient echo, and DIXON TSE. Two radiology-led workshops were organized and inter-observer agreement was assessed for OARs. These led to a consensus-based OAR atlas. A study is being prepared to compare the image quality of the current standard CBCT and MR images at baseline and mid-treatment for treatment verification and set-up correction.

Stage 1: we will investigate the clinical feasibility of the MRL for standard of care radiotherapy and the scope for adaptive radiotherapy (margin reductions) and detecting changes in oxygenation during treatment on the MRL in patients with locally advanced (LA) NSCLC .

Stage 2a/b : Based on the results from stage 1 we will design a study aiming to reduce margins around the tumour and dose escalate in patients with LA NSCLC. **Conclusion:** The aim of this programme of work is to generate robust evidence to support the introduction of the MRL and to improve outcomes of patients with LA NSCLC.

Keywords: MR, MR-linac, LA NSCLC

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-27 CHARACTERIZATION AND SENSITIZATION OF NON-SMALL CELL LUNG CANCER CELL LINE VARIANTS SELECTED FOR RESISTANCE TO OSIMERTINIB

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Background: Many non-small cell lung cancers (NSCLC) are oncogenically driven by mutant epidermal growth factor receptor (EGFR). EGFR tyrosine kinase inhibitors (TKIs) are commonly used as first-line treatments against such tumours, but NSCLC tumours recur with novel EGFR mutation(s) (often a T790M mutation in exon 20) that confers resistance to these drugs [Ther Adv Respir Dis 10(6): 549-565, 2016]. Third generation EGFR TKIs (e.g., osimertinib) have been designed that are highly active against both T790M EGFR and the original oncogenic EGFR lacking the T790M mutation. Clinical resistance to third generation TKIs has been observed, but model systems in which to study the mechanisms of resistance are few. The human NSCLC cell line H1650 has the EGFR-activating mutation del E746-A750. The human NSCLC line H1975, derived from an EGFR-TKI-resistant tumor, contains EGFR-activating mutation L858R as well as resistance-conferring T790M. To explore mechanisms mediating resistance to third generation TKIs, we selected variants of the H1650 and H1975 cell lines for resistance to osimertinib to create models in which mechanisms of resistance can be characterized and tested for potential methods to overcome that resistance. **Method:** Cells were exposed continuously to a single concentration of osimertinib, in some cases with the inclusion of verapamil to avoid possible selection of multidrug-resistant cells. After 4 weeks, with weekly changes of drug-medium, clonal cell lines were selected from H1650 cultured in the presence of 25 or 50 μM osimertinib plus 10 μM verapamil, and selected from H1975 cultured in 6 or 10 μM osimertinib alone or 5 μM osimertinib plus 10 μM verapamil. **Result:** The H1650 osimertinib-resistant cell lines (H1650/osi-25a/VPL and H1650/osi-50a/VPL) are 1.6- to 1.8-fold resistant to osimertinib. The H1975 osimertinib-resistant cell lines (H1975/osi-6b, osi-10c, and osi-5b/VPL) were, respectively, 90-, 95-, and 38-fold resistant to osimertinib. None of the cell lines was cross-resistant to imatinib. The compound 2-(benzylsulfonyl)-1-(1H-indol-3-yl)-1,2-dihydroisoquinoline (IBR2) is an inhibitor of the DNA repair protein RAD51 and enhances cytotoxicity of EGFR inhibitors against numerous cell lines (Ferguson et al., JPET 2018, doi.org/10.1124/jpet.117.241661). IBR2 decreased osimertinib-resistance by up to 80% in the H1650- and H1975-derived osimertinib-resistant cell lines. Further analyses of the resistant cell lines are being undertaken. **Conclusion:** The H1650 and H1975 osimertinib-resistant cell lines are a valuable resource in which to test methods to circumvent resistance to third generation EGFR TKIs.

Keywords: Resistance, EGFR-TKI, osimertinib

P3.01-28 THE CLINICAL IMPACT OF COMPREHENSIVE CFDNA GENOMIC TESTING IN LUNG CANCER

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Background: Next-generation sequencing (NGS) of cell-free circulating tumor DNA (cfDNA) enables a non-invasive option for comprehensive genomic analysis of non-small cell lung cancer (NSCLC) patients. Although plasma-detected genomic alterations have been shown to predict targeted therapy response, evidence of durability of response is lacking or limited to small cohorts as is the impact of cfDNA NGS results on clinical decision making. **Method:** In this retrospective study, data was collected on stage IIIB/IV NSCLC patients between the years 2014-2017 in Israel. We utilized cfDNA NGS (Guardant360) which covers the seven genes targetable with FDA-approved therapies in NSCLC. **Result:** 116 consecutively NSCLC patients were tested, 41.4% (48/116) before 1st line therapy (Group A), 34.5% (40/116) upon progression on chemotherapy or immunotherapy (Group B1) and 24.1% (28/116) upon progression on EGFR TKIs (Group B2). Targetable genomic alterations were found in 65% of group A (15/48), 53% in group B1 (21/40) and 71% in group B2 (20/28). Treatment decision was changed to targeted therapy based on cfDNA NGS analysis in 23% (11/48), 25% (10/40) and 32% (9/28), respectively (total cohort 26%; 30/116). Response assessment (RECIST) showed complete response in 4% (1/28), partial response in 39% (11/28), stable disease in 32% (9/28) and progressive disease in 25% (7/28). Total objective response rate (ORR) was 43% and disease control rate was 75% for 5 months treatment duration. **Conclusion:** Comprehensive cfDNA testing impacted clinical decisions in 23% of naïve patients, 25% in patients who progressed on chemotherapy and 32% in EGFR TKI progressors. Median treatment duration was 5 months. This retrospective study extends previous reports by showing that responses based on cfDNA are durable and change treatment decisions at initial presentation and at progression.

Keywords: liquid biopsy, non-small cell lung cancer, next generation sequencing

P3.01-29 ST.IV LUNG ADENOCARCINOMA TREATED BY FIRST-LINE EGFR-TYROSINE KINASE INHIBITORS-SURVIVAL, EGFR MUTATION, HISTOLOGIC SUBTYPE

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Background: The aim of the study is to evaluate the correlation of survival, EGFR mutation and histologic subtype of stage IV lung sensitive mutant adenocarcinoma treated with first-line EGFR–tyrosine kinase inhibitors (EGFR-TKI). o:p> **Method:** We retrospectively analyzed the clinical outcomes of 60 consecutive patients with EGFR-TKI sensitive mutations (exon 19 deletion or exon 21 L858R) who received first-line erlotinib, gefitinib or afatinib therapy between October 2011 and September 2017. Histologic subtype was classified according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society pulmonary adenocarcinoma classification. **Result:** There were 60 patient enrolled, including 26 men, mean age 68.88 years (range: 49-89) and 34 women, mean age 65.68 years (range: 44-82). The average survival in women was 14.1 months and in men it was 13.3 months. Average survival in 28 patients were treated with Erlotinib was 14.51 months, in 18 patients treated with Gefitinib it was 12.79 months and in 14 patients treated with Afatinib it was 13.55 months. In 30 patients with the mutations (exon 19 deletion), the mean survival was 14.56 months. In the group of 26 patients with mutations (exon 21 L858R), the mean survival was 12.68 months. The mean survival in the group of patients with acinar adenocarcinoma was 15.49 months, and in solid adenocarcinoma - 4.8 months. Currently, 21 patients are alive and remain in observation, 12 of them are treated and 39 patients died. In the multidimensional linear regression analysis, smoking was a factor decreasing the survival at p = 0.12, male gender decreased the survival rate p = 0.04, and the type of cancer subtype increased the survival rate p = 0.04. Erlotinib influenced the increase in survival at p = 0.15 **Conclusion:** Mutation in (exon 19 deletion), histological subtype of tumor and Erlotinib treatment are factors significantly affecting the survival of patients with stage IV adenocarcinoma of the lung.The EGFR mutation frequency is higher in the acinar subtype than in other subtypes.

Keywords: Lung adenocarcinoma, EGFR mutation, EGFR- tyrosine kinase inhibitors, IASLC/ATS/ERS classification

P3.01-30 TREATMENT SEQUENCING IN PATIENTS WITH ANAPLASTIC LYMPHOMA KINASE (ALK)-POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC) IN JAPAN

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Background: Limited data are available on real-world treatment patterns and outcomes of ALK inhibitors used sequentially. Access to a large medical records database and availability of multiple ALK inhibitors in Japan, the first country to approve alectinib in 2014, presents a unique opportunity to evaluate real-world treatment sequencing and outcomes in ALK-positive NSCLC patients. **Method:** This descriptive, retrospective observational study used inpatient/outpatient medical and prescription records, claims and diagnoses from the Japan Medical Data Vision (MDV) Database. Included patients had confirmed diagnosis of lung cancer, an ALK test and first prescription order for an ALK inhibitor (prescription date = index date) on or before March 31, 2017. Descriptive analyses included demographics, baseline characteristics, treatment patterns including ALK inhibitor sequences, non-ALK inhibitor treatments received, and treatment duration. **Result:** Overall, 378 patients (mean age 61 years; 53% female; 48% no history of smoking) met inclusion criteria. Baseline characteristics were similar among mutually exclusive groups of patients receiving 1, 2, or 3 ALK inhibitors. Similar proportions of patients received crizotinib (52%) and alectinib (48%) as index ALK inhibitor. Prior to the index date, 40% of patients received chemotherapy. ALK inhibitor sequences are shown (Table). In patients who had discontinued all ALK inhibitors, the next treatments were chemotherapy (46%) and immunotherapy (6%). The most common sequence was a crizotinib-led sequence of 2 ALK inhibitors; median duration of treatment was 53 months. Changes in treatment patterns over time and further duration of treatment data will be presented.

Sequence	Overall Population N = 378
	n (%)
1 ALK inhibitor (n=261)	
Crizotinib	91 (24.07)
Alectinib	170 (44.97)
2 ALK inhibitors (n=98)	
Crizotinib -> Alectinib	89 (23.54)
Crizotinib -> Ceritinib	1 (0.26)
Alectinib -> Crizotinib	7 (1.85)
Alectinib -> Ceritinib	1 (0.26)
3 ALK inhibitors (n=19)	
Crizotinib -> Alectinib -> Ceritinib	16 (4.23)
Alectinib -> Crizotinib -> Ceritinib	3 (0.79)

Conclusion: Treatment patterns in ALK-positive NSCLC patients have evolved over time. The most common sequence for patients receiving > 1 ALK inhibitor was crizotinib-led. Median duration of treatment with crizotinib-led sequences is consistent with what has been reported previously. Additional research is warranted to evaluate non-crizotinib-led sequences as data mature.

Keywords: ALK-positive NSCLC, treatment sequencing, tyrosine kinase inhibitor

P3.01-31 PROGNOSTIC FACTORS IN PATIENTS WITH RESECTED PATHOLOGICAL N2 NON-SMALL CELL LUNG CANCER

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Background: Postoperative outcome for non-small cell lung cancer (NSCLC) patients with mediastinal lymph node metastasis is unfavorable even after complete resection. To identify the subgroup of NSCLC patients with mediastinal lymph node metastasis whom we recommend surgical treatment, we sought to investigate prognostic factors in these patients. **Method:** We retrospectively reviewed NSCLC patients with pathologically identified mediastinal lymph node metastasis who underwent complete resection with systematic nodal dissection between 2000 and 2016. Demographic, clinical, and pathologic factors (sex, age, Brinkman index, performance status [PS], % vital capacity, forced expiratory volume % in 1 second, preoperative carcinoembryonic antigen [CEA], histological subtype, pathological tumor size, p-T factor [7th edition], pleural invasion, pulmonary metastasis, histological grade, number of positive mediastinal nodal stations [single station vs multiple stations], number of positive mediastinal lymph nodes [1-2 vs ≥3], epidermal growth factor receptor [EGFR] mutation status, and adjuvant chemotherapy) were analyzed using the log-rank test as univariate analyses and a Cox proportional hazards regression model for multivariate analyses to identify independent predictors of favorable overall survival (OS). **Result:** Of the 54 eligible patients, 38 were male and 16 were female. The median age and CEA were 65 years and 5.3 ng/mL, respectively. Lobectomy, bilobectomy, and pneumonectomy were performed in 49/3/2 patients. Histological subtypes were adenocarcinoma in 29 patients, squamous cell carcinoma in 17, and others in 8. EGFR was inspected in 33 patients, and 10 patients were EGFR mutated. Adjuvant chemotherapy was performed in 26 patients. The details of adjuvant chemotherapy were cisplatin-based combination chemotherapy in 18 patients, and carboplatin-based combination chemotherapy in 8. The 3-year and 5-year OS were 64.9% and 44.7%, respectively, with a median follow-up period of 41 months. The preoperative CEA <5.3 ng/mL (HR: 0.2151) and undergoing adjuvant chemotherapy (HR: 0.3580) were identified as significant predictors of favorable OS. The 3-year and 5-year OS in patients with CEA <5.3 and ≥5.3 ng/mL were 88.3/70.8% vs 41.0/17.9%, respectively (p<0.001). The 3-year and 5-year OS in patients who underwent adjuvant chemotherapy or none were 75.3/70.3% vs 55.3/23.1%, respectively (p = 0.009). **Conclusion:** Even if NSCLC patients have mediastinal lymph node metastasis, favorable postoperative prognosis may be expected in patients with low preoperative serum CEA. Adjuvant chemotherapy should be considered in patients with mediastinal lymph node metastasis on pathological examination.

Keywords: p-N2 NSCLC, Prognostic factors

P3.01-32 AN OPEN-LABEL, NON-RANDOMIZED, BIOMARKER STUDY OF CONCORDANCE IN NON-INVASIVE AND TISSUE TESTS FOR T790M DETECTION IN NSCLC

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Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are recommended first-line treatment for patients with advanced NSCLC and EGFR-TKI sensitizing mutations (EGFRm). However, most patients develop resistance to first- and second-generation EGFR-TKIs, with approximately 50% of the patients acquiring a secondary EGFR T790M resistance mutation. Osimertinib is a third-generation, irreversible, CNS-active oral EGFR-TKI that potently and selectively inhibits both EGFRm and T790M resistance mutations, and is approved for treating patients with T790M-positive advanced NSCLC who have progressed on first- or second-generation EGFR-TKIs. Tumor tissue is the preferred sample for T790M testing at progression; however, a tumor biopsy may not always be feasible because of tumor inaccessibility, inadequate tissue, and/or safety considerations. Non-invasive options to detect T790M include circulating tumor DNA analyses from plasma or urine. The RADIANCE study is designed to determine if plasma and urine tests combined can deliver a T790M detection rate similar to biopsy testing. **Method:** RADIANCE (NCT03137264) is an open-label, prospective biomarker study planned to be conducted at approximately 50 sites in the US and Canada. The primary objective is to assess the analytic concordance between non-invasive testing (Guardant360™, plasma; Trovera™, urine) and tissue testing (cobas® EGFR Mutation Test v2) for T790M detection in patients with advanced NSCLC. Patients with EGFRm NSCLC (N=470) with evidence of disease progression during or after first- or second-generation EGFR-TKI therapy will be eligible for enrollment in the study. Patients who received prior treatment with osimertinib or another T790M-directed therapy will be excluded. In this two-part study, Part 1 (diagnostic analytic validity) will include testing all enrolled patients for T790M using plasma (cobas/Guardant360), urine (Trovera), and tumor biopsy (cobas) tests. Patients with T790M-positive NSCLC detected by the cobas tissue and/or cobas plasma test may choose to receive osimertinib (recommended dose, 80 mg once daily) and continue to Part 2, while patients with T790M-negative NSCLC will be ineligible to continue in the study. In Part 2 (clinical outcomes), patients with T790M-positive NSCLC receiving osimertinib will be followed for 18 months or until disease progression or death and evaluated for tumor response rate, duration of response, and progression-free survival (investigator-assessed RECIST v1.1), as well as safety. The study is currently enrolling patients. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: osimertinib, liquid biopsy, non-small cell lung cancer

P3.01-33 EGFR MUTATION IN PATIENTS WITH NSCLC AND ITS RELATIONSHIP BETWEEN SURVIVAL AND CLINICOPATHOLOGICAL FEATURES: AN UPDATE ANALYSIS

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Background: There has been important developments in NSCLC since the understanding of molecular pathways. The aim of the study is to find the EGFR mutation frequency and its correlation to survival and clinicopathological features. We reported our data in this subject three years ago. We aim to resubmit our updated data. **Method:** In this multicenter study, 1352 NSCLC (adenocarcinoma) patients were included retrospectively to find out the EGFR mutation status with age, sex, performance status, histopathological diagnosis, smoking status and stage. Survival correlates were determined. The aim of the study was to find out the EGFR mutation status with all of the features in the database. **Result:** The median age was 59 (24-87) years. Median follow-up time was 14 (2-117) months. 26,2 % were female. 85,2% were stage IIIB-IV and 86 % was adenocarcinoma. EGFR mutation frequency was 22,3 % including exon 19 (63,0%). There was no correlation between mutational status and age, performance status, and stage at diagnosis (p>0,05). However, there was a correlation between gender and, smoking. (p= 0.000 and 0,000. respectively). The frequency of mutation in female patients was more pronounced in non-smokers/ex-smokers. In the group that can perform survival analysis (827 pts), median progression-free survival was 9 months and overall survival was 20 months. The overall survival was 27 (SE:5; 95% CI 17-36) months in EGFR positive cases whereas 19 (SE:1; 95% CI 16-21) months in EGFR negative cases (p=0,008). The multivariate analysis showed good performance status, early stage disease and presence of EGFR mutation as a prognostic factor (p<0,05).

Conclusion: Our investigation shows that the EGFR mutation rate in our patient population with adenocarcinoma of the lung was higher than in Western countries population and was lower than the East Asian population. The determination of EGFR mutation will lead the pathway for a better treatment outcome and individualized therapy.

Keywords: EGFR mutation, NSCLC, treatment

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-34 SHORT HYDRATION REGIMEN WITH A MODIFIED DOSE OF MAGNESIUM SUPPLEMENTATION FOR LUNG CANCER PATIENTS RECEIVING CISPLATIN-BASED CHEMOTHERAPY

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Background: Intravenous administration of magnesium is recommended for patients receiving high-dose cisplatin with a short hydration regimen in terms of protection against cisplatin-induced nephrotoxicity. However, the optimal dose of the magnesium supplementation has not been clarified. The aim of this trial was to investigate the safety and efficacy of short hydration regimen with 20mEq of magnesium supplementation for lung cancer patients receiving cisplatin-based chemotherapy. **Method:** The key eligibility criteria included cytologically or histologically proven lung cancer, candidates for cisplatin (≥60 mg/m2) based chemotherapy or chemoradiotherapy, no prior chemotherapy, age ranged 20 and 75 years old and adequate renal function. Cisplatin was administered with pre-hydration containing 20 mEq of magnesium sulfate. Mannitol was administered just before the cisplatin infusion as an enforced diuresis. The primary endpoint was the proportion of patients without a Grade 2 or higher elevation in creatinine. The study was registered at UMIN-CTR as UMIN000011687. **Result:** Forty patients with a median age of 66 years (range, 35-74) were enrolled in the study. Of these, 16 had adenocarcinoma, 12 had squamous cell carcinoma, 5 had small cell carcinoma, 2 had large cell carcinoma and 5 had other histology. The median baseline creatinine value was 0.71 mg/dl. The median dose of cisplatin at the first cycle was 80 mg/m2. Twenty-nine patients received cisplatin and vinorelbine as their most frequent regimen and 24 patients received 4 cycles of chemotherapy. In the first cycle, no patients developed Grade 2 creatinine toxicity. During the whole treatment period, one patient developed Grade 2 creatinine elevation, and thus, the proportion of patients without a Grade 2 or higher elevation in creatinine was 97.5% (95%CI 86.8-99.9). Grade 1 hypermagnesemia was observed in 3 patients. **Conclusion:** This study indicates short hydration regimen with 20mEq of magnesium supplementation was safe and feasible for lung cancer patients receiving cisplatin-based chemotherapy without risk of severe nephrotoxicity.

Keywords: lung cancer, Cisplatin, hydration

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-35 OUTCOMES IN ADVANCED NON-SMALL CELL LUNG CANCER AFTER DISCONTINUATION OF PD-1 CHECKPOINT INHIBITOR DUE TO TOXICITY. A RETROSPECTIVE STUDY

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Background: Programmed cell death ligand (PD-1) checkpoint inhibitors have been shown to improve survival in advanced non-small cell lung cancer. Although immune-related adverse events from single agent anti PD-1 or PDL-1 are manageable, severe toxicities require treatment discontinuation. There are limited data on patient outcomes after treatment discontinuation and the necessary cessation of treatment can cause concern of disease control for the patient and clinician. This retrospective study examined disease outcomes in patients after discontinuation of PD-1 checkpoint inhibitor due to toxicity. **Method:** Patients treated with pembrolizumab or nivolumab monotherapy for advanced non-small cell lung cancer at our cancer centre were identified. A retrospective review of electronic and paper records was performed. Information including patient baseline characteristics, progression- free survival, overall survival, toxicity leading to treatment discontinuation and time to progression after treatment cessation were obtained. Imaging was reviewed to confirm events of disease progression. **Result:** 54 advanced non-small cell lung cancer patients treated between 2012 and 2017 with single agent pembrolizumab or nivolumab were included in the analysis. 8 (14.8%) patients experienced toxicity necessitating treatment discontinuation. Baseline characteristics including age, ECOG performance status, prior lines of therapy and smoking status were similar in patients with or without severe immune-related toxicities. Pneumonitis was the most common toxicity requiring treatment cessation (n=4). Other toxicities included colitis (n=1), vasculitis (n=1), myositis (n=1) and bullous pemphigoid (n=1). The overall survival at 1 year was 42.6% for all patients versus 37.5% for patients with toxicities requiring treatment cessation. 2 of the patients with pneumonitis died as a result of this toxicity prior to achieving disease control. The patient with bullous pemphigoid and those survived pneumonitis had not experienced disease progression at time of analysis (all censored, alive and progression free for minimum of 6 months after treatment discontinuation). Time to progression was <5 months in the patients with colitis, myositis and vasculitis. **Conclusion:** With the limitations of this small study at a single site, patients requiring treatment cessation from toxicity had comparable progression-free and overall survival to those without severe toxicities. The risk of Grade 5 immune-related pneumonitis might have contributed to the numerically lower survival rates in the group that experienced toxicity. Prolonged disease control was observed in patients who survived pneumonitis despite treatment discontinuation.

Keywords: non-small cell lung cancer, Immunotherapy, toxicity

P3.01 ADVANCED NSCLC
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P3.01-36 PROGNOSTIC FACTORS IN ELDERLY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: There is no consensus method for identifying frail older patients. A number of clinical screening tests are now available but the prediction of outcome of treatment is difficult. Sarcopenia, as simply determined by a baseline Computed Tomography (CT) image, has been shown to be predictive of prognosis in Lung Cancer (LC). The purpose of this analysis was to determine the prognostic significance of CT determined sarcopenia, and other clinical parameters, on overall survival (OS) among elderly patients with advanced-stage Non-Small Cell Lung Cancer (NSCLC) and on active treatment. We also sought to determine the OS of this population, according to the different clinical parameters evaluated. **Method:** A retrospective analysis of 77 patients older than 65 years old with advanced NSCLC and ECOG PS 0-2 treated between 2014 and 2017 was performed. The variables tested were age, gender, ECOG PS, polypharmacy (the use of 5 or more medications), The Charlson Comorbidity Index (CCI), Body Mass Index (BMI), Lactate dehydrogenase value and sarcopenia. For the quantification of Sarcopenia two methods were used: Total Psoas Index (TPI) and the Hounsfield Unit Calculation (HUAC). Both obtained from a single axial Computed Tomography (CT) image at L3 level. Median OS was assessed by Kaplan-Meier method. Cox survival analysis was performed for a 95% CI for the hazard ratios, considering a p value of 0.05 as an indicator of statistical significance. Analyses were performed with use of SPSS v.18 software. **Result:** On our population we found sex, CCI and polypharmacy as independent risk factors associated with mortality. Median OS of the population was 14 months. Men and patients who presented with ECOG PS 2, BMI below 22 Kg/m2 and sarcopenia had worse outcome, but without statistical significance. **Conclusion:** Clinical variables may help to discuss prognosis with elderly LC patients. The identification of these factors can be used to improve patient selection for the different treatment options.

Keywords: lung cancer, Elderly patients, prognostico factors

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-37 PHASE II STUDY OF AMRUBICIN PLUS ERLOTINIB IN PREVIOUSLY TREATED, ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS WITH WILD-TYPE EGFR: TORG 1320

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Background: The combination of amrubicin (AMR) and erlotinib (ERL) was reported to have synergistic effect on non-small cell lung cancer (NSCLC) cell line with wild-type EGFR in vitro. We accomplished a phase I study of AMR plus ERL in previously treated advanced NSCLC patients, and determined the maximum tolerated dose (MTD). Furthermore, we observed a high response rate of 33% (Am J Clin Oncol 2015). **Method:** We conducted a multi-center, single-arm phase II trial to evaluate the efficacy of AMR and ERL combination therapy in patients with previously treated, advanced NSCLC with wild-type EGFR. Patients were treated at 3weeks intervals with AMR (35mg/m^2 on days 1-3) plus ERL (100mg/day on days 1-21). The patients without disease progression after 4 cycles continued ERL until disease progression or unacceptable toxicity. The primary endpoint is progression free survival (PFS). Secondary endpoints are response rate (RR), disease control rate (DCR), time to treatment failure (TTF), overall survival (OS), and toxicity. The concentration of trough ERL was measured after first cycle of treatment and in maintenance phase as an exploratory research to analyze relation between effectivity/safety and pharmacokinetics. **Result:** From June 2013 to July 2016, 25 patients were enrolled. With a median follow-up of 14.3 months (95%CI: 10.9 – 17.6), median PFS was 3.6 months (95%CI: 2.1 - 5.1). The RR and the DCR were 24.0% and 64.0%, respectively. Median OS was 15.4 months (95%CI: 13.4 – 17.4). We observed grade 3 or 4 toxicities such as leukopenia (68%), neutropenia (72%), anemia (8%), febrile neutropenia (12%), anorexia (12%), oral mucositis (12%) and rash (8%). We had no treatment related death. In pharmacokinetic analysis, the mean (±SD) trough concentrations (C_{trough}) of ERL in induction and maintenance phase were 1.070±0.463μg/mL and 0.879±0.427μg/mL, respectively. The C_{trough} of ERL in induction phase was higher than that in maintenance phase (p=0.0371). There was no relation between C_{trough} of ERL and any toxicity/response. **Conclusion:** Although the primary endpoint was not met in this trial, the PFS of AMR and ERL combination therapy was superior to that of AMR monotherapy which was previously reported. In this study, pharmacokinetic analysis showed that C_{trough} of ERL were elevated in combination therapy. This combination therapy might be an optional treatment as cytotoxic chemotherapy for NSCLC patients after platinum-doublet failure. Clinical trial information: UMIN 000010582.

Keywords: NSCLC, Amrubicin, Erlotinib

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-38 THERAPEUTIC EFFECTS OF FMNP-MSC FOR HYPERTHERMIA ON LUNG CANCER A549 IN NUDE MICE

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Background: To study therapeutic effects of fluorescent magnetic nanoparticles labeled mesenchymal stem cells (FMNP-MSC) for hyperthermia induced by an alternating magnetic field on lung cancer A549 in nude mice. **Method:** The fluorescent magnetic nanoparticles (FMNP) was prepared and characterized, and then were used to label mouse mesenchymal stem cells(MSCs) in vitro. The FMNPs-labeled MSCs were injected via tail vein into nude mice bearing non-small cell lung cancer A549 cells. The subcutaneous lung cancer tissues in the nude mice models were subsequently treated in external alternating magnetic field once a week for four weeks, temperature of tumor was detected by optical fiber. Four weeks after treatment, the tumor were collected after euthanizing the animals. Pathology change of tumor tissue was detected by light microscope, cell apoptosis proteins (Bax, Caspase-3) and anti-apoptotic protein (Bcl-2) were detected by Western blot **Result:** In vivo experiments confirmed that MSC FMNP can be carried to the tumor area. Temperature of tumor can heat up to 53 ℃ under alternating magnetic field. FNMP - MSC thermal therapy group mice tumor volume and weight growth was significantly inhibited, FMNP-MSC group of mice with tumor volume growth is restrained, the weight was not significantly inhibited. Apoptosis and necrosis change of tumor tissue could be detected by light microscope. Western blot confirmed, Bax protein expression in two treatment group obviously, and Caspase 3, the Bcl-2 in the two treatment groups have no significant expression **Conclusion:** FMNP-MSC can accurately targeting to the tumor area, which heat up to the effective temperature under alternating magnetic field, the growth of tumor in mice was significantly inhibited; apoptosis and necrosis could be seen in tumor, may be achieved by increasing the expression of Bax

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-39 ANALYSIS OF ACQUIRED EGFR T790M MUTATION IN PATIENTS WITH NON-SMALL CELL LUNG CANCER WHO RECEIVED ICOTINIB PROGRESS

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Background: As the first epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) in China, icotinib shows promising anticancer activity in vitro and vivo. The phase III clinical study (ICOGEN) showed that icotinib has a good efficacy and tolerability in Chinese patients with advanced non-small cell lung cancer (NSCLC) compared with gefitinib. The aim of this study is to investigate the acquired EGFR T790M situation of the non-small cell lung cancer patients who received icotinib treatment progress. **Method:** The ARMS method was used to detect the samples in 209 cases of EGFR 19del or L858R mutation non-small cell lung cancer. **Result:** There were 123 cases accompanied 19del and 86 cases accompanied L858R in 209 cases non-small cell lung cancer samples who received icotinib treatment progress, the acquired T790M mutation type patients was 45.93% (96/209), icotinib treatment. resistance after the acquired T790M mutation with 19 del/L858R group had statistical difference (P<0.034). **Conclusion:** 19 del patients who received treatment for icotinib are more likely to appear acquired T790M mutation than L858R patients from NSCLC, and we should attach importance to it.

Keywords: L858R, 19del, T790M

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-40 TREATMENT OF SUPER ELDERLY PATIENTS FOR NON-SMALL CELL LUNG CANCER IN JAPAN

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Background: Japan is the one of the country with the longest life expectancy in the world; many elderly Japanese are treated for lung cancer. The number of people dying from lung cancer is consistently increasing, and nearly half of lung cancer patients are older than 75 years of age. It is said that 60% patients died of the lung cancer are patients over 75 years. Approximately half of lung cancers are found in advanced stage, and are treated by chemotherapy. However, many clinical trials of lung cancer treatment using conventional anticancer drugs are targeted toward patients younger than 70years old. No clear evidence on treatment for elderly patients over 80 years has been established. We conducted a retrospective analysis of patients over 80 years old who were diagnosed with advanced non small cell lung cancer. **Method:** We retrospectively reviewed the outcome of patients over 80 years old who were diagnosed with advanced non small cell lung cancer between 2012 to 2016. **Result:** 48 patients were incorporated in the study; 26 were treated by chemotherapy (Median age 84years (80-89), 16 males), 22 were in BSC (Median age 84 years (80-96years), 13 males). 69%(18/26) of the treatment group were in Performance Status 0-1, compared to 18%(4/22) in the BSC group.(*p=0.0005)* Adenocarcinoma was the most common type in the treatment group(16/28), followed by Squamous cell carcinoma (7/28). Half of the treated patients were in stage IV, 6 cases were stageIIIb, and 6 cases stageIIIa. The median overall survival in treatment group was 378 days, median number of regimen conduced was 1 (average 1.37). In BSC group, it was difficult to follow until death, therefore comparison with the treatment group is not analyzed. **Conclusion:** It was suggested that the prognosis was prolonged by chemotherapy in the treatment group, compared to the previous chemotherapy trials for elderly patients. Chemotherapy should also be considered in super elderly patients over 80 years old, when he/she has good PS. However, regarding chemotherapy for the elderly patients with non small cell lung cancer, it is important to carefully consider adverse events.

Keywords: chemotherapy, advanced non small cell lung carcinoma, super elderly patients

P3.01-41 ANATOMICAL AND CLINICAL BASIS OF #11 LN BY SYSTEMATIC BILATERAL MEDIASTINAL NODAL DISSECTION FOR LEFT LUNG CANCER THROUGH MEDIAN STERNOTOMY

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Background: Patients with mediastinal lymph node metastasis have a poor prognosis, and lung operation is not typically indicated. We performed bilateral mediastinal lymph node dissection by median sternotomy to resect lung cancer and dissect the bilateral mediastinal lymph nodes. Although some studies have examined the communications between the left and right lymphatic pathways in lung cancer cases, we anatomically analyzed this technique of bilateral lymph node dissection, and confirmed its usefulness. There are some reports on #11LN positive cases and other lymph node metastasis cases. We investigated metastatic status between #11 lymph node positive cases and other lymph nodes by systematic bilateral mediastinal nodal dissection for left lung cancer through median sternotomy. **Method:** We performed this operation in 314 patients with primary left lung cancer excluding small cell carcinoma and stage IV since 1987. From among the 314 patients, 25 had in p-N1, 50 in p-N2, 24 in p-N3 lymph node metastases. Based on macroscopic dissection procedures, dissection of the lymphatics from the lungs to the supraclavicular lymph nodes was performed by sequential removal of the related organs. In particular we examined the metastatic status and clinical significance of #11 lymph node in N1-3 52cases. We systematically compared and analyzed the route of lymphatic communications to the contralateral side with emphasis on the anatomical significance of the left-to-right lymphatic communications of the bilateral mediastinal lymph nodes. **Result:** The overall 5-year survival rate (Kaplan-Meier method), including operative deaths and deaths due to unrelated diseases, was 65.5%(MST11.3yrs) in the patients with left lung cancer. With respect to the p-N factor, the 5-year survival rate were 40% in p-N1, 48.7% in p-N2, 53.6% in p-N3, 38.3% in #11LN positive in left lung cancer patients. We will report the investigation of the prognosis of left non small cell lung cancer patients who underwent initially our extended bilateral mediastinal dissection, focused on the patients with #11LN positive cases. **Conclusion:** We identified the route of lymphatic communications to the contralateral side, and systematically analyzed the anatomical significance of the left-to-right lymphatic communications in #11 LN positive cases. The overall 5-year survival rate (Kaplan-Meier method), including operative deaths and deaths due to unrelated diseases, was 65.5%(MST11.3yrs) in the patients with left lung cancer. With respect to the p-N1-3 factor, the 5-year survival rate were 40% in p-N1, 48.7% in p-N2, 53.6% in p-N3, 38.3% in #11LN positive in left lung cancer patients.

Keywords: Systematic Bilateral Mediastinal Nodal Dissection, Left Lung Cancer through Median Sternotomy, #11 lymph node

P3.01-42 PHASE II TRIAL ALLOWED SURGERY AFTER INDUCTION CHEMOTHERAPY OF CBDCA+PTX, BEVACIZUMAB IN PATIENTS WITH STAGES IIIA-IV NONSQUAMOUS NSCLC

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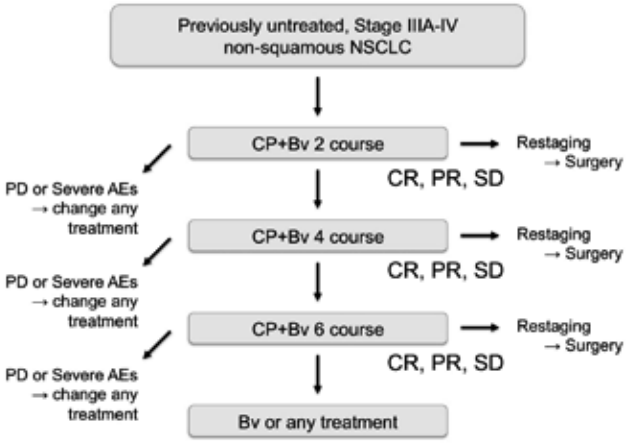
Background: Surgery remains the best therapy for cure in non-small cell lung cancer (NSCLC). However, the treatment strategy for advanced NSCLC patient including Stage III with N2 remains controversial. Bevacizumab (Bv), a humanized monoclonal antibody targeting VEGF, combined with the standard platinum doublet-based chemotherapy is approved for the first-line treatment of NSCLC. This study aimed to determine whether the treatment allowed surgery after induction chemotherapy of carboplatin (CBDCA) and paclitaxel (PTX) with Bv provides a reduction in the risk of progression in patients with stages IIIA to IV non-squamous NSCLC. **Method:** This clinical trial was an open-label, multicenter, single-arm study involving 10 institutions in Akita, Japan (UMIN000007916). Chemotherapy/radiation-naive patients > 20 years of age, ECOG performance status of 0 to 1, and adequate hematologic, hepatic, and renal function with cytologically or histologically confirmed stages IIIA to IV nonsquamous NSCLC not amenable to surgical resection or radiation with curative intent, were eligible. Treatment plan is showed in Figure 1.



Result: Between April 2012 and October 2017, a total 29 patients were enrolled. The overall response rate was 72.4%, 10 of 29 patients underwent radical surgery included lymph node dissection 2a-2 basically after the chemotherapy. Complete resection was achieved in 7 patients of them (70%) in the induction chemotherapy group. Bronchial stump and anastomoses were buttressed with a pericardial flap or intercostal muscle flap in some cases. The 30-day hospital mortality was 0% in the all patients who underwent operation. Grade 3 or 4 adverse events occurred in 72.4% such as neutropenia, just one case has pulmonary hemorrhage and GI bleeding. **Conclusion:** These results suggest that CBDCA+PTX, Bv which has higher response rate will introduce the better potential to reduce tumor size, increase operability, and eradicate micro-metastases. However, a survival benefit might be limited even though surgery was added after induction chemotherapy.

Keywords: bevacizumab, induction chemotherapy, non small cell lung cancer

P3.01-43 PREDICTIVE VALUE OF COMPUTED TOMOGRAPHY CHARACTERISTICS FOR NIVOLUMAB RESPONSE IN PRETREATED NON-SMALL CELL LUNG CANCER

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Background: The efficacy and safety of nivolumab for the treatment of pretreated non-small cell lung cancer (NSCLC) have been established. We conducted a retrospective multicenter trial to determine the significance of computed tomography (CT) morphologic characteristics as a predictor of nivolumab efficacy for advanced NSCLC patients. **Method:** From April 2013 to March 2017, 78 pretreated NSCLC patients were enrolled. Our radiologist assessed the following tumor characteristics on CT before nivolumab treatment; interstitial septal thickening, peritumoral ground-glass opacity, spiculated margin, air bronchogram, cavity or necrosis, adjacent organ invasion, bulky lymph node (≥ 2.5 cm), and accumulation of small lymph nodes. After nivolumab treatment, objective response rate (ORR), disease control rate (DCR) and progression free survival (PFS) were analyzed with logistic regression and Cox proportional hazards regression models. Patient and CT morphologic characteristics were retrospectively analyzed. Significant parameters identified by univariate analysis were included in a multiple analysis. **Result:** Of the 78 patients, 60 (77%) were male, and 72 (92%) patients were of performance status 0 to 1. Heavy smoking was related to higher ORR than light or never smoking (28% vs 0%, p=0.01). No morphologic characteristics were related to ORR or DCR. Interstitial septal thickening was significantly associated with shorter PFS (p=0.015, 77 vs 126 days). Adjacent organ invasion was also significantly associated with shorter PFS (p=0.047, 72 vs 118 days). However, they were not found to be significant on multivariate analysis. **Conclusion:**

Interstitial septal thickening and adjacent organ invasion may be negative prognostic factors of nivolumab treatment for NSCLC.

Keywords: non-small cell lung cancer, immune check point inhibitor, Morphologic characteristics

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-44 CYFRA 21-1 AS A PREDICTOR TO RESPONSE TO CHEMOTHERAPY AND OVERALL SURVIVAL IN PATIENTS WITH ADVANCED NSCLC

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Background: In era of ever evolving, promising new therapies for advanced NSCLC, early predictors of response are needed. We evaluated early variations in serum CYFRA 21-1 of patients with advanced NSCLC receiving first line chemotherapy and correlated the results with objective tumor response and overall survival. **Method:** 29 consecutive untreated patients of advanced NSCLC with measurable disease on CTscan were evaluated. All patients were treated with conventional systemic chemotherapy. Serum samples were obtained before start of 1st and 2nd cycles. CYFRA 21-1 was measured with an electrochemiluminescense immunoassay. All patients were followed for a period of five years. Response was evaluated using RECIST. **Result:** 10 patients had partial response, 9 had stable disease and 9 had progression. None had complete response. 21/29 patients had elevated baseline value of CYFRA. 18/29 patients had decrease in CYFRA 21-1 after 1 cycle of chemotherapy. The average reduction in 2nd reading was irrespective of baseline value being normal or not. The average reduction was statistically significant (P = 0.002). 8/10 patients with partial response had reduction in their 2nd reading which was significant. We observed that 6/9 patients whose disease remained stable had a decrease in their subsequent reading (P=0.0106), though was not significant statistically. 5/9 patients who had an increase in their 2nd reading had progression, it was not statistically significant (P= 0.537). 14/19 who had partial response or stable disease, had a reduction in their 2nd value of CYFRA 21-1 and was significant statistically (P 0.004). We observed that except for 1, all patients who had decrease of 42% or more were responders (P 0.001), which was statistically significant.We followed all patients for five years. None was alive at 5 years. 10 patients were alive at 3 years and 6 were alive at 4 years. All patients who progressed after chemotherapy died within 1 year. 7/10 and 4/6 patients had reduction in their CYFRA 21-1 but was not statistically significant (P 0.24 95%CI -9.7-15.7). We observed that 3/4 patients who were alive at 4 years had a decrease of 30% or more in their subsequent CYFRA 21-1 level. **Conclusion:** We conclude that monitoring CYFRA 21-1 early during first-line chemotherapy may be useful prognostic tool for evaluation of early tumor response in patients with advanced NSCLC. Although decrease in CYFRA 21-1 was non statistically significant for monitoring overall survival, it can be used as surrogate marker in identifying patients for aggressive treatment but it needs validateion by large RCT

Keywords: CYFRA 21-1, ADVANCED NSCLC, OVERALL SURVIVAL

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-45 MULTIFACTORIAL GENE ALTERATIONS IN EGFR BYPASS PATHWAY ARE INDUCED BY AFATINIB IN T790M-MUTANT NSCLC RESISTANT TO OSMERTINIB

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Background: The 3rd generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) was developed to target the EGFR T790M resistance mutation in non-small cell lung cancer patients resistant to 1st or 2nd generation EGFR-TKIs. Although some mechanisms of acquired resistance to 3rd generation EGFR-TKI such as *EGFR C797S* mutation have been reported, the effect and resistant mechanisms to afatinib followed by osmertinib has not been well-known. **Method:** Nine patients with *EGFR* T790M-mutant NSCLC resistance to 3rd generation EGFR-TKI were enrolled in this study and treated with afatinib. Plasma samples were collected before treatment, 4 weeks after treatment, and at disease progression. Mutation profile and tumor mutation burden (TMB) in plasma cell free DNA (cfDNA) were analyzed by CAPP-seq. **Result:** The objective response rate and median progression-free survival of afatinib were 0% and 2.0 months, respectively. At the time of 4 weeks after treatment, four patients developed disease progression and five patients showed stable disease. A total of 36 somatic mutations or amplification were detected in plasma cfDNA before afatinib treatment; EGFR activating mutations in 8 patients, T790M mutation in 4, TP53 mutations in 6, PIK3CA mutations in 3, BRAF mutations in 3, MET amplification in 3, CTNNB1 mutations in 2, ERBB2 mutations in 2, C797S mutation in 1, SMAD4 mutation in 1, EGFR minor mutation in 1, KRAS mutation in 1, and APC mutation in one patient. *EGFR* C797S mutation in cfDNA was detected during afatinib treatment in two cases. In the patients having stable disease at 4 weeks after treatment, mutant allele frequency and TMB tended to decline once, and then increased in association with disease progression. **Conclusion:** Detection of mutant allele frequency and TMB of ctDNA by CAPP-seq could monitor the effectiveness and resistance to afatinib. Resistant mechanisms to afatinib might be characterized by multifactorial bypass pathway activation.

Keywords: CAPP-seq, Epidermal growth factor receptor, Afatinib

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-46 PROGNOSTIC UTILITY OF ADVANCED LUNG CANCER INFLAMMATION INDEX (ALI) IN THORACIC MALIGNANCIES: A META-ANALYSIS

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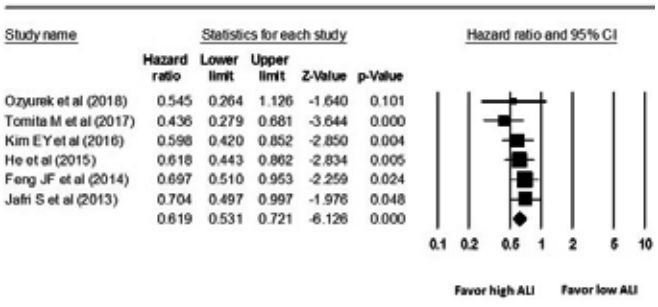
Background: We developed ALI as a prognostic marker in metastatic non-small cell lung cancer. ALI has now been validated in a variety of cancers. Here we report a meta-analysis of ALI as a prognostic marker in thoracic malignancies **Method:** ALI is calculated as follows: ALI= BMI x ALB/NLR, where BMI= body mass index, ALB=serum albumin, NLR=Neutrophil/lymphocyte ratio. ALI <18 is a marker of shorter progression free and overall survival. We searched database in PubMed up until January 31, 2018. We selected all the studies that compared the survival of patients with thoracic malignancies according to their ALI. We used the random effect model to calculate the pooled hazard ratio of overall survival. Meta-regression analyses, heterogeneity of data and publication bias were also appreciated. **Result:** A total of 6 studies, all retrospective in design, were included in the meta-analysis. Among these, 3 evaluated the prognostic value of ALI score in non-small-cell lung cancer, 2 in small cell lung cancer and 1 in esophageal cancer. By random effect model, we detected a statistically significant higher overall survival for patients with high ALI score (AL≥18). This corresponded to a pooled of hazard ratio of death of 0.619 (95% confidence interval: 0.531-0.721, p-value <0.001), with the subgroups of patients with low ALI score used as reference. Interestingly, no heterogeneity of data was found (Q-value=3.598, I-square = 0.000, p=value=0.609). By meta-regression analysis, the covariate "type of tumor" (non-small cell lung cancer vs. others) did not influence the predictive value of ALI score (test of model Q-value=0.34, p-value=0.55). No publication bias was detected by Egger test (p-value=0.24).



Conclusion: ALI significantly correlate with prognosis in thoracic malignancies regardless of tumor type and should be used in clinical practice and research to identify high-risk patients.

Keywords: prognostic marker, Advanced lung cancer inflammation index, Thoracic malignancies

P3.01-47 CLINICAL CHARACTERISTICS AND OUTCOME FOR PATIENTS WITH ADVANCED LUNG ADENOCARCINOMA TREATED WITH FIRST-LINE PEMETREXED PLUS PLATINUM

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Background: To evaluate the efficacy and safety of pemetrexed combined with platinum first-line therapy for advanced lung adenocarcinoma, as well as the clinical factors influencing outcomes. **Method:** We retrospectively evaluated the data from 450 pemetrexed-treated patients with stage IIIb/IV lung adenocarcinoma that confirmed by cytology or histology from February 2011 to August 2017. Patients were divided into 2 groups according to the presence of maintenance therapy (yes or no) after the first-line chemotherapy. The primary endpoint was progression-free survival (PFS), secondary endpoints included objective response rate (ORR), disease control rates (DCR), and safety. **Result:** A total of 292 received only first-line pemetrexed-based therapy, while 158 patients received maintenance pemetrexed after induction. The overall median PFS was 5.83 months (95% CI was 0.33 to 55.72 months). The maintenance treatment group had longer PFS (9.92 months, 95%CI: 3.98 to 5.21 months) than (P < 0.001) the non-maintenance treatment group (4.60 months, 95%CI: 8.70 to 11.14 months) after the first line chemotherapy (P < 0.001). The ORR and DCR of 450 patients with lung adenocarcinoma was 33.6% and 87.6%, respectively. Single-factor and multiple-factor analysis showed that positive mutation of epidermal growth factor receptor (EGFR), PS 0, exposure more than 4 cycles, and the addition of maintenance treatment were the positive prognostic factors for survival. The main adverse reactions of the patients were hematological toxicity, gastrointestinal reaction, abnormal and asthenia of liver function. However, low incidence of grade 3 or higher toxicity was seen in this study. **Conclusion:** First-line therapy with pemetrexed combined with platinum is safe and effective for advanced lung adenocarcinoma, and pemetrexed maintenance therapy has a better survival benefit.

Keywords: advanced lung adenocarcinoma, first-line and maintenance therapy, pemetrexed

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-48 THE EFFICIENCY OF LOW-DOSE APATINIBIN TREATMENT OF ADVANCED LUNG SQUAMOUS CELL CARCINOMA

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Background: Chemotherapy is the main treatment for advanced lung squamous cell carcinoma(LSCC) patients due to lack of effective targeted agents. Previous studies proved that apatinib, which is an antiangiogenic and small-molecule targeted drug, showed clinical benefit in patients with advanced non-squamous non-small cell lung cancer. In this study, we assessed the efficacy and safety of low-dose (125mg or 250mg, QD, oral) apatinib in the treatment of advanced LSCC. **Method:** A total of 8 advanced LSCC patients clinical data were reviewed retrospectively including 1 patient treated only by apatinib and 7 patients combined with other anti-tumor therapies (i.e., bronchial artery embolization (BAE), chemotherapy, radiotherapy or surgery) between May 2016 to July 2017. Efficacy was evaluated with the RECIST version 1.1 and adverse effects (AEs) were graded using the NCI CTC version 4.0. **Result:** One SD and 7 PR were confirmed, resulting in an objective response rate of 87.5% (7/8) and a disease control rate of 100% (8/8), respectively. The median progression-free survival (PFS) was 197 days (95% CI, 122-272 days), and the median overall survival (OS) was 252 days (95% CI,161-342 days). Both PFS and OS were 93 days for the patient with monotherapy, while the median PFS and median OS were 212 days (95% CI, 132-292 days) and 274 days (95% CI,182-366 days), respectively for the 7 patients with combined treatment. Patients with grade 3 or 4 AEs included 2 hemoptysis, 1 leukopenia and 1 fatigue. Patients characteristics are shown in the table below.

No.	Gender	Age (years)	PS	Line of apatinib therapy	Dose of apatinib (mg)	Therapeutic regimen	Efficacy	PFS (days)	OS (days)	Grade 3/4 AEs
1	Male	79	2	First-line	125	Apatinib plus BAE	PR	96	96	Grade 3 fatigue
2	Male	68	2	First-line	250	Apatinib plus BAE plus chemotherapy	SD	80	132	/
3	Male	63	1	First-line	250	Apatinib plus chemotherapy plus surgery (after down-staging)	PR	268+	268+	/
4	Male	56	1	Second-line	250	Apatinib plus chemoradiotherapy	PR	252	354	/
5	Female	43	1	Second-line	250	Apatinib plus chemoradiotherapy	PR	194	405+	/
6	Male	68	2	Second-line	250	Apatinib plus BAE plus chemoradiotherapy	PR	175	175	Grade 4 leukopenia
7	Male	59	1	Third-line	250	Apatinib plus BAE (after hemoptysis)	PR	343	379	Grade 3 hemoptysis
8	Female	59	1	Third-line	250	Apatinib	PR	93	93	Grade 4 hemoptysis

Remarks: + indicates that the patient was not deceased or whose tumor did not progress at the date of last follow-up.

Conclusion: Low-dose apatinib combined with BAE, chemotherapy, radiotherapy or surgery is effective and well tolerated in advanced LSCC patients. Risk of massive hemoptysis should be considered in LSCC patients treated with apatinib alone. BAE or radiotherapy may play a role in the prevention and treatment of severe hemoptysis associated with apatinib.Further prospective studies with larger numbers of patients are required.

Keywords: Apatinib, antiangiogenesis, Lung Squamous cell carcinoma

P3.01-49 EFFCIENCY OF LOW-DOSAGE APATINIB MONOTHERAPY IN TREATMENT OF ADVANCED LUNG SQUAMOUS CELL CARCINOMA

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Background: Lung squamous cell carcinoma (SqCC) is the second most common histology in non-small-cell lung carcinomas (NSCLCs). Chemotherapy of two drugs based on platinum is the standard treatment of advanced lung SqCC. However, few drugs could be selected when the disease progressed after second-line treatment. Apatinib, a small molecule inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2), have shown benefit in advanced NSCLC patients. This study aimed to preliminarily assess the efficacy and safety of apatinib at a lower dosage (125-500mg/d) in patients with advanced lung squamous cell carcinoma. **Method:** Eligible patients should be definitive diagnosed SqCC, who refused chemotherapy or failed first line, second line or even later lines of chemotherapy. Key exclusion criteria included major blood vessel involvement and massive haemoptysis with the amount more than 20ml. Apatinib was given every day, and treatment was continued until disease progression or unacceptable toxic effects. Progression free survival (PFS) was assessed by Kaplan–Meier test. Tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). **Result:** Total 19 patients were enrolled from June 2015 to August 2017. Among them, 12 patients suffered from distant metastases before apatinib administration; 11 patients were with ECOG 2-3. Ten patients (52.6%) received 250mg daily of apatinib, 4 received 125mg, 1 received 375mg, 2 received 425mg and 2 received 500mg daily. Two patients failed to evaluate efficacy for personal reason so that 17 patients were eligible for tumor response to apatinib evaluation. Followed up to April 2018, 14 of 19 patients were dead, and 1 year survival rate was 21.1% (4/19). The median PFS was 5.3 months (95% CI: 2.7–7.9 months). Three patients achieved partial response (PR) and the objective response rate (ORR) was 17.6% (3/17) and the total disease control rate (DCR) was 76.5% (13/17). There was no significant associations between the dose of apatinib and efficacy (p=0.648). The main adverse events were fatigue (47.4%), hypertension (36.8%), hemoptysis (26.3%), loss of appetite (26.3%), proteinuria (21.1%) and hand-foot reaction (15.8%). No grade 4 adverse event was reported. All the dead events were not drug-related by physician's judgment. **Conclusion:** Apatinib monotherapy at a lower dosage might be an optional choice for patients with advanced lung squamous cell carcinoma. Perspective clinical studies with large sample size are needed to validate our results.

Keywords: Apatinib, lung squamous cell carcinoma, efficacy

P3.01-50 IDENTIFICATION OF EGFR MUTATIONAL PROFILE IN LUNG CANCER MOROCCAN COHORT

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Background: Despite recent progress in diagnostic and oncology therapy, lung cancer constitutes the leading cause of cancer-associated mortality worldwide, with approximately 85% of lung cancer cases being non-small cell lung cancer (NSCLC) histological type. The study of epidermal growth factor receptor (EGFR) gene mutational profile in non-small cell lung cancer patients has a special clinical significance in the selection of patients for tyrosine-kinase inhibitor therapy. The aim of this study was to identify the frequency and spectrum of EGFR mutations in a cohort of Moroccan patients with lung cancer using the ADx-ARMS technology. **Method:** We performed a retrospective study by processing 125 cases of NSCLC patients recruited between March 2015 and December 2017. Using the DNA extracted from the FFPE tissue, we attempted to identify somatic mutations in exons 18 to 21 of the tyrosine-kinase "TK" domain of EGFR gene. We evaluated EGFR mutations using HRM polymerase chain reaction (PCR) and real time PCR "ADx-ARMS technology" for results confirmation. **Result:** Most of our patients were males (69.6%) in the age range of 32-82 years old, with an average age of 61,5 ± 8.62. The most represented histological type in the studied sample was adenocarcinoma (ADK: 88%) and only 12% of squamous cell carcinoma (SCC) subtype. In regards to the smoking status 57.6% of the analyzed patients were smokers and 42.4% were nonsmokers. Six different point mutations were detected in 25 patients, representing 20% of our study population. Among the mutant positive cases, the resulting mutations were as follows : 60% of patients have a deletion in exon 19, 16% in exon 20 (12% T790M and 4% S768L), 12% in exon 18 (G719A/C) and 12% in exon 21(L858R). The EGFR mutations were more frequent among males compared to females (64,0% and 36,0% respectively), all of the positive patients with EGFR mutations were ADK and 40,0% of them were smokers. **Conclusion:** The presented method can be implemented at the laboratories to identify the most frequent EGFR mutations that are important for targeted therapy of advanced lung cancer patients.

Keywords: lung cancer, ADx-ARMS technology, Targeted therapy

P3.01-51 OUTCOMES WITH SYSTEMIC CHEMOTHERAPY IN ADVANCED NSCLC PATIENTS WITH PERFORMANCE STATUS 2 AND ABOVE AND WITHOUT DRIVER MUTATION

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Background: Platinum-based combination chemotherapy is recommended as the standard treatment for patients with advanced NSCLC, but its benefit is limited to patients with performance status (PS) of 0 or 1. However, it is not clear whether these benefits apply to patients with poor performance status ((PS 2 and above)). These patients have inferior outcomes and have been excluded from clinical trials. This population accounts for a significant portion (up to 30%) of patients of our practice and some of them have been treated with systemic chemotherapy based on clinician's discretion. We have analyzed the outcome of these patients who have been treated with chemotherapy despite poor performance status. **Method:** We performed a retrospective analysis of patients of advanced NSCLC with poor PS (ECOG PS 2 or more) registered at our lung cancer clinic between January 2016 and September 2017 and treated with systemic chemotherapy. Patients with driver mutations who were treated with first line TKIs were excluded. Hospital case records were reviewed for baseline characteristics, treatment details and outcome data. **Result:** A total of 78 patients were found to be eligible for this analysis. Median age was 60 years (33-77 years) including 15% patients 70 years or above. At presentation out of these 78 patients, 48 (62.5%) were smokers, 24 patients (30 %) had pleural effusion, 8 patients (10%) had brain metastasis and 30 patients (38%) had bone metastasis. Majority patients had ECOG PS 2 but 35 % had PS 3 or 4 also and 38(48 %) had one or more associated comorbidities. The most common chemotherapy regimen used was weekly paclitaxel and carboplatin (50 %) followed by pemetrexed and carboplatin (23 %). Majority (61.5 %) patients could complete 4 or more cycles of chemotherapy however 10 patients (13%) could receive only one cycle and 21 (27%) patients even received maintenance chemotherapy. Chemotherapy was interrupted or stopped due to toxicity in 33% patients. At least one point improvement in ECOG PS from baseline was observed in 44 patients (56%) after 2 cycles of chemotherapy. Objective response and disease control rates were 21 % and 48.6 % respectively. After a median follows up of 8.6 months, median progression free survival was 5.8 months. **Conclusion:** Systemic chemotherapy in modified doses and schedules in advanced NSCLC patients with PS 2 and above is feasible and may be associated with better symptom palliation with clinical benefit and improvement in survival. Further studies addressing this neglected subgroup are indicated.

Keywords: Improved performance status after chemotherapy, clinical benefit, advanced NSCLC

P3.01-52 THE ROLE OF SERUM CARCINOEMBRYONIC ANTIGEN TO PREDICT THERESPONSE OF TREATMENT IN NONSMALL CELL LUNG CANCER PATIENTS

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Background: Imaging techniques are routinely used in non-small cell lung cancer (NSCLC) to monitor response to chemotherapy. Biomarkers have been investigated in NSCLC for monitoring treatment response. We have measured tumor marker levels at the time of diagnosis and response assessment. In this study, the change in serum carcinoembryonic antigen (CEA) levels and the association with treatment response was evaluated. **Method:** One hundred patients with NSCLC diagnosed in our institution between 2013-2017 has been included retrospectively in this study. One hundred and thirty-five treatment responses were evaluated from 100 patients. Age, sex, stage, histologic subtype, tumor marker levels in the diagnosis, the change in serum CEA levels and the association with treatment response were analyzed. The treatment responses of the patients were evaluated as those with clinical response [stable response (SD) + complete response (CR) + partial response (PR)] versus progression disease (PD)] and relations with CEA level were assessed. **Result:** Seventy-four (74%) patients were male, and the median age was 57.5 (23-83) years. Thirty-one (31%) were locally advanced and inoperable, and 68 patients (68%) were metastatic. Histologic subtype was adenocarcinoma in 73 patients (73%). At the time of diagnosis, median CEA level was 16.2 ng/ml (1.53-1.000), CA19-9 level was 16 U/ml (0.6-1611), CA 15-3 level was 42 U/ml (8.4-895) and CA 125 level was 70 U/ml (7-1111). There was a high baseline level of serum; CEA in 54 of 88 patients (61.4%), CA19-9 in 20 of 70 patients (28.6%), CA 15-3 in 29 of 39 patients (74.4%) and CA125 in 34 of 43 patients (79.1%) at the time of diagnosis. İn 135 evaluated responses; clinical response and progression were observed in 100 (74.1%) and 35 (25.9%) patient, respectively. CEA level was stable or decreased in 86/100 (86%) clinical responsive patients, while it was elevated in 26/35 (74.3%) progressive patients. The change in CEA level, predict response to therapy with 86% sensitivity and 74.2% specificity. The positive predictive and negative predictive value were calculated as 90.5% and 65%, respectively. The baseline level of CEA was not a prognostic factor. **Conclusion:** CEA levels were associated with treatment response in the previous studies and similar results were obtained in our study. CEA is readily detected in serum samples making it a valuable tool for the follow-up of patients and may better predict response to treatment.

Keywords: Non-small cell lung cancer, treatment response, tumor markers, CEA, Lung cancer, response

P3.01-53 COMPARISON OF THE TREATMENT EFFICACY OF OSIMERTINIB IN YOUNG AND ELDERLY PATIENTS WITH T790M-POSITIVE NSCLC

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Background: Osimertinib is a third generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). The AURA3 trial showed that osimertinib is superior to platinum doublet chemotherapy in T790M-positive non-small cell lung cancer (NSCLC) with acquired resistance to first or second generation EGFR-TKIs in patients, irrespective of age. In contrast, another study showed that first or second generation EGFR-TKIs may have poorer efficacy and prognosis in young subjects than in elderly patients with EGFR mutation-positive NSCLC. Thus, we aimed to determine whether osimertinib exerted similar effects on young and old patients with T790M-positive NSCLC. **Method:** We retrospectively investigated T790M-positive NSCLC patients with acquired resistance to first or second generation EGFR-TKIs who were administered osimertinib therapy from May 2015 to January 2018 by referring to their charts in the Tokyo Metropolitan Cancer and Infectious disease Center, Komagome Hospital, Japan. We defined patients > 65 years old as elderly and those < 65 years old as young. We compared the clinical characters, overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) of the two age groups. **Result:** Total 31 patients with acquired resistance to first or second generation EGFR-TKIs were administered osimertinib. Twenty-three subjects belonged to the older age group, while 8 belonged to the younger age group. The median ages of the elderly and young patients were 75 years (range: 65–88 years) and 54 years (34–64) years, respectively. There were no significant differences in their clinical characteristics (sex, Eastern Cooperative Oncology Group Performance Status, smoking history, histology, type of de novo EGFR mutation, initial EGFR-TKI therapy, re-biopsy sample, central nervous system metastasis, and osimertinib line). The median PFS duration after initial EGFR-TKI treatment was greater in the elderly patients (17.2 vs. 10.5 months; hazard ratio; 2.86; 95% confidence interval [CI] , 1.03–7.97; P = 0.0022); the ORR of osimertinib in the elderly and young patients was 53.3% and 37.5%, respectively. The median follow up interval after osimertinib initiation was 10.1 months. The total median PFS duration was 5.6 months. The median PFS duration tended to be greater in elderly patients (3.5 vs. 9.1 months; hazard ratio; 1.90; 95% CI, 0.75–4.78; P = 0.17). The median OS duration after osimertinib initiation was significantly greater in elderly patients (5.3 months vs. NA; hazard ratio; 3.36; 95% CI, 1.11–10.1; P = 0.027). **Conclusion:** Osimertinib showed poorer efficacy in younger patients than in elderly patients with T790M positive NSCLC.

Keywords: NSCLC, EGFR-TKI, osimertinib

P3.01-54 A HISTORICAL COMPARISON OF PATIENTS WITH ADVANCED NSCLC HARBORING UNCOMMON EGFR MUTATIONS BEFORE AND AFTER THE APPROVAL OF AFATINIB IN JAPAN

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Background: Afatinib demonstrated durable responses in patients with metastatic non-small cell lung cancer (NSCLC) harboring uncommon non-resistant epidermal growth factor receptor (*EGFR*) mutations (G719X, L861Q, and/or S768I) in a pooled analysis of three clinical trials. However, the clinical impact of afatinib therapy in patients with these uncommon *EGFR* mutations remains unclear. **Method:** We retrospectively evaluated patients with advanced NSCLC whose tumors have uncommon *EGFR* mutations, and who had received first-line systemic therapy at the Shizuoka Cancer Center between January 2010 and December 2017. Patients with resistant *EGFR* mutations (T790M, exon 20 insertions) and patients who had received investigational EGFR-TKIs were excluded from this study. Characteristics, therapy regimens and survival outcomes were compared between patients who had received a systemic therapy before (Group A) and after (Group B) the approval of afatinib in Japan. Overall survival (OS) was measured from the first day of first-line systemic therapy until death or the final day of the follow-up period. **Result:** A total of 23 patients (11 in Group A, and 12 in Group B) were included in this study. The characteristics of the 23 patients were: median age 69 years (range: 41 to 82); 39% male; 26% performance status (PS) 0, 57% PS 1, 13% PS 2 and 4% PS3; 48% with brain metastasis; and 57% current or former smokers. With regard to *EGFR* mutation type, 30% had G719X, 30% had L861Q, 5% had S768I, 22% had a complex of uncommon mutations, and 13% had both uncommon and common mutations. Patient characteristics were similar in the two groups except for PS. First-line systemic therapy regimens were: gefitinib 73%, erlotinib 9% and platinum-doublet chemotherapy 18% in Group A; gefitinib 8%, erlotinib 25% and afatinib 67% in Group B. Median OS was 10 months for Group A and 25 months for Group B. A significant difference in OS was observed between the two groups (P = 0.018). In a subgroup analysis of patients with PS 0 or 1, there was also a significant difference in OS between the two groups (median, 10 months for Group A vs. 25 months for Group B; P = 0.033). **Conclusion:** After the approval of afatinib in Japan, a majority of patients with advanced NSCLC harboring uncommon *EGFR* mutations received afatinib therapy as first-line systemic therapy, and it may be related to OS improvement.

Keywords: non-small cell lung cancer, EGFR-TKI, uncommon EGFR mutation

P3.01 ADVANCED NSCLC
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P3.01-55 SF2: A PCYT-2 INHIBITOR PROTOTYPE IS CAPABLE OF INDUCING CITOTOXICITY IN NSCLC

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Background: Lung cancer is one of the most common malignant tumors in the world and in most cases this disease has an unfavorable prognosis. Due to the relative failure of current therapeutic protocols, there is an urgent need for the development of new treatments. Then, new classes of drugs may be considered. The development of new drugs could benefit a large portion of the population affected by lung cancer. The enzyme CTP: phosphoethanolamine cytidylstransferase (Pcyt-2), which has phosphoethanolamine as the substrate, is a key regulator in the Kennedy pathway for the production of membrane phospholipids. Phosphoethanolamine is one of the most abundant phospholipids in eukaryotic cells and, therefore, the reduction of its production could directly affect cell division and apoptosis. **Method:** In the present study it was evaluated the cytotoxic effects of a new prototype, named as SF2, in NSCLC. In order to evaluate the effect of SF2 on Pcyt-2; the radiolabeling assay of the intermediates of the Kennedy pathway was performed. The cytotoxic activity was investigated in A549 and NCI-H460 cell lines by the MTT colorimetric assay. Mitochondrial membrane depolarization and apoptosis analysis were performed by High Content Screening (HCS) using TMRE probe and double annexin V / PI labeling, respectively. **Result:** SF2 was able to reduce the activity of Pcyt-2 enzyme (65% related to control group, p<0.01). This reduction also lead to the decrease of the CDP-ethanolamine (CDP-Etn) production (29%, p<0.001) and the transport of ethanolamine (Etn) (69% related to control, p<0.0001). SF2 presented IC_{50} values of 40 and 90 μM for A549 and NCI-H460 cell lines, respectively. In addition, SF2 was able to induce cell death by apoptosis in A549 (35% p<0.01) and in NCI-H460 (33%, p<0.03) and to reduce mitochondrial membrane potential of NCI-H460 cell line (27% related to control, p<0.05). **Conclusion:** Therefore, SF2 is a potential candidate of antitumor drug by the inhibition of Pcyt-2 enzyme in NSCLC models.

Keywords: Phosphatidylethanolamine, NSCLC, CTP: phosphoethanolamine-cytidyl-transferase

P3.01 ADVANCED NSCLC
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P3.01-56 HYPERPROGRESSION AND PSEUDOPROGRESSION IN PATIENTS WITH NON-SMALL CELL LUNG CANCER ON CHECKPOINT BLOCKING IMMUNOTHERAPY

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Background: Immune checkpoint inhibitors in metastatic non-small cell lung cancer (NSCLC) can result in improved quality of life and survival when compared with cytotoxic chemotherapy. While immune checkpoint inhibitors are disrupting the management of patients with cancer, some patients experienced pseudoprogression,On the other hand there is another special response pattern of occurrences of rapid progression (i.e., hyperprogressive disease or HPD), suggesting potentially effects of these drugs. Due to HPD is not only different from the pseudoprogression, but also tremendous progression, clinicians must evaluate the efficacy of these novel drugs and avoid either premature withdrawal of the treatment or prolonging ineffective treatment **Method:** We idendified the medical records of all consecutive in non-small cell lung cancer patients (n=118) analyzed retrospectively who treated with monotherapy by anti-PD-1 or an anti-PD-L1 at Seoul & Bucheon St. Mary's Hospital between December 2015 and April 2018. Tumor size (D) was defined as the sum of the longest diameters of the target lesions as per the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. We calculated the TGK across clinically relevant treatment periods. As per the RECIST system, patients with nonmeasurable disease only at baseline could not be assessed by TGK. For patients who had disease progression with new lesions, the TGK was computed on the target lesions only (new lesions were not included in the RECIST sum). **Result:** Median age was 65.4 years with a majority being Male(94.4%) and non current smoker (66.6%, consists in never smoker 11.1% and Ex smoker 55.5%). Their average smoking history was 38.6 pack years The rate of over-growth was 15.2%(n=18), among them, the rate of hyperprogression was 72.2%(n=13). The probability of expression of the EGFR gene mutation on the over-growth group was 16.6%. We found increasing the probability of hyperprogression was seen at the EGFR expression group compared to non-hyperproliferation group(p=0.440) **Conclusion:** While immunotherapy can produce a significant and durable response in patients with NSCLC, physicians must be recognized of the potential for an aggressive pattern of accelerated progression in a subset of patients. Even though the improved recognition of hyperprogression and pseudoprogression, the etiology of HPD remains unclear, apart from the pseudoprogression. However we found that patients with EGFR genetic mutations may show the hyperprogression-excess growth when they used immune checkpoint inhibitors.

Keywords: immune checkpoint inhibitor, EGFR, hyperprogression

P3.01 ADVANCED NSCLC
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P3.01-57 REAL-WORLD (RW) PREDICTORS OF IMMUNO-ONCOLOGY (IO) VS CHEMOTHERAPY (C) USE IN ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC)

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Background: For patients with aNSCLC without known mutations, demographic and clinical characteristics may impact second-line (2L) treatment decisions. Describing predictors of 2L RW drug utilization may help optimize outcomes of patients with aNSCLC who eventually progress. This study evaluated predictors for 2L IO vs. C use in patients with aNSCLC treated with 1L C (proxy for patients without treatment-altering mutations). **Method:** A retrospective cohort of continuously enrolled adult patients with lung cancer initiating 1L C ≤6 months of diagnosis was identified from Inovalon's MORE² Registry® claims post IO approval in lung cancer (Mar 2015 - Dec 2016). Patients receiving 2L systemic therapy following 1L C were selected, excluding patients with SCLC, treated for secondary malignancies, with <1 month follow-up, or on clinical trials. The influence of baseline characteristics on choice of 2L IO vs C was evaluated using binary multiple logistic regression (LR), excluding targeted therapy (TT) due to small sample. Odds ratio (OR) >1 indicated greater chance of IO use. P-value <0.05 was considered significant. **Result:** Of 2,700 patients initiating 1L C, 829 (31%) received 2L: 539 (65%) received C, 262 (32%) IO, 28 (3%) TT. By subgroup (C, IO, TT), 46%, 54%, 57% (p=0.055) were female; mean age at 2L start was 65.3, 66.0, 61.0 years (p=0.045); Charlson comorbidity index: 2.8, 2.0, 1.5 (p=0.001); lines of therapy per patient: 2.4, 2.3, 2.5 (p=0.012); comorbidity count: 1.5, 1.1, 0.7 (p<0.001); follow-up from 1L start: 11.3, 10.9, 11.6 months (p=0.499); 18%, 26%, 21% (p=0.028) commercially insured; 70%, 68%, 39% (p=0.003) had evidence of smoking cessation/ counselling; 30%, 13%, 11% (p<0.001) had evidence of another malignancy at diagnosis; and 7%, 3%, 0% (p=0.032) had evidence of diabetes with chronic complications at diagnosis. LR model showed factors increasing likelihood of 2L IO use included evidence of chronic obstructive pulmonary disease (COPD) at diagnosis (OR=1.54, p=0.025), longer time to 1L discontinuation (1.27, p<0.001), and commercial insurance (2.29, p=0.001). Factors negatively impacting IO choice were: 1L combination therapy use (0.48, p<0.001), evidence of secondary malignancy at diagnosis (0.21, p=0.001), and evidence of diabetes with chronic complications at diagnosis (0.33, p=0.031). **Conclusion:** This retrospective RW study showed that aNSCLC patients with COPD, longer 1L treatment, on 1L monotherapy, and private insurance are more likely to receive 2L IO vs C. As such, early consideration needs to be given in order to monitor these patients more closely.

Keywords: Real-world study, advanced non-small cell lung cancer NSCLC, immuno-oncology immunoncology IO

P3.01 ADVANCED NSCLC
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P3.01-58 RELATIVE ABUNDANCE OF EGFR MUTATIONS IN PLASMA PREDICTS TUMOR RESPONSE TO EGFR-TKI IN ADVANCED LUNG ADENOCACARCINOMA

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Background: It is unclear whether relative abundance of EGFR mutations in plasma predicts tumor response treatment with EGFR–TKIs in advanced lung adenocarcinoma. **Method:** The present prospective study enrolled

patients with advanced lung adenocarcinoma in the first affiliated hospital of Wenzhou Medical University from 1 April 2016 to 1 January 2017. EGFR mutations detection in tumor tissues by ADx-ARMS and in plasma cfDNA by ADx-ARMS and ADx-SuperARMS were all tested. We enrolled patients with EGFR-mutant in tumor tissue and receiving EGFR-TKIs. Mutation-positive plasma by both methods carried high abundance of EGFR mutations. Plasma that was mutation positive by ADx-SuperARMS but the result by ADx-ARMS was negative harbored medium abundance. Mutation-negative plasma by both methods was recognized as low abundance group. The correlation between EGFR mutation abundance and clinical benefit from EGFR-TKIs treatment was analyzed using Kaplan-Meier curve, Chi-square test and Cox proportional hazards model. The study protocol was approved by the Institutional Review Board of the first affiliated hospital of Wenzhou Medical University(2016-017). **Result:** 71 patients were enrolled, 42 harbored EGFR mutations in plasma detected by ADx-ARMS, while 53 were found positive result in plasma by ADx-SuperARMS. Median PFS was 10.0m and ORR was 64.8% in the patients with EGFR-mutant in tumor tissue. According to the results of the plasma detected by ADx-ARMS and ADx-SuperARMS, 42 were found high abundances of EGFR mutations, 11 were recognized as medium abundances group while the other 18 as low abundances. The ORRs were 69.0%,63.6% and 55.6% for patients with high,medium and low abundance of EGFR mutations, respectively. Pwith high abundances of EGFR mutations were seemed to acquire high ORRs, the difference was significant between high and low abundances group(P=0.006) but the differences were not significant when compared high abundances group with medium abundances group (P=0.732) and medium abundances group with low abundances group (P=0.114). Medium PFS for high,medium and low abundances groups were 11.0m, 8.5m and 9.0m, respectively(P<0.001). For the patients with 19-Del in tumor tissues, the ORRs were 70.4%,57.1% and 54.5% in high,medium and low abundance of EGFR mutations groups, respectively. Medium PFS of high abundance group was longer than medium and low abundance groups (12.0m vs 9.0m vs 9.0m). As for L858R, the ORRs were 66.7%,50.0% and 50.0%,respectively, Medium PFS were 9.6m, 5.5m and 9.5m. **Conclusion:** The relative EGFR mutation abundance in plasma could predict tumor response to EGFR-TKI treatment for advanced adenocarcinoma. The higher the EGFR mutation abundance is, the better efficacy of EGFR-TKI is.

Keywords: Abundance, EGFR, lung adenocarcinoma

P3.01 ADVANCED NSCLC
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P3.01-59 COMPARISON OF LOBECTOMY, SEGMENTECTOMY AND WEDGE RESECTION FOR EARLY STAGE NSCLC: A DIRECT AND NETWORK META-ANALYSIS

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Background: Aim: The purpose of this study was to compare the effect of lobectomy, segmentectomy and wedge resection for early stage non-small cell lung cancer (NSCLC) treatment. surgical section is a first choice for surgical treatment of early stage NSCLC (5). However, it is not applied for most NSCLC with advanced stages owing to its high metastasis and recurrence rates . In addition, video-assisted thoracoscopic surgery (VATS) as a less invasive surgical method is widely used for clinical stage I NSCLC during lobectomy, segmentectomy, and wedge resection . Lobectomy is a traditionally gold standard for early stage NSCLC treatment . In recent years, segmentectomy and wedge resection as alternative sublobar resection to lobectomy are recommended. Many studies have indicated that sublobar resection results in equivalent outcomes in patients with stage I NSCLC in comparison with lobectomy, and it is gradually considered that pneumonectomy is unnecessary . However, sublobar resection for NSCLC treatment remains controversial due to an increased risk in local recurrence and poorer long-term survival compared to lobectomy, thus additional local therapy is recommended to patients undergoing sublobar resection . **Method:** Eligible studies were retrieved from PubMed, Embase, and Cochrane Library. The 1, 2 or 5-year overall survival (OS) and disease-free survival (DFS), and complications rates were used as outcomes indictors. The pooled results for comparison indicators were measured by odds ratios (ORs) with 95% confidence interval (CI) as dichotomous variables. The random effects model was used for all test models in the present study. The consistency assessment in this network meta-analysis was conducted by Node-splitting analysis. **Result:** A total of 23 studies encompassing 13406 early stage NSCLC patients were included into this network meta-analysis. The results revealed that although 1, 2 and 5-year OS and DFS of lobetomy was superior to segmentectomy and wedge resection, and segmentectomy was better than wedge resection, except for 2-year OS, only result of 5-years OS between groups (wedge resection vs. segmentectomy, OR= 0.56, 95%CI: 0.36-0.87; wedge resection vs. lobetomy, OR= 0.51, 95%CI: 0.33-0.79) were significant difference. On the contrary, the complications rate in wedge resection was significant lower than that of lobetomy (lobetomy vs. wedge resection, OR= 1.73, 95%CI: 1.05-2.72) and segmentectomy (segmentectomy vs. wedge resection, OR= 1.66, 95%CI: 1.02-2.74), and it was highest in lobetomy. **Conclusion:** Segmentectomy might be recommended as a reasonable alternative to lobectomy with lower complications rate for early stage NSCLC treatment.

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P3.01-60 A NOVEL MET D1246H MUTATION AFTER PROGRESSION OF EGFR-TKI/MET INHIBITOR COMBINED THERAPY IN A NSCLC PATIENT WITH ACQUIRED MET AMPLIFICATION

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Background: MET amplification was the second common acquired resistance mechanism to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) in patients with advanced non-small cell lung cancer (NSCLC). It may be benefited by combinations of EGFR TKIs and the MET inhibitor. However, the acquired resistance mechanism to this combination therapy remains to be identified. **Method:** A patient with advanced lung adenocarcinoma harboring both EGFR L858R mutation and acquired MET amplification, progressed after the combination of MET inhibitor gefitinib and EGFR-TKI crizotinib. The next generation sequencing (NGS) based circulating tumor DNA (ctDNA) assay was performed. Results were applied to discover a novel mutation after resistance to target therapy. **Result:** A 52-year-old Chinese never-smoking woman with EGFR L858R mutant adenocarcinoma had systemic progression after gefitinib, pemetrexed/platinum-pemetrexed maintenance, and SBRT local progressed lung metastasis. The NGS-based ctDNA analysis revealed that the MET amplification was found besides continually present EGFR L858R mutation. The patient started treatment with crizotinib (250mg Bid) and gefitinib (250mg/d). The NGS was performed after progression of this combined therapy. It revealed two novel mutations of MET D1246H (MAF 0.9%) and EGFR T790M mutation (MAF 0.2%), in addition to the initial presence of EGFR L858R mutation (MAF 9.8%) and MET amplification (LR 6.7). The patient started to receive osimertinib (80mg/d) and cabozantinib (20mg/d and later increased to 40mg/d). The patient tolerated this combination well while the symptoms did not relief. After 8 weeks, the re-scan CT showed pulmonary lesions progressed. The NGS-based ctDNA assay performed again and it showed that L858R mutation (MAF 11.4%) and MET amplification (LR 4.9) presented while the EGFR T790 mutation and MET D1246H disappeared. Then the patient received osimertinib (80mg/d) and crizotinib (250mg Bid). The patient felt symptoms improved greatly after 1 week's administration and CT scan after 2 months showed good response. However,one more month later, the patient felt deteriorative symptoms of dyspnea and chest X-ray showed increasing pleural effusion , progressing pulmonary lesions. The NGS-based ctDNA assay at that time revealed that MET D1246H (MAF 14.4%) appeared again, in addition to the initial presence of EGFR L858R mutation (MAF 22.4%) and MET amplification (LR 8.2) while the EGFR T790 mutation was not existed. However, the patient died because of respiratory failure. **Conclusion:** MET mutations might be a potential acquired resistance mechanism after progression during EGFR-TKI /MET inhibitor combined therapy in advanced NSCLC patient with primary EGFR mutation and secondary acquired MET amplification.

Keywords: non-small cell lung cancer, Met mutation, acquired resistance mechanism

P3.01 ADVANCED NSCLC
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P3.01-61 EGFR AND KRAS MUTATIONAL STATUS AND SIGNIFICANCE IN GREEK PATIENTS WITH ADVANCED NON SMALL CELL LUNG CANCER

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Background: *KRAS* mutations are reported in 20-25% of non-small cell lung cancer (NSCLC); their prognostic role in advanced NSCLC is still under dispute. Given that ethnicity may play a role on mutational

profiles of NSCLC, we report here on *KRAS* mutations in Greek NSCLC patients. **Method:** *KRAS* and *EGFR* genotypes were evaluated in 424 NSCLC patients diagnosed from March 2000 to December 2012 and associated with clinicopathological parameters. Outcome comparisons were performed in 234 metastatic patients with available treatment data, following 1st line chemotherapy without tyrosine kinase inhibitors. **Result:** *KRAS* mutations were found in 71 tumors of all histologies (22.2% in adenocarcinomas); most common types were p.G12C (39.5%), p.G12D (32%) and p.G12V (14%). *EGFR* mutations were found in 45 tumors (14.8% in adenocarcinomas; 72.6% of the classical type) and were mutually exclusive with *KRAS* mutations except for one case. At a median 3-year follow-up for all patients, *KRAS* status was a strong negative prognostic factor for overall survival (OS, p=0.0213) but not for progression-free survival (PFS), irrespective of mutation type. *KRAS* mutations conferred 64% increased risk of death in all 1st line treated patients and the worst OS compared to *EGFR* and any wild-type status in 1st line platinum-treated patients (p=0.0547). Rare *EGFR* mutations conferred significantly better outcome to platinum-treated patients (OS, p=0.0074; PFS, p=0.0338). **Conclusion:** The presence of KRAS mutations seemed of adverse prognostic significance for survival, also in the presence of platinum-based 1st line treatment, while no prognostic differences were seen among different types of mutations.

Keywords: KRAS, EGFR, NSCLC

P3.01 ADVANCED NSCLC
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P3.01-62 A NEW METHOD FOR NON-INVASIVE PREDICTION OF RADIOTHERAPY: SDH5 DEPLETION ENHANCES RADIOSENSITIVITY BY REGULATING P53

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Background: Radiotherapy is an important and effective treatment for lung cancer. Some molecules can predict the effect of radiotherapy, but it is an invasive test that will cause trauma to patient. So the development of reliable non-invasive methods for predication of radiotherapy has become essential to guide therapy. **Method:** We initiated an analytical, observational, open, and retrospective study (ChiCTR1800014878) of 53 patients with stage III lung adenocarcinoma who were ready for radiotherapy. The performance status (PS) scores of the patients are all over 2. Blood and tumor tissue before treatment were collected to detect SDH5 concentration. We then evaluated the prognostic role of SDH5 expression in these patients. To further verify the effect of SDH5 on radiosensitivity, two mice models (orthotopic mice bearing lung cancer and SDH5 gene knock-out mice) were established and the internal mechanism between SDH5 and radiotherapy was explored. **Result:** The patients whose tumor shrink significantly one month after radiotherapy had lower expression of SDH5 in tumor, and loss of SDH5 expression correlated with down regulation of DNA-PKcs^{Thr2609} and ku86. More importantly, SDH5 can be directly detected in blood by qRT-PCR, and the result is consistent with that in tissue. And more exciting, patients with deficiency of SDH5 had longer PFS and OS after radiotherapy, and the results in blood and in tumor are consistent. To further verify the effect of SDH5 on radiosensitivity, in vivo experiments were carried out. In the orthotopic model, SDH5 knock down tumors showed higher radiation sensitivity with smaller volume. In SDH5 knock-out mice, lung epithelial cells exhibited elevated DNA damage after radiation. Moreover, our data indicated that SDH5 depletion causes P53 translocated from cytoplasm to nucleus, which enhances radiosensitivity of non-small cell lung cancer. Furthermore, consistent with in vivo data, the tumor growth was partially reversed when p53 was co-depleted with SDH5. **Conclusion:** In this experiment we found that SDH5 regulated radiosensitivity by P53 and it can be detected in tumor tissue. It is a suitable marker for predicting radiosensitivity. More than this, the expression of SDH5 can be directly measured by qRT-PCR in the blood, and it is consistent with that in the tumor tissue. This provides a novel non-invasive method for predicting the radiosensitivity of the patients unable to tolerant the biopsy.

Keywords: SDH5, non-invasive, Radiotherapy

P3.01 ADVANCED NSCLC
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P3.01-63 BASELINE BIOMARKERS FOR OUTCOME OF ADVANCED NSCLC PATIENTS RECEIVING ANTI-PD1/PD-L1 TREATMENT—DATA FROM A CHINESE POPULATION

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Background: Immune checkpoint inhibitor therapy has shown optimal efficacy in advanced non-small-cell lung cancer (NSCLC). However, the biomarkers of immunotherapy response are not well established. In the present study, we aimed to determine baseline prognostic factors associated with progression-free survival (PFS) in anti-PD1/PD-L1 treatment and to identify a predictive biomarker for immunotherapy response. **Method:** Data of 54 advanced NSCLC patients receiving anti-PD1/PD-L1 treatment were prospectively collected in Shanghai Chest Hospital from Dec. 2015 to May 2017. Clinical data included baseline routine blood examination and demographic characteristics of patients prior to immunotherapy. Systemic inflammatory biomarkers were obtained from routine blood tests to calculate leukocyte-to-lymphocyte ratio (LLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR) and systemic immune-inflammation index (SII, neutrophil × platelet/lymphocyte). Receiver operating characteristic (ROC) and area under the curve (AUC) were used to identify the optimal cut-off value of LLR, NLR, PLR, LMR and SII for survival analysis. Endpoints were PFS and objective response rate (ORR) following anti-PD1/PD-L1 treatment. Univariate survival analysis for PFS was used by Kaplan-Meier method and statistical differences were determined by Log rank test. The Cox proportional hazards model was used for multivariable analysis. **Result:** A total of 54 cases were analyzed, with 38 treated with Atezolizumab and 16 treated with Nivolumab. Median PFS was 2.8±0.18 and 1.8±1.2 months, respectively (P = 0.988). 44 patients received second-line anti-PD1/PD-L1 treatment and 10 patients underwent three-line or above. The median PFS of the two groups were 2.8±0.88 and 2.8±0.23 months, respectively, (P=0.851). ROC and AUC identified LLR=6.3, NLR=4.5, PLR=124.45, LMR=3.4 and SII=1066 as the best cut-off values. Univariate survival analysis showed that LLR, age, pathological type, neutrophil percentage, hemoglobin, platelet count, albumin, serum lactate dehydrogenase (LDH), NLR and SII were associated with PFS (P<0.05). Cox multivariate analysis showed that LLR (P=0.003;HR 2.99;95%CI: 1.45-6.17), albumin (P=0.000;HR 8.11; 95%CI: 2.63-25.06) and LDH (P=0.000;HR 4.55;95%CI: 2.13-9.73) were independent prognostic factors for PFS . For patients with favorable (1 IN 3 factors), (2 IN 3 factors) and (3 IN 3 factors) biomarker profile median PFS were 0.94, 1.63 and 8.17 months, respectively (P=0.000) . **Conclusion:** Blood markers predict survival in advanced NSCLC treated with immune checkpoint blockade. Our findings show that baseline LLR≤6.3, normal serum levels of albumin and LDH were independently and advantageously associated with the PFS of patients receiving anti-PD1/PD-L1 treatment , and they may help identify patients with benefit from immune therapy.

Keywords: anti-PD1/PD-L1 treatment, Biomarkers, Non-small-cell lung cancer

P3.01 ADVANCED NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.01-64 PRELIMINARY DATA OF DIVERSE THERAPIES IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER HARBOURING RET-REARRANGEMENT

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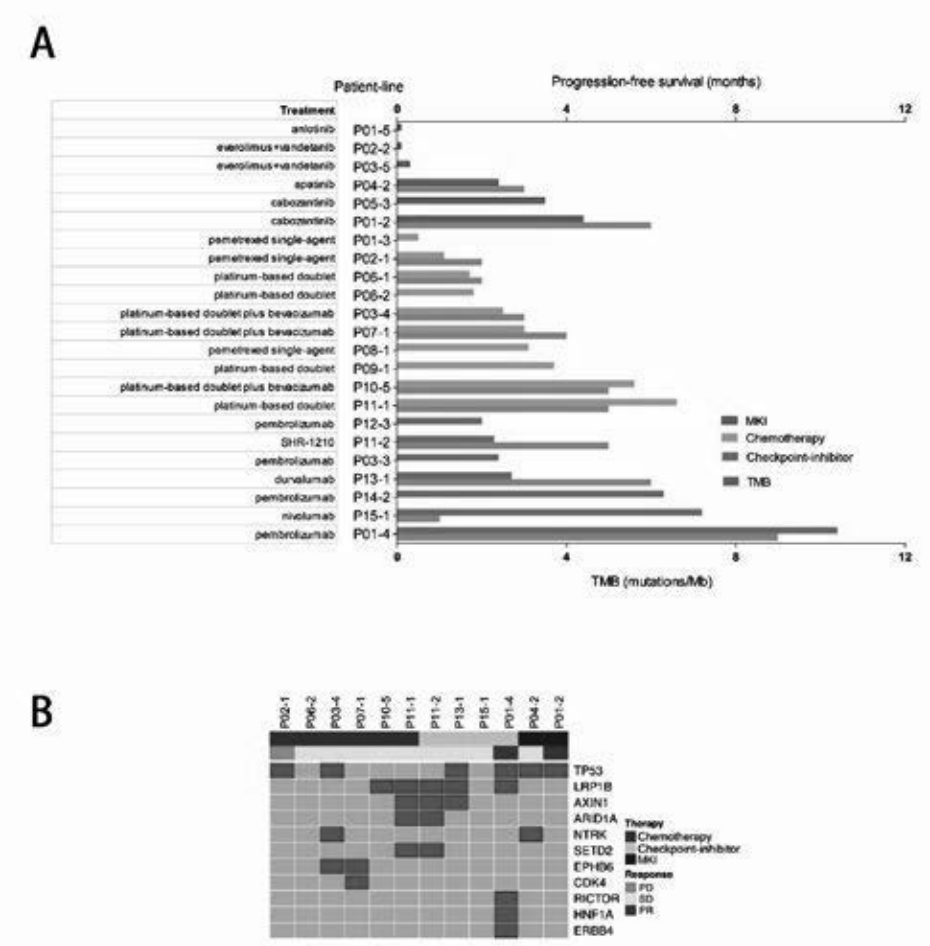
Background: Activating RET-rearrangement has been discovered to play a crucial role in NSCLC tumorigenesis. However, the lack of specificity narrowed efficacy of multi-kinase inhibitors (MKIs) and the optimal treatment remains unknown. In this study, we compared chemotherapy, immunotherapy and MKIs in this group of patients. **Method:** We retrospectively evaluated the efficacy of these three treatments in advanced, RET-rearranged NSCLC patients between January 2013 and April 2018 at our institution. RET-rearrangements were assessed by Next-generation sequencing (NGS) or any of FISH, IHC, RT-PCR. Treatment data were collected after the patients had been diagnosed with RET-rearranged advanced NSCLC. Progression-free survival (PFS) was measured from treatment start to disease progression, all-cause

mortality or last follow up. Median follow-up time was 5.1months. NGS was performed to assess somatic mutation of available samples. **Result:** A total of 30 patients with RET-rearrangement were investigated in this study. After the diagnosis, 15 patients, genetic profiles confirmed by NGS, received chemotherapy (n=10), checkpoint-inhibitors (n=7) and RET targeted MKI (n=6) with evaluable response. Several patients take any two of these three treatments as different line therapies. The disease control rate of chemotherapy, immunotherapy, MKI group was 70.0%, 71.43% and 50%, respectively. While the median PFS of three groups was 2.50 months, 2.70 months, 0.30 months, respectively, which of no significance. The NGS data of 10 patients showed that RET-rearrangement co-occurred with several other genes, including TP53, NTRK, CDK4, ERBB4. A low mutation burden (mean 4.5 mutations) was observed (Figure 1).

Conclusion: We confirmed relatively low PFS in advanced RET-rearranged NSCLC with MKIs reported in previous studies. But further investigation is warranted. Treatment with checkpoint-inhibitors seemed to encouragingly prolong PFS but a larger group of patients is needed to draw a definite conclusion.

Keywords: Immunotherapy, RET rearrangement, advanced NSCLC



P3.01 ADVANCED NSCLC
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P3.01-65 FIRST-LINE RADICAL LOCAL THERAPY MAY PROVIDE ADDITIONAL SURVIVAL GAIN FOR PATIENTS WITH EGFR-MUTANT METASTATIC NSCLC RECEIVING TKIS

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Background: Tyrosine kinase inhibitors (TKIs) have been widely accepted as first-line therapy for patients with EGFR-mutant metastatic non-small cell lung cancer (NSCLC), achieving a median progression free survival (PFS) and overall survival (OS) of 8.0 to 13.1 months and 19.3 to 30.9 months respectively. Patterns-of-failure studies suggest that the first progression after first-line TKIs occurs most often at sites of disease known to exist at the baseline. In this retrospective study, we aimed to investigate whether the radical local therapy could offer survival benefit in addition to st **Method:** NSCLC patients with activating EGFR mutations and treated with TKIs as first-line management after the diagnosis of stage IV disease (either synchronous or metachronous) between 2010 and 2017 at our institution were reviewed. All enrolled patients should receive radical local therapy (either surgery or radiotherapy with curative intent) at least to the main site of disease. We defined the main site as the primary site for synchronous IV-stage patients and at least 1 progression site for metachronous IV-stage patients. OS and PFS were calculated from the first day of IV-stage treatment. Kaplan-Meier method was used for survival estimation and Log-rank test was rendered for survival comparison between groups. **Result:** A total of 45 patients entered into the final analysis, including 18with synchronous stage IV diseases and 27patients with metachronous diseases. A total of 208 gross tumor sites were identified and 130 of them received local treatment, including 90 sites treated with radical approaches and another 30 sites with palliative therapy. At a median follow-up period of 37.8months, the median OS was 51.4 months, with 1-, 3- and 5-year rate of 97.7%, 58.7% and 25.2%, respectively. The median PFS was 16.4months, with 1-, 2- and 3-year rate of 64.7%, 29.1% and 6.8%, respectively. There was no difference between synchronous and metachronous groups. In 38patients who progressed, 19 (42.2%) involved new metastatic sites only, 12(26.6%) involved initial sites only, and 3 (6.7%) involved both. **Conclusion:** Metastatic EGFR-mutant NSCLC patients who received TKIs and radical local therapy in our study obviously provided longer OS and PFS compared with historical results using TKIs alone. Prospective randomized evidences are warranted to clarify the clinical efficacy of additional local therapy to first-line TKIs for this highly selective subgroup of patients.

Keywords: Tyrosine kinase inhibitors, non-small cell lung cancer, Radical local therapy

P3.01-66 CLINICOPATHOLOGICAL CHARACTERISTICS AND MUTATION STATUS OF PULMONARY INVASIVE MUCINOUS ADENOCARCINOMA

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Background: In the 2015 classification, invasive mucinous adenocarcinoma(IMA)is categorized as one but an uncommon subtype of lung adenocarcinoma. This study attempted to clarify the clinicopathological characteristics and mutation status of IMA. **Method:** A total of 37 patients with IMA from among 1376 surgically resected patients with lung adenocarcinoma were enrolled. We analyzed them from the standpoints of clinicopathological characteristics, mutation status and the prognosis. **Result:** KRAS mutations were observed in 9 patients and all of them were Codon 12 mutations. A total of 10 cases exhibited EGFR mutations. ALK rearrangement was detected in only 1 case. The DFS at 5 years were 68.0%. On univariate analysis for DFS, high CEA level (p =0.024), lymphatic permeation and vascular invasion (p =0.015), pleural invasion (p =0.031), tumor size (p=0.023) and N staging(p=0.027) were poor prognostic predictors for DFS.

Characteristic	n(%)
Age(years)	
<65	23(62.2)
≥65	14(37.8)
Sex	
Male	15(40.5)
Female	22(59.5)
Smoking	
Positive	13(35.1)
Negative	24(64.9)
Tumor size(cm)	
<3	18(48.6)
≥3	19(51.4)
CEA level(ng/ml)	
<5	25(67.6)
≥5	12(32.4)
SUVmax	
<5	9(40.9)
≥5	13(59.1)
Pleural invasion	
Positive	13(35.1)
Negative	24(64.9)
Lymphatic permeation and Vascular invasion	
Positive	4(10.8)
Negative	33(89.2)
N stage	
N0	24(64.9)
N1 and N2	13(35.1)

Mutation	n(%)
EGFR	
Exon 18	1(3.0)
Exon 19	4(12.1)
Exon 20 and 21	1(3.0)
Exon 21	4(12.1)
None	23(69.7)
KRAS	
Codon 12	9(29.0)
Codon 13	0
None	22(71.0)

EGFR, epithelial growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene.

Conclusion: The results revealed that different mutation statuses were observed in IMA. So, we believe that IMA would be subclassified into distinct subtypes with mutation status. And CEA level, lymphatic permeation and vascular invasion, pleural invasion, tumor size and N staging may be the factors related to mitigating DFS in IMA.

Keywords: mutations, Prognosis, Mucinous Adenocarcinoma

P3.01-67 INTEGRATED NETWORK ANALYSIS TO UNDERSTAND THE POTENTIAL MECHANISMS OF HYDROXYCHLRORQUINE IN NON-SMALL CELL LUNG CANCER TREATMENT

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Background: The aim of this study is to investigate the novel mechanisms of hydroxychloroquine in non-small cell lung cancer. **Method:** The primary targets and their related genes of hydroxychloroquine were compiled from open portals (DrugBank and STRING). Functional enrichments and pathway network were mined in DAVID and GlueGO databases. The cBioportal, Oncomine and Kaplan Meier Plotter were used to analyze the genetic alterations, mRNA expression as well as prognosis of target genes enriched in non-small cell lung cancer pathway. **Result:** The biological effects of hydroxychloroquine depended on 3 primary targets (DNA, TLR7 and TLR9), and there was no common gene in all 3 primary directed protein targets. Functional enrichments indicated that hydroxychloroquine exerted beneficial effects on anticancer and anti-infectious disease, especially on non-small cell lung cancer. Pathway network and genetic alternatives of 5 enriched genes (CDKN2A, EGFR, KRAS, AKT1 and TP53)implied TP53 was the axis of pathway interactions in non-small cell lung cancer . Statistically significant prognoses of the 5 genes were also exhibited in lung adenocarcinoma, but not in squamous cell lung carcinoma. **Conclusion:** This study indicates that hydroxychloroquine may exert anti-tumor effect in non-small cell lung cancer via TP53 signaling axis.

Keywords: TP53 signaling axis, hydroxychloroquine, NSCLC

P3.01-68 EARLY SBRT TO THE PRIMARY TUMOR MAY OVERCOME THE ICOTINIB RESISTANCE IN PATIENTS WITH ADVANCED NSCLC HARBORING EGFR MUTATIONS

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Background: Icotinib resistance is common in first-line setting for non-small-cell lung cancer (NSCLC) harboring EGFR mutations in China. It has been reported that 47% of EGFR-TKI drug resistance was from the primary tumor, 32.6% the primary and distant, and only 20.4% was distant alone (JTO, 2015). We hypothesized that effective local radiation to the primary tumor will delay Icotinib resistance. This study aimed to investigate the safety and efficacy of primary tumor stereotactic body radiotherapy (SBRT) in combination with the first-line Icotinib therapy in advanced NSCLC patients harbouring EGFR mutations. **Method:** This is a prospective pilot study (ChiCTR-OIN-17013920) from a single institution. Eligible patients included pathologically confirmed primary NSCLC with 19/21 EGFR mutation. Patients have to have no disease progression, i.e. stable disease or partial response after one month of Icotinib treatment (125 mg, three times daily). Stereotactic body radiotherapy (SBRT) was given to the primary tumor, using 50Gy/5F or 60Gy/8F for peripheral and central primary, respectively. The primary endpoint was progression

free survival (PFS). The adverse events (AEs) were assessed. **Result:** A total of 20 patients were enrolled between September 2016 and March 2018. Median age was 69 years (range 62-80). There were 9 males and 11 females. The baseline KPS was scored above 70 in 18 patients, 60 in 2 patients. Sixteen patients had stage IV disease and 4 had IIIb. There were 11 patients with 19Del and 9 patients with L858R mutations. After a median follow-up time of 10.4 months (range 3-19.3),only one patient had disease progression around the treated primary tumor. Nine patients had disease progression distantly outside of radiated region. Median PFS was 15.2 (95% CI 8.5-21.9) months for the whole cohort. At 10 months of follow-up, the rates of OS, PFS, local and distant PFS were 100%, 67.2%, 100% and 67.2% respectively. There were no acute or late grade 3+ treatment related toxicities. **Conclusion:** Early primary tumor SBRT improved primary tumor control without causing serious side effects. SBRT may delay the development of icotinib resistance in patients with advanced NSCLC harboring EGFR mutations. Randomized study is needed to determine whether early SBRT can improve PFS and over survival.

Keywords: icotinib, Stereotactic body radiotherapy (SBRT), EGFR mutations

P3.01 ADVANCED NSCLC
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P3.01-69 STEREOTACTIC ABLATIVE RADIOTHERAPY IMPROVES PROGRESSION-FREE SURVIVAL & LOCAL CONTROL IN OLIGOMETASTATIC LUNG CANCER PATIENTS

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Background: Non-small cell lung cancer (NSCLC) represents approximately 75% of the histological types of lung cancer. In patients with oligometastatic NSCLC, definitive treatment to primary tumor and low thoracic tumor burden are associated with better outcomes. The use of stereotactic ablative radiotherapy (SABR) has demonstrated high rates of local control for lung metastases and long-term survival improvement. The aim of this study is to evaluate Local Control (LC), Progression Free Survival (PFS) and toxicity of patients with oligometastatic NSCLC treated with SABR. **Method:** A prospective study was conducted with oligometastatic NSCLC patients. From July 2016 to December 2017, with a median follow up of 21.7 months, eighteen patients were enrolled. All patients received systemic therapy, those with partial response (PR), assessed by PET CT, were referred for SABR treatment (45-60 Gy in 3-7 fractions) to the thoracic lesion (primary or metastatic) depending on location, size and number of lesions, always keeping BED (Biologically Effective Dose) >100 Gy for tumor. **Result:** Eighteen patients were treated with SABR, response to treatment was as follows: global response was 94%, partial response 22% and complete response 72.2%. Mean time to progression after SABR treatment was 7.04 months (CI 95% 0.27-17.84 months). Progression free survival since beginning of any treatment was 20.14 months (CI 95% 12.92 - 27.35 months). The pattern of recurrence/ progression was as follows: local (in field) 1/18, regional (mediastinal lymph node) 1/18 and systemic 4/18, 12/18 did not show any recurrence. Sixteen patients developed grade 1 pneumonitis; one patient developed grade 2 pneumonitis and grade 3 pneumonitis was reported in one patient. Only three patients required treatment with steroids (16.7%). **Conclusion:** SABR is a suitable and well-tolerated therapeutic option for patients with oligometastatic NSCLC. SABR have shown to improve local control and increase progression-free survival. Future clinical trials are required to fully evaluate the effects of this treatment.

Keywords: NSCLC, Oligometastatic, Radiotherapy

P3.01 ADVANCED NSCLC
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P3.01-70 META-ANALYSIS OF METFORMIN IN COMBINATION WITH PLATINUM CHEMOTHERAPY IN ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

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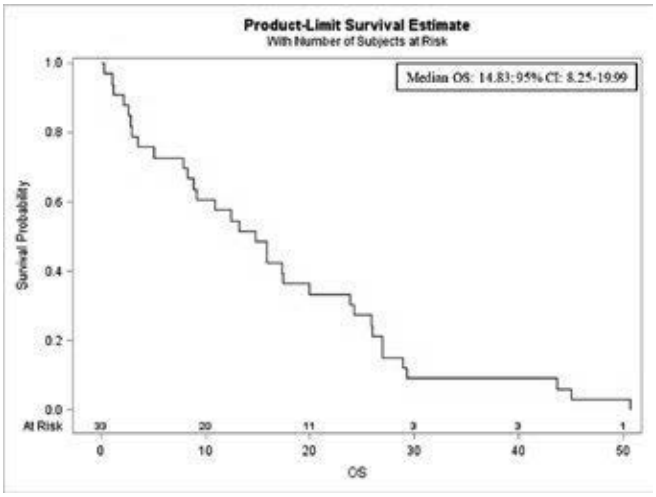
Background: Metformin has been shown to have a variety of insulin-dependent and –independent antitumor effects, primarily through cellular growth inhibition via the AMP-activated protein kinase (AMPK) pathway and the IGF1-insulin axis. Two prospective trials evaluating metformin with platinum doublet chemotherapy +/- bevacizumab have demonstrated competitive outcomes in non-diabetic, chemotherapy-naïve advanced non-small cell lung cancer (NSCLC) patients. Outcomes in KRAS-mutated NSCLC, an area of interest due to potential co-occurring LKB1 mutations, an AMPK pathway upstream kinase, is currently unknown. **Method:** This meta-analysis is of two phase II study treatment arms (NCT02019979, NCT01578551), evaluating the use of concurrent metformin and platinum-based doublet chemotherapy +/- bevacizumab. Patient's demographic, molecular and adverse event (AE) profiles were summarized with descriptive statistics. Kaplan-Meier curves for progression free survival (PFS) and overall survival (OS) were generated for all patients, as well as known KRAS and EGFR mutation subsets. **Result:** 33 non-squamous NSCLC patients were treated; 60% were female and the median age was 64 (Range: 37-77). The most common AE was neutropenia (Grade 3-4: 30%). No patients required study treatment cessation due to metformin-related toxicity. Across all patients, mPFS was 6 months (95% CI: 1.36-7.96); mOS was 14.83 months (95% CI: 8.25-19.99). In KRAS-mutated patients (n=13), mPFS was 7.21 months; mOS was 17.46 months. In EGFR-mutated patients (n=7), mPFS was 6.57 months; mOS was 13.25 months.



Conclusion: Combination metformin and chemotherapy +/- bevacizumab was safe and well-tolerated in advanced, chemotherapy-naïve non-squamous NSCLC across two phase II clinical trials. Metformin appeared particularly effective in KRAS-mutated NSCLC. Data for LKB1 status was unknown for a majority of patients, but may be an important co-mechanism for benefit. Metformin appeared to underperform in the EGFR subset, perhaps due to lack of TKI use. Given the tolerability, low cost and activity observed in NSCLC, further investigation into metformin's antitumor effects in molecularly defined subsets is needed.

Keywords: combination therapies, metformin, KRAS

P3.01 ADVANCED NSCLC
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P3.01-71 RESULTS OF EXTENDED RESECTION IN T4 NON-SMALL CELL LUNG CANCER

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Background: The strategy for T4 non-small cell lung cancer remains controversies. Extended resection carried a high mortality rate and high advances in surgical technique was needed. However, extended resection may improve survival in selected patients. **Method:** Between 2000 and 2015, 41 patients with pT4 non-small cell lung cancer, undergoing extended mediastinal resection, were selected. Patients with pulmonary metastasis were excluded. The type of extended resection was carina in 11 (27%), superior vena cava in 9 (22%), the aorta in 6 (15%), esophagus in 2 (5%), left atrium in 7 (17%) and mediastinal tissue in 4 (10%). We investigated the results of surgical resection and over-all survival. **Result:** There were p-stage IIIA in 26 and p-stage IIIB in 15. In histology, squamous cell carcinoma was observed in 22, adenocarcinoma in nine, pleomorphic carcinoma in four and others in six. The median of in-hospital days was 17d, that of operative time was 302m, and that of operative bleeding was 470cc. The rate of induction therapy was 10%. Pneumonectomy was performed in 22 (54%) and bronchoplasty was did in 18 (44%). The rate of morbidity was 66% and that of reoperation was 17%. 30-day mortality was 5%, 90-day mortality was 7% and in-hospital death was 2%. The median follow-up time was 34 months and

overall 3- and 5-year survival was 57% and 39%. Significant prognostic factors were complete resection (p-value=0.0485) and smoking status (p-value=0.0498) in univariate analysis. Multivariate analysis did not reveal significant prognostic factors. **Conclusion:** Surgical resection for T4 lung cancer was feasible in this study. But, the frequency of morbidity and reoperation was high because of high ratio of pneumonectomy and mediastinal extended resection. So, we need to care for patients after operation, intensively.

Keywords: extended resection, non-small cell lung cancer, T4

P3.01 ADVANCED NSCLC
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P3.01-72 PULMONARY RESECTION IN A PRONE POSITION FOR LUNG CANCER INVADING THE SPINE: TWO CASES REPORT

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Background: The prone position is usually not selected for pulmonary resection. The intraoperative body position is an important issue in surgery for non-small cell lung cancer (NSCLC) invading the spine because the standard intraoperative body position for vertebrectomy is a prone position, while that for pulmonary resection is a lateral decubitus position. Intraoperative changes in body position are correlated with disadvantages such as the risks of infection and nerve injury. We have previously reported significantly favorable clinical outcome of induction chemoradiotherapy (iCRT) followed by surgery among patients with clinical T3 or T4 locally advanced NSCLC, compared with initial surgery. iCRT can prevent cancer cell microresidues at local sites and to eradicate micrometastatic disease at distant sites. **Method:** Case 1: A 60-year-old man was found to have squamous cell carcinoma of the left lung with invasion of the adjacent chest wall and vertebral bodies from Th3 to Th5 and his clinical stage (UICC 7th edition) was diagnosed as c-stage IIIA (cT4N0M0). Case 2: A 63-year-old man was found to have adenocarcinoma of the right lung with invasion of the adjacent chest wall and Th3 and Th4 vertebral bodies and was diagnosed as c-stage IIIA (cT4N1M0). They were treated with iCRT consisting of two cycles of cisplatin plus docetaxel with concurrent radiotherapy of total 46 Gy. **Result:** They obtained a moderate decrease in tumor size after iCRT (restaging ycT4N0M0: Case 1, ycT4N0M0: Case 2). The surgery was started in the prone position. After partial vertebrectomy and chest wall resection were performed using an O-arm with a navigation system, upper lobectomy with systemic lymph node dissection (sLND) was performed through the chest wall defect via the posterior approach. Firstly, all pulmonary arterial branches to upper lobe were divided. Next, after division of the posterior and anterior interlobar fissure, the upper lobe bronchus was transected. Finally, the upper pulmonary vein was divided, and sLND was performed under an excellent view. Pathologic examination confirmed complete resection of squamous cell carcinoma invading the vertebral bodies and a diagnosis of Ef3 and ypN0 in Case 1, and complete resection of adenocarcinoma adjacent to the vertebral bodies, which had not been infiltrated, and a diagnosis of Ef2 and ypN0 in Case 2. **Conclusion:** Lobectomy with systemic LND in the prone position, especially after wide resection of the bony thorax, can be performed via the posterior approach without any significant difficulties in the patients with NSCLC invading the spine.

Keywords: prone position, posterior approach, locally advanced lung cancer

P3.01 ADVANCED NSCLC
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P3.01-73 TALC VERSUS MINOCYCLINE AND OK-432 PLEURODESIS FOR MALIGNANT PLEURAL EFFUSION.

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Background: Globally, talc pleurodesis is the standard treatment for malignant pleural effusion. In Japan, a combination of minocycline (MINO) and OK-432 has been commonly used for treating pleurodesis of malignant pleural effusion; however, data comparing talc and MINO + OK-432 are insuffient. To compare the success rates and adverse events of talc and MINO + OK-432. **Method:** *We retrospectively assessed 73 patients receiving pleurodesis for malignant pleural effusion (lung cancer, 60; malignant mesothelioma, 3; others, 10) for the first time between January 2010 and January 2017 at our hospital. We assessed the rates of fever, pain, after drug administration and success of pleurodesis. Moreover, we assessed the difference in success rates according to the pathology of the disease or chemotherapy.* **Result:** Of the 73 patients, 51 were men and 22 were women, the median age was 75 years (range 47-98). The rate of fever was significantly low in the talc group, although no statistical difference was observed in the success rate (talc, 75.9%, MINO + OK-432, 85.1%), period of drainage tube insertion (3.2 and 3.6 days) and the rate of pain (30% and 50%). No statistical difference according to the pathology of the disease or chemotherapy was observed. **Conclusion:** Thus, we can perform pleurodesis in patients with talc less invasively than with MINO + OK-432.

Keywords: pleurodesis, malignant pleural effusion

P3.01 ADVANCED NSCLC
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P3.01-74 CLINICAL AND RADIOLOGICAL PREDICTORS OF EFFICACY TO NIVOLUMAB IN NSCLC: A MULTI-INSTITUTIONAL, RETROSPECTIVE COHORT STUDY.

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Background: Identification of sub-populations of patients with a greater likelihood of response to anti-programmed death-1 (PD1) inhibitors in non-small cell lung cancer (NSCLC) would enable treatment to be directed to those most likely to benefit, thereby increasing efficacy and cost effectiveness. The relationship, however, between clinical and radiological parameters with efficacy of single agent Nivolumab remains unclear in advanced NSCLC. **Method:** A retrospective analysis was conducted for patients who received second-line Nivolumab following progression after platinum based chemotherapy for advanced NSCLC on a Compassionate Access Program across seven oncology institutions in Queensland, Australia. ECOG Performance status (PS), immune related adverse events (IrAEs), and baseline CT texture analysis (as a surrogate for tumour heterogeneity) was assessed. The endpoints were overall survival (OS), progression free survival (PFS) and objective response rate (ORR). An institutional ethical approval was obtained. **Result:** Two hundred and fourteen patients were enrolled over two years, median age 67 (range 42 to 84 years). PS 0-1 (64 %); PS 2-3 (36%). The median OS was 8.9 months (95% CI, 6.6 to 11.67); 13.3 months in PS 0-1 patients and 4.9 months in PS 2-3 patients. At 1 year, the OS rate was 41%; 55% in patients with PS 0-1 and 19% in PS 2-3 patients. ORR was recorded in 23% of patients (50/214), an additional 27% (58/214) had stable disease. Toxicity data was available for 90% of patients (N=194). The presence of IrAEs of any grade occurred in 36% of patients and was associated with a longer median PFS of 5.9 months versus 2.3 months in patients with no immune toxicity (P value <0.01, 95% CI). In patients with IrAE the ORR was 32% versus 18%, 1 year OS 59% versus 29% in those without any immune mediated toxicity. CT texture analysis findings (N=47) consistent with increased tumour heterogeneity showed significantly longer PFS (median NR versus 1.5 months, Hazard Ratio: 2.05, p=0.018). **Conclusion:** We found Nivolumab had clinically significant long-term benefits in the treatment of locally advanced and metastatic NSCLC with 12 month survival rates in keeping with clinical trials in PS 0-1 patients. An ECOG PS 0/1, the development of IrAEs and increased tumour heterogeneity by CT texture analysis was associated with a significantly longer PFS and increased clinical benefit in this cohort. The combination of these clinical and radiological parameters may identify subgroups of patients benefitting from this therapy.

Keywords: immune related adverse events, CT Texture Analysis, Nivolumab

P3.01 ADVANCED NSCLC
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P3.01-75 RELAY+, AN EXPLORATORY STUDY OF GEFITINIB WITH RAMUCIRUMAB IN UNTREATED PATIENTS WITH EGFR MUTATION-POSITIVE METASTATIC NSCLC

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Background: RELAY is a randomized, double-blind phase 1b/3 study investigating the efficacy and safety of the addition of ramucirumab (a human IgG1 monoclonal antibody that binds to Vascular Endothelial Growth Factor (VEGF) Receptor 2) to erlotinib (an EGFR TKI) in treatment-

naïve EGFR-mutant metastatic NSCLC. Results from the Phase 1b cohort showed that combining ramucirumab with erlotinib was safe with encouraging clinical activity and a median PFS of 17.1mo (Reck et al., Clinical Lung Cancer 2017). While enrolment for the RELAY Phase 3 cohort has been completed, the RELAY+ cohort was recently added to explore the safety and efficacy of the combination of ramucirumab with gefitinib, a frequently used EGFR TKI in East Asia. **Method:** RELAY+ is an open-label, 2-period, single-arm exploration of the efficacy and safety of the addition of ramucirumab to gefitinib in previously untreated East-Asian patients with EGFR mutation-positive metastatic NSCLC (Period 1) and of ramucirumab to osimertinib in patients whose disease progressed in Period 1 and harbors the T790M mutation (Period 2). The trial is planned to be conducted in Japan, Taiwan and South-Korea and is currently open for enrollment. Approximately 80 patients will be enrolled. In Period 1 patients will receive ramucirumab (10mg/kg) every two weeks and gefitinib (250mg/day) until disease progression, unacceptable toxicity or other withdrawal criteria are met. The study objectives are to determine the 1-yr PFS rate, safety and patient reported outcomes (Lung Cancer Symptom Scale and EQ-5D-5L]). In Period 2 the efficacy and safety of ramucirumab (10mg/kg) every two weeks with osimertinib (80mg/day) will be explored. Both RELAY+ and RELAY participants will be enrolled in a liquid biopsy exploratory substudy. ctDNA (circulating tumor DNA) from plasma samples will be used for ddPCR (droplet digital PCR) and NGS (Next Generation Sequencing) to characterize mechanisms of acquired resistance and to test the hypothesis if the addition of ramucirumab to an EGFR TKI delays or modifies the emergence of EGFR TKI resistance. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Metastatic NSCLC, ramucirumab, RELAY+

P3.01 ADVANCED NSCLC
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P3.01-76 CLINICAL BACKGROUND AND RESPONSE TO CHEMOTHERAPY IN NSCLC PATIENTS WITH MET EXON14 SKIPPING MUTATION OR HIGH MET GENE COPY NUMBER

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Background: MET exon14 skipping mutation (SM) and high gene copy number (HGCN) are present in 3-4% and <1% of NSCLCs. The response to MET inhibitor treatment has been reported in ongoing clinical trials; however, the response to chemotherapy, including immunotherapy, is currently unknown. We conducted a retrospective analysis of patients with MET gene alteration. **Method:** We collected the clinicopathological data of NSCLC patients with MET gene alteration. The response to chemotherapy was evaluated according to RECIST v1.1. **Result:** Systemic chemotherapy was given to 10 patients: SM (n=5) and HGCN (n=5). The median age was 67.5 (range 41- 77) years. Thirty percent of the patients were female and 40% were never smokers. The most common histology was adenocarcinoma (40%), followed by pulmonary sarcomatoid carcinoma (20 %). The tumor PD-L1 expression was >50% in 57% (4/7) of the cases and 1-49% in 43% (3/7) of the cases. Platinum doublet, MET inhibitor, immunotherapy (I-O), and I-O+chemotherapy were given to 6, 8, 2 and 1 patients. The overall response rate was 50%, 83%, 0% and 100%, respectively. Hyper-progressive disease after immunotherapy was observed in one patient with SM. **Conclusion:** The responses to platinum doublet and MET inhibitor treatment were good, while the response to immunotherapy was poor in NSCLC patients with MET gene alteration. MET gene alterations should be identified before the administration of immunotherapy.

Keywords: MET gene alteration, Immunotherapy, chemotherapy

P3.01 ADVANCED NSCLC
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P3.01-77 CLINICAL CHARACTERISTICS OF KOREAN LUNG CANCER PATIENTS WITH PROGRAMMED DEATH-LIGAND 1 EXPRESSION

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Background: Programmed death-ligand 1 (PD-L1) is a transmembrane protein that binds to the programmed death-1 (PD-1) receptor and anti-PD-1 therapy enables the immune response against tumors. The aim of this study was to assess the clinical and pathologic characteristics of PD-L1 positive lung cancer patients in Korea. And we examined correlation between immunohistochemical assays. **Method:** We retrospectively reviewed the clinical and pathologic data of pathologically proven lung cancer patients, and collected 267 cases of formalin-fixed, paraffin-embedded tissue sample from single institution. PD-L1 expression was detected by qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, Clone 22C3. PD-L1 protein expression is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining. We categorized according to the percentage of TPS; more than 1% or more than 50%. Among 267 patients, 34 were analyzed by both 22C3 and SP263 assays. We examined the concordance correlation between IHC assays. **Result:** A total of 267 patients were enrolled and major histologic types were adenocarcinoma (69.3%). The majority was smoker (67.4%) and clinical stage IV (60.7%). Thirty one (11.6%) cases of EGFR mutation and 17 (6.4%) cases of ALK FISH positive were included. The patients who showed TPS ≥ 1% and 50% were 116 (42%) and 58 (21%), respectively. More than 1% of TPS group was consisted of adenocarcinoma (67.8%), squamous cell carcinoma (29.6%), and small cell carcinoma (1.9%) histology. And more than 50% of TPS group was composed of adenocarcinoma (72.4%), squamous cell carcinoma (22.4%). More than 1% of TPS group was significantly older than less than 1% of TPS group (64.83 ± 9.38 vs. 61.73 ± 10.78 years, p=0.014). The rate of poorly differentiated pathology was significantly higher in TPS ≥ 1% group (40.8% vs. 25.8%) and TPS ≥ 50% group (53.2% vs. 27.2%). There was no difference in smoking, EGFR mutation, ALK rearrangement status or biopsy site. Among 34 patients analyzed by both 22C3 and SP 263, 27 patients showed positive by both 22C3 and SP263, at the cut-off of 1% or higher. The concordance correlation coefficient was 0.826 (95% confidence interval: 0.736-0.916). **Conclusion:** In Korean lung cancer patients, PD-L1 positive group defined as TPS ≥ 1% was older than negative group. And major histology was poorly differentiated non-small cell lung cancer in both TPS ≥ 1% and 50% groups. And our results showed a high correlation between PD-L1 IHC expression data analyzed by 22C3 and SP263 assays.

Keywords: Tumor Proportion Score (TPS), non-small cell lung cancer, programmed death-ligand 1 (PD-L1)

P3.01 ADVANCED NSCLC
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P3.01-78 THE CYTOLOGY SAMPLES AND PLASMA SPECIMENS WERE FEASIBLE FOR THE EGFR MOLECULAR TESTING.

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Background: EGFR mutation detection with real-time PCR is standard method to identify eligible patients for EGFR-TKI treatments in daily routine practice. Surgically resected tissues or biopsy specimens are mainly used as the sample materials for testing. However, the biopsy samples sometimes have a certain limitation in their volume and so the cytology specimens are chosen for EGFR testing instead. Plasma has also become an option especially in EGFR-TKI resistant cases in which often have difficulties to obtain the adequate tumor yield. In this study, we evaluated the feasibilities of using cytology samples and plasma specimens for the EGFR molecular testing. **Method:** atients provided written informed consent for use of the samples were participated in this prospective research. Cytology samples were obtained from biopsy and cells were suspended into liquid-based cytology (LBC) media. Tumor contents in the samples were confirmed with Papanicolaou stained slides. Plasma samples were also collected from patients shortly before the tissue biopsy. EGFR mutations in these samples were analyzed by cobas EGFR Mutation Test v2. Also, EGFR testing result of tissue specimens of the patients corresponded were collected from the medical records measured by cobas EGFR Mutation Test v2 as reference.The feasibilities of both cytology and plasma specimen were evaluated comparing with the tissue samples. **Result:** One-hundred fifty-eight patients were registered to this study. Among those patients, 77 patients with matched set of samples were enrolled to this study. EGFR mutation rates in tissue, cytology, and plasma were 37.7, 29.9 and 16.9 %, respectively. Overall agreement rate of the cytology specimens and the plasma specimens against the tissue samples were 87.0 and 75.3%, respectively. All eightT790M mutation positive cases were perfectly matched between tissue and cytology specimens. **Conclusion:** The results suggested that tissue specimen is the most suitable sample for detecting mutations. Since high specificities were confirmed in both cytology and plasma specimens, the results are reliable as long as the call is positive. Choosing cytology or plasma specimens for EGFR testing can be the considerations for the patients who have difficulties in collecting tissue samples in the real world setting.

Keywords: LBC, EGFR mutation, liquid biopsy

P3.01-79 INTRACEREBRAL EFFICACY OF IMMUNE CHECK-POINT INHIBITORS IN NSCLC PATIENTS WITH BRAIN METASTASES

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Background: The brain is a common site of metastatic disease in patients with non-small cell lung cancer (NSCLC). Approximately 30–50% of patients will develop brain metastases during the course of treatment. Several immune check-point inhibitors (ICIs) have shown efficacy against non–small-cell lung cancers (NSCLCs) and approved in second line setting. However, regarding ICIs intracerebral efficacy and tolerability in NSCLC patients with active brain metastases (BMs) remains unkown. **Method:** We reviewed the medical charts of 49 patients with advanced NSCLC treated with ICIs between January 2016 and March 2018. The intracranial activity of ICIs in patients with brain metastases was assessed by brain magnetic resonance imaging (MRI) using RECIST v. 1.1 criteria. The primary endpoint was intracerebral objective response rate (IORR). Secondary endpoints included intracerebral control rate, intracerebral and general progression-free survival (PFS), overall survival (OS) and tolerance. **Result:** Ten NSCLC patients with BMs were identified. The median age of patients was 61 years (range 44–80 years) and the majority of patients were male (n = 9; 90%). All patients were pretreated with stereotaxic radiosurgery (n = 7) or whole brain radiation therapy (n = 3). All but one patients received prior systemic treatment for NSCLC. Three patients received two prior lines of systemic therapy. Two patients were treated with pembrolizumab. Median follow-up was 5.7 (95% CI: 2.7–8.4) months. IORR and extracerebral response rate were, respectively, 0% (95% CI: 0–25.9%) and 20% (95% CI: 2.5–55.6%). Intracerebral control rate was 60% (95% CI: 26.2–87.8%). Median intracerebral and general PFS lasted 1.8 (95% CI: 0.9–7.1) and 2.8 (95% CI: 1.8–4.6) months, respectively. Median OS was 8.9 (95% CI: 4.9–not reached) months. No neurological adverse events occurred. **Conclusion:** ICIs might have the efficacy and favorable safety profile in NSCLC patients with BMs.

Keywords: NSCLC, immune check-point inhibitors, Brain metastasis

P3.01-80 RETROSPECTIVE ANALYSIS OF THE IMPACT OF EGFR T790M MUTATION DETECTION BY RE-BIOPSY IN PATIENTS WITH NSCLC HARBORING EGFR MUTATIONS.

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Background: EGFR-TKIs show a good response to most of patients with advanced non-small cell lung cancer (NSCLC) harboring EGFR activating mutations. However, it ultimately becomes the acquired resistance to EGFR-TKIs after various periods. We currently attempt to detect EGFR-T790M mutation by re-biopsy that induced a half of acquired resistances to them, because the third generation EGFR-TKI osimertinib had an effective response against the refractory tumors with EGFR-T790M mutations. However, the re-biopsy from tumors is relatively invasive and some cases are impossible to perform them. Therefore, it is a critical issue to select the population with EGFR-T790M mutations. In this study, we analyzed the refractory cases to initial EGFR-TKIs with successful re-biopsy samples to disclose these clinical questions. **Method:** 78 advanced NSCLC patients with EGFR mutations who had successful re-biopsy samples after the resistance to initial EGFR-TKI treatment are enrolled at five institutions in Japan. We validated for the association between the emergence of EGFR-T790M mutation and their profiles, such as clinical outcomes with EGFR-TKI treatment and EGFR activating mutation status. **Result:** s Of 78 advanced NSCLC patients with EGFR mutations, 39 cases were EGFR-T790M positive and 39 were negative in the re-biopsy samples. Of EGFR-T790M positive patients, 2 cases achieved a complete response (CR), 33 a partial response (PR), and 4 stable desease (SD). In contrast, 1 patients experienced a CR, 19 a PR, 18 SD, and 1 progressive disease (PD) in T790M negative patients. The objective response rate was higher in patients with T790M positive mutations than in those with T790M negative mutations (89.7% versus 51.2%, p< 0.01). There were no difference between each patients in progression free survival and time to failure treated with initial EGFR-TKIs. **Conclusion:** The response to initial EGFR TKI treatment might be one of good predictors for emerging of refractory tumors with EGFR-T790M mutations. Further experiments are needed to identify them.

Keywords: EGFR-TKI, T790M

P3.01-81 LONG-TERM OUTCOME OF SURGICALLY RESECTED UNSUSPECTED N2 LUNG ADENOCARCINOMA

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Background: This study was performed to assess the long-term outcome of lung adenocarcinoma in patients without clinical suspicion of mediastinal lymph node involvement and whose tumors were finally proven to be pathologic N2. **Method:** This is a retrospective study of a prospective lung cancer database at our institution from January 2004 to December 2014. We retrospectively reviewed the medical records of 299 patients with unsuspected pathologic N2 disease. **Result:** The median follow-up time was 51.5 months (range, 1.1 to 172.3 months). The median recurrence-free survival (RFS) was 25.3 months and the 1-year, 3-year, and 5-year RFS rates were 78.2%, 41.0%, and 29.5%. The median overall survival (OS) was 75.2 months and the 1-year, 3-year, and 5-year OS rates were 92.6%, 85.9%, and 62.7%, respectively. The most common type of resection was lobectomy (88.6%). Adjuvant therapy was administered in 255 patients (85.3%). N2 involvement was single station without N1 involvement ("skip" metastasis, N2a1) in 73 (24.4%), single station with N1 involvement (N2a2) in 148 (49.5%), and N2 at multiple stations (N2b) in 78 (26.1%). The median RFS and 5-year RFS rate of N2a1 were 42.9 months and 44.8%. The median and 5-year OS and OS rate of N2a1 were 86.2 months and 69.0%. In multivariate analysis, N2a1, low T-stage, and adjuvant therapy were significantly associated with a longer RFS, whereas pneumonectomy was significantly associated with a worse RFS. **Conclusion:** The long-term outcome of unsuspected pN2 group of patients with lung adenocarcinoma was better than expected. Especially the RFS and OS of pN2a1 group of patients were similar to the those of N1 group of patients reported for survival in our group. Therefore, resection of properly staged unsuspected pathologic N2 lung adenocarcinoma is reasonable and should not be avoided if a complete resection without pneumonectomy can be done.

Keywords: N2, Adenocarcinoma, locally advanced

P3.01-82 SURVIVAL IMPACT OF SURGERY IN THE TREATMENT OF STAGE IIIB-IVA NON-SMALL CELL LUNG CANCER

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Background: Surgery is usually not indicated in far advanced stage non-small cell lung cancer (NSCLC), but a few recent clinical trials demonstrated aggressive local therapy such as (chemo) radiotherapy or surgical resection improved survival outcomes in oligometastatic NSCLC. This study aimed to evaluate survival impact of cytoreductive surgery in stage IIIB-IVA (based on the 8th TNM classification) NSCLC in the era of effective anticancer drugs. **Method:** Patients with stage IIIB, IIIC or IVA NSCLC was recruited from the Hallym Lung Cancer Registry for this retrospective analysis. Other eligibility criteria were ECOG performance 0-1, age under 85 years old and good adherence to lung cancer treatment. **Result:** A total of 203 patients were analyzed. All the patients received adequate anticancer drugs during their disease courses. Twenty-two patients (10.8%) received cytoreductive surgery. Significantly better overall survival (OS) was observed in surgery group compared with non-surgery group; Kaplan-Meier estimation for OS was 33.1 months [95% CI, 15.6-50.6] vs. 16.6 months [14.0-19.2] (p=0.007). The Cox proportional hazard ratio (HR) for death was 0.528 [0.290-0.961] (p=0.037) in surgery group when it was analyzed with covariates such as age, sex, performance, histology, stage, and smoking status. ECOG performance 0 and adenocarcinoma histology were also revealed as independent favorable prognostic factors for OS (HR .0.660 [0.474-0.919], p=0.014 and HR 0.481 [0.328-0.707], p<0.001, respectively). Table. Cox proportional hazard ratio for death (See next page)

Variable		HR	[95% CI]	p-value
AGE	< 65 y.o. vs. ≥ 65 y.o.	0.722	0.520-1.002	0.052
Sex	Female vs. Male	1.950	0.955-3.984	0.067
ECOG performance	0 vs. 1	0.660	0.474-0.919	0.014
Histology	ADC vs. non-ADC	0.481	0.328-0.707	<0.001
Stage	IIIB/C vs, IVA	0.761	0.520-1.114	0.160
Smoking	≤ 10 p.y. vs. > 10 p.y.	0.488	0.145-1.639	0.246
Surgery	(+) vs. (-)	0.528	0.290-0.961	0.037

Conclusion: Surgery backed up with adequate anticancer treatments may be a treatment option in far advanced stage NSCLC.

Keywords: Surgery, survival, advanced NSCLC

P3.01 ADVANCED NSCLC
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P3.01-83 USE OF BLOOD OUTGROWTH ENDOTHELIAL CELLS AS A CELLULAR CARRIER FOR ONCOLYTIC VESICULAR STOMATITIS VIRUS IN PRECLINICAL MODELS OF NSCLC

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Background: Oncolytic virus therapy has demonstrated efficacy in numerous tumor models including non-small cell lung cancer. One of the limitations of viral therapy for metastatic lung cancer is that systemic administration can be hindered by complement and antiviral immunity. Thus, we investigated the possibility of using ex-vivo infected blood outgrowth endothelial cells with tumor-homing properties to deliver oncolytic VSV-IFNβ in preclinical models of NSCLC. **Method:** BOECs were obtained from either human donors or C57/Bl6 mice. Cells were confirmed to maintain the BOEC phenotype and growth characteristics. Indiana strains of VSV were engineered to produce GFP or IFNβ and were titered on Vero cells using either plaque assay or limiting dilution assay. Human NSCLC cell lines, H2009 and H2030 were used for in vitro assays. A549 expressing firefly luciferase cells were used to induce lung metastasis in NOD/SCID mice and treated with BOECs, VSV-IFNβ, or BOECs-infected with VSV-IFNβ. Additionally, syngeneic murine adenocarcinoma cell line, LM2 was used in vivo in A/J mice (n=5). **Result:** BOEC cells were able to home to metastatic LM2 lung tumors and were retained there for up to 72 hours post-infusion. BOEC cells were retained within lung tumors of mice bearing tumors, but there were none detected in lungs of mice without lung tumors. Both human and murine BOECs could be infected and lysed by VSV-GFP and VSV-IFNβ, however, VSV-IFNβ was attenuated compared to VSV-GFP. Maximal viral titer was obtained at 24 or 48 hours for VSV-GFP and VSV-IFNβ, respectively. Co-culture experiments showed near complete lysis of H2009 cells using infected BOECs. Both H2009 and H2030 cells were lysed efficiently by infected BOECs while naked VSV was completely inhibited in the presence anti-VSV neutralizing antibodies. Using Firefly luciferase-expressing A549 cells, metastatic lung tumors were induced in NOD/SCID mice. Compared to BOEC alone and PBS-treated mice, VSV-IFNβ-infected BOECs resulted in superior antitumor efficacy as measured by luciferase activity ($p<0.02$). Infected BOECs resulted in superior survival of mice compared to VSV-IFNβ alone (n=10, $p<0.05$). Using immune competent A/J mice, infected BOECs trended toward improved antitumor efficacy to BOEC alone and intravenous VSV-IFNβ treatment (n=5, $p=0.09$). Replicating virus was recovered only from lungs of infected BOEC treated mice. **Conclusion:** BOECs can be used as cellular carrier for systemic delivery of oncolytic VSV-IFNβ. For clinical translation, the use of cellular carriers might be an effective method of virotherapy for metastatic NSCLC.

Keywords: Oncolytic virotherapy, BOEC, NSCLC

P3.01 ADVANCED NSCLC
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P3.01-84 THE ASSOCIATION OF CDKN2A GENE MUTATION WITH CLINICOPATHOLOGICAL FEATURES AND PROGNOSIS IN ADVANCED LUNG CANCER PATIENTS

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Background: The cell cycle-dependent kinase inhibitor gene (CDKN2A) is a tumor suppressor gene, and encodes two kind of cell cycle inhibitor proteins p16INK4a and p14ARF to regulate cell cycle. The aim of this study was to evaluate the association of CDKN2A gene mutation with clinicopathological features and prognosis in Chinese advanced lung cancer patients. **Method:** CDKN2A gene mutation was screened in tumor specimens using second generation sequencing technology. The correlation between CDKN2A gene mutation and clinicopathological characteristics was analyzed by Spearman's correlation. The overall survival (OS) and progression free survival (PFS) were analyzed by using the Kaplan–Meier method and compared by the log-rank test. The COX model was used to study the single factors and multiple factors. Statistical data was obtained by using SPSS for Windows version 20.0. P values < 0.05 were considered to indicate statistically significant results. **Result:** CDKN2A gene mutation was 4.57 % (10/219) in lung cancer patients. Patients harboring CDKN2A mutation were more commonly observed in squamous carcinoma patients (P=0.002). Most of patients with CDKN2A gene mutation were progression disease (PD) in the assessment of first-line treatment efficacy, while the patients without CDKN2A mutation were disease control rate (DCR) (P = 0.011). The OS in patients with CDKN2A gene mutation was 19.1 months compared to 42.8 months in patients without mutation (P = 0.010). The PFS in patients with CDKN2A mutation was 3.5 months compared to 9.7 months in patients without mutation (P = 0.000). In addition, multi-factor analysis showed that CDKN2A gene mutation (HR=2.385, P = 0.025), age 60 years or older (HR=1.588, P = 0.027), T4 stage (HR=1.533, P = 0.019) and high ECOG score (HR=1.694, P = 0.009) were independent risk factor for the survival of lung cancer patients. **Conclusion:** CDKN2A gene mutation had an important influence on the clinicopathological features and prognosis of Chinese advanced lung cancer patients. The patients with CDKN2A gene mutation had more poor survival.

Keywords: Prognosis, lung cancer, CDKN2A

P3.01 ADVANCED NSCLC
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P3.01-85 REAL-WORLD GEFITINIB 1ST LINE TREATMENT OF PATIENTS WITH ADVANCED NSCLC AND EGFR MUTATIONS - SERBIAN SINGLE CENTER EXPERIENCE

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Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) revealed their efficacy in advanced non-small cell lung cancer (NSCLC), in patients with EGFR mutated tumors, in large scale of clinical trials. Here we present data from clinical practice, patient characteristics and clinical outcome of consecutive patients treated with gefitinib in first-line setting at the Institute for Oncology and Radiology of Serbia between 2011-2016. **Method:** Previously untreated patients with lung adenocarcinoma in stages IIIB and IV and PS 0 or 1 have been reviewed by institutional multidisciplinary tumor board and selected for molecular EGFR testing since 2011. Patients with activating EGFR mutations (9.5%) received gefitinib, at that time the only approved EGFR TKI for the first line treatment **Result:** Sixty consecutive patients were included in this analysis. M/F ratio was 21/39, median age 60 years, non-smokers 48%, PS 0/1 85%, metastatic sites (more than 5% of patients) were lungs and pleura in 40%, bones in 27%, liver in 15%, pericardium in 10%, brain in 7% of patients. Only one metastatic site was present in 56% of patients, two sites in 35% and three sites in 6%. Del19 and L858R were detected in 82% of patients (del19 55% and L858R 27%) and umcommon mutations in 18%. Median duration of gefitinib treatment was 8 months, median follow-up 12.5 months. Partial response (PR) was achieved in 33% of patients, stable disease (SD) in 47%, progressive disease (PD) in 18%. Type of progression was a new lesson(s) in 20% of patients, progression of existing lesion(s) in 42% and both in 10%. Second-line treatment was administered to 38% of patients, and 63% were dead at the time of analysis. Median overall survival was 19 months, median progression-free survival 12 months. In patients with PR median OS was 26 months, in SD patients 22 months and in PD patients only 5 months. No statistically significant differences were shown in OS with regards to age, gender,

M1a/M1b stage, exon19/21 mutations, common/uncommon mutations or different sites of metastatic disease. **Conclusion:** Serbian patients with EGFR mutated lung adenocarcinoma treated with gefitinib in first-line have similar characteristics and outcome compared with published data, particularly when compared with similar analysis on Caucasian population. Probably due to small number of patients, we were not able to select subpopulations of patients with greater benefit from receiving gefitinib

Keywords: EGFR mutated NSCLC, gefitinib, real-world data

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P3.01-86 TREATMENT OUTCOMES WITH REDUCED FREQUENCY OF NIVOLUMAB DOSING AS SECOND-LINE THERAPY IN PATIENTS WITH ADVANCED NSCLC

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Background: Nivolumab (Nivo) was approved as second-line therapy in 2015 for patients (pts) with advanced NSCLC. The optimal effective interval between doses is not well-established. We want to evaluate the effect of reduced dose density on the efficacy and safety of Nivolumab. **Method:** This is a single-institution, IRB approved retrospective review of stage IIIB/IV NSCLC who received Nivo after prior platinum-based chemotherapy in the second line setting or beyond between April 2015-January 2018. Characteristics of pts who received Nivo 240mg every(q) 4 weeks or longer, reasons for alternate dosing and their treatment outcomes are described. **Result:** Out of 181 pts with NSCLC who received Nivo during this time frame, 32 pts (18Male:14 Female) received an alternate dosing schedule (median q 4 weeks, range q 3-12 weeks). Median age was 65 years. Majority were former smokers (62%) and had adenocarcinoma (81%). 17 pts started on a regular schedule q 2 weeks and then switched to an alternate schedule, the remaining 15 pts started on an alternate schedule. 28% (9/32) patients were on an alternate schedule due to adverse event. Median expected total cumulative dose (240mg*no. of expected doses until disease progression or death) per pt is 4032mg (range 480 -15840). Median actual cumulative dose (240mg*actual no. of doses) received per pt is 1920mg (range 480 - 10560). This represents a median of 52% of the expected total cumulative dose received. Objective response rate (CR+PR) in the entire cohort was 66%. Median progression-free survival(PFS) from start of alternate schedule is 17.1 months (95% CI 5.2- not reached). 6-month PFS is 65% (95% CI 46%-79%) starting from when alternate schedule of Nivo was begun. We will present updated toxicity and treatment outcomes in the meeting. **Conclusion:** Nivolumab 240mg administered at q 4 weeks or longer is feasible. Further investigation is needed to optimize patient selection for alternate dosing schedule.

Keywords: Nivolumab, alternate, schedule

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P3.01-87 EFFICACY AND SAFETY OF PEMBROLIZUMAB IN NON-SMALL CELL LUNG CANCER IN OUR INSTITUTION: A RETROSPECTIVE STUDY

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Background: Pembrolizumab, an anti-PD-1 antibody, showed a clear advantage compared with chemotherapy in the advanced non-small cell lung cancer selected by histological PD-L1 expression in response rate, progression-free survival time and overall survival time. **Method:** We retrospectively reviewed a total of 51 patients who received Pembrolizumab in advanced non-small cell lung cancer in our institution from March 2017 to February 2018. **Result:** The median age was 70.0 [37 - 87] years. Male/female : 10/41. Median follow-up duration was 6.4 months [4.1 - 8.5]. The ECOG-PS was 0/1/2/3 : 20/24/5/2. The histologic type was adenocarcinoma/squamous cell carcinoma/non-small cell carcinoma/pleomorphic carcinoma : 23/6/9/3. PD-L1 total proportion score was 1%-49%/≥50% : 11/40. EGFR mutation status was 19 deletion+T790M/G719C/T790M : 1/3/1. ALK rearrangement/ROS1 rearrangement/BRAF mutation of V600E : 1/1/1. The number of treatment line was 1st/2nd/3rd/4th/8th : 23/21/4/2/1. Among 51 patients, response was showed PR/SD/PD/NE : 17/15/15/4, ORR was 33.3% and DCR was 62.7%. Median PFS time was 8.9 months and median OS time was not reached. The most common all-causality adverse events were fever/rash/pruritus : 1/3/3(All were Gr1). Oral mucositis: Gr1/2 : 1/1,liver dysfunction: Gr2 : 1,renal dysfunction: Gr1 : 3, pneumonitis: Gr1/2/3/4/5 : 1/2/0/1/2, colitis: Gr1/2 : 0/3. **Conclusion:** The response rate was 33.3%, PFS was 8.9 months in our institution. However the reported response rate was 18.0%, PFS was 2.6 months. Therefore higher response rate and PFS prolongation were showed. The frequency of pneumonitis in our institution was 6 cases (11.7%), which tended to be higher than the previously reported 4.7%.

Keywords: Pembrolizumab institution retrospective

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P3.01-88 CLINICAL AND MOLECULAR ANALYSIS OF LONG-TERM SURVIVORS WITH ADVANCED NON-SMALL CELL LUNG CANCER: A MULTICENTER EXPERIENCE IN MADRID

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Background: Long survivors (LS) in non-small-cell lung cancer (NSCLC), defined as an overall survival (OS) greater than 2 years, are less than 10% in most series. Classical prognosis factors include stage, weight loss and ECOG, but there are other factors whose influence on the evolution of these patients is uncertain. Recently, different drugs targeted against EGFR, ALK and ROS 1 reach OS longer than 2 years in a limited number of patients (less than 20%). Immunotherapy in NSCLC has demonstrated very promising results with more LS compared to chemotherapy in first and second line setting. In this study, we have focused in the analysis of LS patients with advanced NSCLC EGFR wt (wild type) and ALK nt (non-translocated), defined as those with OS greater than 36 months, in 8 hospitals in Madrid. **Method:** In this serie, first of all, we will try to make a clinical, histopathological and immunological characterization collecting data from clinical reports according to a previously defined information. In a second step, we will carry out a genetic analysis of these patient samples comparing to an opposite extreme short survivors (SS) samples (OS less than 9 months) from same centers. We used a NGS method of RNA-seq technology with the idea of identify differentiating profiles of gene expression between the two opposite populations with a later confirmation by RT-PCR in the rest of the tissue samples and liquid biopsy. **Result:** We have obtained a differential transcriptome expression between samples from 6 LS and 6 SS, resulting 13 overexpressed and 42 under-expressed genes in LS comparing to SS transcriptome expression. Some of the genes involved in this profile belong to different families and cellular pathways: Secretin receptor, Surfactant Protein, Trefoil Factor 1, Serpin Family, Ca bindings protein channel and Toll like Receptor family. A further confirmation of this profile is carrying on by RT-PCR in the rest of the samples and liquid biopsy from the rest of the patients included in the study. **Conclusion:** We present the first data from a genetic analysis of a LS population with NSCLC EGFR wt (wild type) and ALK nt (non-translocated), obtaining a differential RNA profile

Keywords: long survivors, non small cell lung cancer

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P3.01-89 UPFRONT SURGERY VERSUS NEOADJUVANT TREATMENT FOLLOWED BY SURGERY IN PATHOLOGIC N2 NON-SMALL CELL LUNG CANCER

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Background: Non-small cell lung cancer (NSCLC) patients with ipsilateral mediastinal nodal metastases (N2) had poor prognosis. Although definitive chemoradiation was frequently used as a standard of care for clinical N2 NSCLC, surgery can be a preferred treatment option in selected patients with upfront surgery plus adjuvant treatment or neoadjuvant treatment followed by surgery. Before starting a prospective study in our institution, we checked a treatment outcome of pathologic N2 NSCLC patients treated by upfront surgery or neoadjuvant treatment approach. **Method:** The present study evaluated 21 patients with pathologic N2 NSCLC at St. Vincent hospital from February 2007 to September 2017. Patient with upfront surgery or neoadjuvant treatment followed by surgery was included, and pathologic N2 was confirmed before surgery in neoadjuvant group. Taxane and platinum was used as a neoadjuvant treatment or post-operative therapy in both group. Chemotherapy alone or combined with radiotherapy was conducted. Disease free survival (DFS) and overall survival (OS) was evaluated and Kaplan-Meier survival analysis was used for these analyses. **Result:** Eleven (52%) underwent upfront surgery, and 10 patients (48%) underwent neoadjuvant treatment followed by surgery. Clinical T1N2, T2N2 and T3N2 were 4 (19%), 11 (52%) and 6 (29%), respectively. Baseline characteristics did not show significant difference in these two groups. Upfront surgery group received post-operative treatment including chemotherapy alone (n=7), radiotherapy alone (n=2) or chemoradiotherapy (n=1). Neoadjuvant group received chemoradiotherapy (n=3) or chemotherapy alone (n=10). Regarding DFS, there are no significant differences between upfront surgery group and neoadjuvant group (median DFS, 10.0 months vs. 15.1 months, P=0.925). Five year disease free survival rate was 40% and 30%, respectively. In addition, OS did not show significant differences between two groups (medians OS, 79.5 months vs. 47.7 months, P=0.295). Fiver year overall survival rate were 90% and 50%, respectively. In upfront surgery group, 4 of 7 patients did not complete chemotherapy schedule due to adverse event. But, 9 of 10 patients had a completion of chemotherapy in neoadjuvant group. **Conclusion:** There are no significant survival differences between upfront surgery group and neoadjuvant treatment group, but both strategies can be effective treatment option for selected pathologic N2 NSCLC. Further studied need to be done for these patients, and currently our institution are preparing clinical trials in a prospective manner.

Keywords: Neoadjuvant treatment, pathologic N2, Upfront surgery

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P3.01-90 A PHASE II STUDY EVALUATING CONTINUATION OF EGFR-TKIS BEYOND PROGRESSIVE DISEASE FOLLOWED BY THE ADDITION OF CDDP+PEM+BEV

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Background: *Previous studies demonstrated that EGFR- tyrosine-kinase inhibitors (EGFR-TKIs) have antitumor effects even after disease progression during EGFR-TKI treatment. In this phase II study (NLCTG1301), we assessed the safety and efficacy of continuing EGFR-TKIs beyond progressive disease followed by the addition of cisplatin (CDDP), pemetrexed (PEM) and bevacizumab (Bev) in patients with EGFR mutation-positive advanced NSCLC with acquired resistance to first-line EGFR-TKIs.* **Method:** Eligible patients were aged at least 20 years with histologically confirmed, cytotoxic chemotherapy-naive, stage IIIB–IV *EGFR* mutation-positive NSCLC with previous disease control for at least 6 months with first-line EGFR-TKIs. Patients received CDDP 75 mg/m^2, PEM 500 mg/m^2 and Bev 15 mg/kg on the first day of each cycle *with the continuation of EGFR-TKIs. After completion of a maximum of four chemotherapy cycles, patients continued EGFR-TKIs along with maintenance Bev and PEM until disease progression. The primary endpoint was response rate according to RECIST version 1.1.* **Result:** *The study was terminated because of slow accrual. Between March 2013 and January 2018, 10 patients were enrolled in this trial and were evaluable for safety and efficacy. Their subtypes of EGFR mutation were exon 19 deletions (7 cases), L858R (2 cases), and L858R+790M (1 case). EGFR-TKIs used in initial treatment were gefitinib (7 cases), erlotinib (3 cases), and the efficiency was PR (9 cases) and SD (1 cases). The objective response rate was 70%, median progression-free survival was 11.4 months, and median overall survival was not reached. The reasons for discontinuation were 6 cases with disease progression, 3 cases with toxicity (Gr3 infection, Gr3 g-GTP increased, Gr2 creatinine increased), and one case with bone fracture caused by accidental falling. Although there were 3 cases of treatment discontinuation due to toxicities, no serious adverse events were observed in the current study. After acquisition of resistance to EGFR-TKIs, tumor re-biopsy was performed in 4 cases, of which T790M was confirmed in 2 cases.* **Conclusion:** *This study showed the possibility of benefit of the addition of CDDP+PEM+Bev to EGFR-TKIs in patients with acquired resistance. However, further investigation of this strategy seems to be difficult because of the approval of osimertinib and the results of the IMPRESS study.*

Keywords: The phase II study, EGFR-TKIs, cisplatin pemetrexed bevacizumab

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P3.01-91 COMPUTING THE IMPACT OF IMMUNOTHERAPY ON THE NON-SMALL CELL LUNG CANCER (NSCLC) THERAPEUTIC LANDSCAPE

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Background: The Advanced Non-Small Lung Holistic Registry (ANCHoR) is established to examine the real-world impact of immunotherapy on choice of treatment, clinical outcomes, and patient reported outcomes of patients with Stage IV NSCLC. **Method:** Stage IV NSCLC patients diagnosed or initiating treatment at MD Anderson from January 1, 2017 are enrolled in the ongoing ANCHoR study. Their demographic, clinicopathological, molecular, and treatment data were populated in a prospective database. Treatment patterns by line and PD-L1 status were summarized in this interim analysis. **Result:** At the time of data cut off (Dec 31, 2017) 182 patients were enrolled in the registry, of which 150 were tested for PD-L1. Number of patients initiating first-, second-, and third-line treatment were 163, 42 and 7, respectively. Of the 30 patients not tested for PD-L1, 10 did not have enough tissue and 8 had actionable mutations.

(See next page)

Table 1. Distribution of first-line treatment by PD-L1 status in ANCHoR (Jan 2017-Dec 2017)

Regimen	Overall, N=163		PD-L1 tested, n= 133						PD-L1 Not tested/Unknown, n= 30	
			TPS<1%		TPS≥1% to <50%		TPS≥50%			
	n	%	n	%	n	%	n	%	n	%
Platinum doublet	65	39.88%	25	55.56%	24	48.98%	6	15.38%	10	33.33%
Platinum doublet + angiogenesis inhibitor	2	1.23%	1	2.22%	0	0.00%	0	0.00%	1	3.33%
Platinum doublet + immunotherapy	28	17.18%	10	22.22%	9	18.37%	6	15.38%	3	10.00%
EGFR targeted agent alone or in combination	25	15.34%	5	11.11%	9	18.37%	2	5.13%	9	30.00%
ALK targeted agent alone or in combination	3	1.84%	0	0.00%	1	2.04%	0	0.00%	2	6.67%
Immunotherapy single agent	38	23.31%	4	8.89%	5	10.20%	25	64.10%	4	13.33%
Chemotherapy single agent	1	0.61%	0	0.00%	1	2.04%	0	0.00%	0	0.00%
Investigational agent	1	0.61%	0	0.00%	0	0.00%	0	0.00%	1	3.33%
Total	**163**	**100.00%**	**45**	**100.00%**	**49**	**100.00%**	**39**	**100.00%**	**30**	**100.00%**

Conclusion: The emergence of immunotherapy has had a dramatic impact on the first-line treatment of patient with advanced NSCLC. As of December, 2017 up to 41% of patient received immunotherapy either singly (23%) or in combination with chemotherapy. Only 40% of the patients now receive chemotherapy alone. There has been dramatic decrease in the use of chemotherapy with an anti-angiogenesis agent (1.23%). In our dataset 16% of the patients were eligible for targeted therapy as initial treatment.

Keywords: NSCLC, PDL-1, Immunotherapy

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P3.01-92 BLOOD TEST PARAMETERS AS PROGNOSTIC FACTORS IN EGFR-MUTATED NON-SMALL CELL LUNG CANCER TREATED WITH TKIS

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Background: Systemic inflammation is an important factor contributing to tumor progression. High neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are markers of host inflammation whose association with worse overall survival (OS) in non-small cell lung cancer (NSCLC) has been shown in various studies. However, there are few studies investigating the association of these, and other haematological parameters of inflammation with prognosis of EGFR mutated NSCLC treated with tyrosine-kinase inhibitors (TKIs). We therefore examined the association between various blood test parameters and prognosis in this group of patients. **Method:** This retrospective analysis included 74 consecutive advanced lung adenocarcinoma patients of caucasian descent, stage IIIB or IV, treated with EGFR TKIs in the first line at the Institute for oncology and radiology of Serbia within a five year period. The analysed haematological parameters were derived from the absolute differential counts of a complete blood count (CBC) taken within one week of TKI treatment initiation. Parameters included in this analysis were NLR, PLR, lymphocyte-to-monocyte ratio (LMR), mean platelet volume (MPV), lymphocyte-to-white blood cell ratio (LWR) and neutrophil-to-white blood cell ratio (NWR). Cut-off values were determined using ROC curves. Correlation between each haematological parameter and progression-free survival (PFS) and OS was examined by Kaplan-Meier method and Cox regression **Result:** Median PFS in the whole group was 13.6 months (10.25-16.95, CI 95%) and median OS was 19.48 months (15.91-23.05, CI 95%). Low LWR (< 0.14) was associated with a shorter PFS in this group of patients (9.2 vs 14.29 months, p=0.008). High NLR (≥ 2.63), high MPV (≥ 8.1) and low LWR (< 0.14) were associated with shorter OS (18.0 vs 27.6 months, p=0.05; 15.57 vs 22.18 months, p=0.04 and 16.13 vs 22.19, p=0.038 respectively). No other analysed parameters showed an association with either PFS or OS **Conclusion:** Pre-treatment NLR, LWR and MPV could be reliable, simple and easy to reproduce parameters for prediction of survival and outcome of targeted therapies in caucasian EGFR-mutated NSCLC patients. Further prospective trials are needed to definitively confirm this possible prognostic and predictive role

Keywords: EGFR-mutated NSCLC, markers of inflamation, prognosis

P3.01 ADVANCED NSCLC
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P3.01-93 OSIMERTINIB-RELATED HEMATOLOGICAL AND PULMONARY TOXICITIES IN ADVANCED NSCLC PATIENTS: COMBINED ANALYSIS OF PHASE III TRIALS

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Background: In both epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) sensitizing and EGFR T790M resistance mutations in patients with advanced non-small-cell lung cancer (NSCLC), osimertinib, a third-generation and irreversible oral EGFR-TKI, has been shown to improve survival in studies. We performed a systematic review and meta-analysis of phase III randomized controlled trials (RCT) to determine the risk of hematological and pulmonary toxicities among patients with advanced NSCLC treated with osimertinib. **Method:** We undertook a comprehensive literature search using MEDLINE, EMBASE databases and meeting abstracts from inception through March 2018. Phase III RCTs that mention hematological and pulmonary toxicities as adverse effects were incorporated in the analysis. The primary meta- analytic approach was a fixed effects model using the Mantel-Haenszel (MH) method. It was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI). **Result:** A total of 971 patients with advanced NSCLC from two phase III studies were eligible for analysis. The study arm used osimertinib while the control arm utilized either chemotherapy (carboplatin/cisplatin+ pemetrexed) or standard EGFR-TKIs (gefitinib or erlotinib). The randomization ratio was 1:1 in the FLAURA study and 2:1 in the AURA3 study. Osimertinib was utilized in T790M-positive advanced NSCLC after prior first-line EGFR-TKIs in the AURA3 study (n= 556) and as first-line treatment in the FLAURA study (n= 415). The RR of all-grade side effects were as follows: anemia, 0.594 (95% CI: 0.433 – 0.814, p = 0.001); cough, 1.122 (95% CI: 0.829 – 1.520, p = 0.455); dyspnea, 1.143 (95% CI: 0.784 – 1.666; p = 0.487); and ILD, 2.378 (95% CI: 0.984 – 5.744; p = 0.054). The RR of high-grade adverse effects were as follows: anemia, 0.175 (95% CI: 0.072 – 0.425, p < 0.001); neutropenia, 0.293 (95% CI: 0.138 – 0.623; p = 0.001); thrombocytopenia, 0.183 (95% CI: 0.060 – 0.564, p = 0.003); pneumonia, 1.237 (95% CI: 0.442 – 3.459; p = 0.685); dyspnea, 0.895 (95% CI: 1.192 – 4.175; p = 0.888); and ILD, 1.238 (95% CI: 0.404 – 3.789; p = 0.708). **Conclusion:** Our meta-analysis demonstrated that patients on osimertinib experienced a significant decrease in the risk of hematological toxicities, compared to control arm. Moreover, no increase in the risk of pulmonary toxicities was noted in the osimertinib group.

Keywords: osimertinib, toxicity, meta-analysis

P3.01-94 SAFETY AND EFFICACY OF FIRST-LINE PEMETREXED VERSUS BEVACIZUMAB-CONTAINING REGIMENS IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Previous trial data have documented the efficacy of first-line bevacizumab-based regimens, including bevacizumab-pemetrexed combinations in advanced non-small cell lung cancer (NSCLC). We herein aimed to further assess the safety and efficacy of pemetrexed monotherapy versus bevacizumab-containing or other chemotherapy regimens in a real-world NSCLC population. **Method:** The medical records of 753 patients with advanced-stage non-squamous NSCLC, treated with bevacizumab-based regimens, pemetrexed monotherapy, or other treatments, as first-line therapy, were retrospectively reviewed and analyzed for efficacy and safety endpoints. **Result:** The bevacizumab-based group had the highest percentage of partial response/PR (32.3% vs 22.8% for pemetrexed and 20.0% for other treatments) and a significantly lower incidence of progressive disease/PD (35.92%, 30.17%, and 50.48%, for pemetrexed, bevacizumab-based, and other, respectively; $p < 0.0001$). Bevacizumab-based regimens achieved a better overall survival (OS) rate (measured at the end of treatment) (pemetrexed 29.6%, bevacizumab-based 35.7%, and other treatments 8.9%; $p < 0.0001$). However, median OS was not improved (10 months, 12 months, and 13 months for pemetrexed, bevacizumab-based, and other treatments, respectively; $p=0.007$). A significantly higher incidence of cough ($p = 0.001$) and hemoptysis ($p < 0.0001$) in the bevacizumab-based arm, pain in the pemetrexed arm ($p = 0.007$), and alopecia in the other treatments arm ($p < 0.0001$) was observed during treatment. A significantly higher incidence of hemoptysis in the bevacizumab-based arm ($p < 0.0001$) and alopecia in the other treatments arm ($p < 0.0001$) was seen at the end of first-line treatment. **Conclusion:** Bevacizumab-based regimens resulted in improved treatment response and short-term survival rate, but not in improved OS. An increased, albeit acceptable, toxicity was also observed among bevacizumab-treated patients as compared to those treated with pemetrexed monotherapy.

Keywords: pemetrexed, non-small cell lung cancer, bevacizumab

P3.01-95 EGFR GENOTYPE AS A PREDICTOR OF SURVIVAL IN EGFR MUTANT NON-SMALL CELL LUNG CANCER

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Background: Patients with epidermal growth factor (EGFR)-mutant non-small cell lung cancer (NSCLC) represent a distinct treatment and prognostic subgroup, typically responding to treatment with tyrosine-kinase inhibitors (TKIs) but also displaying a highly variable prognosis. We herein aimed to further investigate the potential value of EGFR genotype as a predictor of survival in EGFR-mutant NSCLC. **Method:** The medical records of 68 patients with NSCLC and positive EGFR mutation status, who had been treated with EGFR-TKIs, were retrospectively reviewed. Demographic, clinicopathological features and EGFR mutation testing results of patients were correlated with survival. **Result:** (EGFR) exon 19 E746-A750 deletion and (EGFR) exon 21 L858R point mutation were the commonest EGFR mutations, observed in 58% and 24% of patients, respectively. Median progression-free survival (PFS) among patients with (EGFR) exon 21, 19 and 18/20 was 22.9, 13.9 and 4.7 months, respectively. Median overall survival (mOS) for the above subgroups was 25.1, 35.8 and 13.8 months, respectively. The presence of (EGFR) exon 21 L858R point mutation was correlated with reduced risk of disease recurrence as compared to (EGFR) 18/20 mutations (HR=0,25, p=0,018); patients with (EGFR) exon 19 mutations had reduced risk of death as compared to those with (EGFR) exon 18/20 mutations (HR=0,29, p=0,007). **Conclusion:** The presence of (EGFR) exon 19 mutations may be associated with increased OS among patients with EGFR-mutant NSCLC.

Keywords: non-small cell lung cancer, genotype, EGFR mutations

P3.01-96 CLINICAL CHARACTERISTICS OF NON–SMALL CELL LUNG CANCER HARBORING MUTATIONS IN EXON 20 OF EGFR OR HER2

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Background: Unlike common epidermal growth factor receptor gene (*EGFR*) mutations that confer sensitivity to tyrosine kinase inhibitors (TKIs) in non–small cell lung cancer (NSCLC), mutations in exon 20 of either *EGFR* or the human EGFR2 gene (*HER2*) are associated with insensitivity to EGFR-TKIs, with treatment options for patients with such mutations being limited. **Method:** Clinical characteristics, outcome of EGFR-TKI or nivolumab treatment, and the presence of coexisting mutations were reviewed for NSCLC patients with exon-20 mutations of *EGFR* or *HER2* as detected by routine application of an amplicon-based next-generation sequencing panel. **Result:** Between July 2013 and June 2017, 206 patients with pathologically confirmed lung cancer were screened for genetic alterations including *HER2* and *EGFR* mutations. Ten patients harbored *HER2* exon-20 insertions (one of whom also carried an exon-19 deletion of *EGFR*), and 12 patients harbored *EGFR* exon-20 mutations. Five of the 13 patients with *EGFR* mutations were treated with EGFR-TKIs, two of whom manifested a partial response, two stable disease, and one progressive disease. Among the seven patients treated with nivolumab, one patient manifested a partial response, three stable disease, and three progressive disease, with most (86%) of these patients discontinuing treatment as a result of disease progression within 4 months. The H1047R mutation of *PIK3CA* detected in one patient was the only actionable mutation coexisting with the exon-20 mutations of *EGFR* or *HER2*. **Conclusion:** Potentially actionable mutations thus rarely coexist with exon-20 mutations of *EGFR* or *HER2*, and EGFR-TKIs and nivolumab show limited efficacy in patients with such exon-20 mutations.

Keywords: EGFR, HER2, Nivolumab

P3.01-97 WHICH IS BETTER PROGNOSTIC FACTOR, PS, INFLAMMATORY MARKER, OR PD-L1 EXPRESSION IN TREATING NSCLC WITH NIVOLMAB; A RETROSPECTIVE ANALYSIS

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Background: Although nivolumab showed the significantly longer overall survival (OS) compared with standard second-line therapy using docetaxel for both squamous and non-squamous non-small cell lung cancer (NSCLC) based on two phase III randomized controlled trials, PD-L1 expression alone is not yet an adequate biomarker in treating NSCLC patients with nivolmab. This single institute retrospective study aimed to analyze which biomarker or pretreatment patients' status were more associated with outcomes in NSCLC patients treated with nivolumab. **Method:** We retrospectively reviewed the medical records of all patients with previously treated advanced NSCLC who received nivolumab between December 2015 and May 2016 in our institute. And we confirmed PD-L1 expression in the patients who were able to examine PD-L1 status. Multivariable logistic regression and Cox proportional hazards models were used to assess the impact of pretreatment PD-L1 expression, performance status (PS), and inflammation parameter (neutrophil-to-lymphocyte ratio (NLR)) on progression-free survival (PFS) and OS. The data cut off was on 31th October 2017. **Result:** A total of 66 patients were included in this analysis. Median age was 66 (range, 46–85) years old, 48 patients were men, 54 patients were non-squamous cell carcinoma, 57 patients had a smoking history, 15 patients had a PS of 2 or higher, 23 patients were NLR ≥4, and 10 patients were PD-L1 expression ≥50 and 19 patients were PD-L1 expression 1-49. As for pretreatment prognostic factors, multivariate analyses revealed that never smoker (hazard ratio (HR): 4.22, 95% confidence interval (CI): 1.23 - 15.90), PS ≥2 (HR: 3.72, 95% CI: 1.80 - 7.52), and no PD-L1 expression (HR: 2.03, 95% CI: 1.10 – 3.84) were significantly associated with poor PFS, and furthermore PS ≥2 (HR: 6.27, 95% CI: 2.72 - 14.65) was independently associated with poor OS. Conclusion: PS is the better prognostic factor than NLR and PD-L1 expression in NSCLC patients treated with nivolumab.

Keywords: non-small cell lung cancer, Nivolumab, prognostic factor

P3.01 ADVANCED NSCLC
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P3.01-99 EFFECT OF PEMBROLIZUMAB ON PATIENTS HARBORING UNCOMMON EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS

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Background: The characteristics of non-small cell lung carcinoma (NSCLC) patients harboring uncommon *epidermal growth factor receptor* (*EGFR*) mutations differ from those of patients with common *EGFR* mutations. For example, male smokers were more common among patients with uncommon mutations. The efficacies of non-afatinib treatment strategies for patients harboring uncommon *EGFR* mutations are uncertain. The efficacy of immune checkpoint inhibitors (ICIs) in advanced NSCLC patients with *EGFR* mutations is limited. Furthermore, the efficacy of ICIs in patients harboring uncommon *EGFR* mutations is unknown. **Method:** We retrospectively reviewed five NSCLC cases with uncommon *EGFR* mutations and high program death (PD)-ligand (L)1 expression (> 50%) on tumor cells that were treated with the ICI pembrolizumab in our institute from April 2017 to April 2018. We collected data include sex, age, performance status, smoking history, PD-L1 expression, EGFR mutations status and clinical outcome. **Result:** Four cases were male, median age was 68 (45-78), 4 cases were former/current smokers, 1 case was stage IIIC, 2 cases were stage IVA and 2 cases were stage IVB, 4 cases had G719X and 1 case had both exon 19 deletion and T790M. Four cases were treated with pembrolizumab as first line treatment and 1 case were treated as second line treatment after afatinib. Median number of pembrolizumab doses were 4 (1-7) and best responses were 2 partial response (PR), 2 stable disease (SD) and 1 progressive disease (PD). As adverse events, 1 case had grade 3 colitis and 1 case had grade 1 pneumonitis. **Conclusion:** Four patients with the G719X mutation were male former/current smokers and were effectively treated (PR of SD) with pembrolizumab. However, one patient with both common mutation and de novo T790M did not respond to pembrolizumab (PD). ICI-based treatment for patients harboring uncommon *EGFR* mutations may be one of the treatment option.

Keywords: Non-small cell lung carcinoma, immune checkpoint inhibitor, epidermal growth factor receptor mutation

P3.01 ADVANCED NSCLC
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P3.01-100 RISK OF GASTROINTESTINAL AND HEPATIC TOXICITIES IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER TREATED WITH OSIMERTINIB

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Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the standard first-line therapy in patients with advanced non-small-cell lung cancer (NSCLC) who harbors EGFR mutation. The presence of T790M point mutation, later, mediates the resistance to first-generation and second-generation EGFR-TKIs. Osimertinib, an oral third-generation EGFR-TKI, targets both EGFR-TKI sensitizing and EGFR T790M resistance mutations. We undertook a systematic review and combined analysis of two phase III randomized controlled trials (RCT) to determine the risk of gastrointestinal and hepatic toxicities among patients with advanced NSCLC treated with osimertinib. **Method:** We conducted a comprehensive literature search using MEDLINE, EMBASE databases and meeting abstracts from inception through March 2018. Phase III RCTs that mention diarrhea, nausea, vomiting, stomatitis and elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) as adverse effects were incorporated in the analysis. Mantel-Haenszel (MH) method was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI). Fixed effects model was applied. **Result:** Two phase III RCTs with a total of 971 patients with advanced NSCLC were included in the analysis. Studies compared osimertinib vs carboplatin/cisplatin + pemetrexed and osimertinib vs gefitinib/erlotinib. The randomization ratio was 1:1 in the FLAURA study and 2:1 in the AURA3 study. Osimertinib was utilized in T790M-positive advanced NSCLC after prior first-line EGFR-TKIs in the AURA3 study (n= 556) and as first-line treatment in the FLAURA study (n= 415). The RR of all-grade side effects were as follows: diarrhea, 1.305 (95% CI: 1.128 – 1.509, p < 0.0001); nausea, 0.480 (95% CI: 0.378–0.611; p < 0.0001); vomiting, 0.783 (95% CI: 0.561–1.092; p = 0.149); stomatitis, 1.262 (95% CI: 0.980 – 1.626, p = 0.071); elevated AST, 0.397 (95% CI: 0.277–0.569; p < 0.0001); and elevated ALT, 0.312 (95% CI: 0.212–0.458; p < 0.0001). The RR of high-grade side effects were as follows: diarrhea, 0.912 (95% CI: 0.354 – 2.347, p = 0.849); vomiting, 0.135 (95% CI: 0.022 – 0.831; p = 0.031); stomatitis, 0.532 (95% CI: 0.124 – 2.293, p = 0.397); elevated AST, 0.296 (95% CI: 0.096 – 0.907; p = 0.033); and elevated ALT, 0.112 (95% CI: 0.034 – 0.372; p < 0.0001). **Conclusion:** Patients on osimertinib noted a significant increase in the risk of all-grade diarrhea. Nevertheless, the risk of developing any-grade nausea, all grades of elevated AST/ALT and high-grade vomiting, was significantly reduced in osimertinib arm, favoring osimertinib.

Keywords: Advanced Non-Small Cell Lung Cancer, Gastrointestinal & hepatic toxicities, Osimertinib

P3.01 ADVANCED NSCLC
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P3.01-101 A RETROSPECTIVE STUDY OF LUNG CANCER THAT HAS PROGRESSED TO BRAIN METASTASIS ALONE

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Background: There is no consensus whether systemic therapy is needed after local treatment of lung cancer that has progressed to brain metastasis alone. To clarify the effect of treatment differences on patient survival, we conducted a retrospective study of treatment outcomes in patients with lung cancer that progressed to brain metastasis alone. **Method:** The study included patients diagnosed with lung cancer at our hospital between January 2011 and December 2016 and those with disease progression to brain metastasis alone by December 2017. We divided the patients according to the treatment administered and compared their characteristics and survival. **Result:** This study included 26 patients. Among them, 7 patients were followed up after local treatment (FU) and 19 patients received systemic therapy after local treatment (ST). The patient characteristics were as follows: median age (years): FU, 71 and ST, 68; sex (male/female): FU, 5/2 and ST, 8/11; disease stage at diagnosis (I/II/III/IV/postoperative recurrence): FU, 3/0/3/1/0 and ST, 0/1/7/9/2; and histology (small cell lung cancer/non-small cell lung cancer): FU, 1/6 and ST, 6/13. There were no significant differences in survival between the two groups (median progression-free survival [PFS; months], FU vs. ST=9 vs. 5, P=0.581; median overall survival [months], FU vs. ST=26 vs. 13, P=0.656). Analysis of prognosis showed significant differences only in disease stage at diagnosis based on univariate Cox analysis of PFS (I–III vs. IV or postoperative recurrence; hazard ratio, 3.440; 95% confidence interval, 1.16-10.22; P=0.026). **Conclusion:** In patients with lung cancer that has progressed to brain metastasis alone, administration of systemic therapy may not be necessary until further disease progression after local treatment.

P3.01 ADVANCED NSCLC
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P3.01-102 POTENTIAL PREDICTORS OF UNEXPECTED READMISSION AFTER LUNG RESECTION

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Background: Postoperative unexpected readmissions are sentinel events that negatively impact patients. Previous analyses of risk factors of unexpected readmission after lung resection have identified several predictive factors. However, both the operative procedures and perioperative care can vary between institutions. The current study aimed to investigate the incidence levels and potential predictors of unexpected readmission after lung cancer surgery at our institution. **Method:** Patients who underwent lung resection for primary lung cancers between January 2016 and December 2017 at our institution were enrolled in this study. Operative procedures included pneumonectomy, lobectomy, segmentectomy, and wedge resection. Pleural biopsy and unresectable cases were excluded from this study. Unexpected readmissions were defined as an unscheduled readmission after surgery to our hospital. All patients were examined at our outpatient clinic within 14 days after initial discharge. Thirty-day readmission rates and diagnoses were edaluated. Univariate analysis was performed to identify perioperative

factors associated readmission. **Result:** During the 24-month study period, 1,000 patients underwent lung resection for primary cancer. The median age was 69 years (32–90 years). Fourteen pneumonectomies, 687 lobectomies, 193 segmentectomies, and 106 wedge resections were performed. The median length of postoperative hospital stay was 4 days (2–117 days). The 30-day mortality rate was 0.3% (3 of 1,000 patients). Forty-three patients (4.3%) experienced an unexpected readmission within 30 days after discharge. The median interval to readmission from the day of discharge was 10 days (1-29 days). The most common diagnoses for readmission were empyema (n=11; 26%), exacerbation of interstitial pneumonia (n=7; 16%), pneumothorax (n=7; 16%), and pneumonia (n=5; 12%). The median length of readmission hospital stay was 10 days (2–90 days). Among readmitted patients, 9.3% (4 of 43) had died in the hospital due to exacerbation of interstitial pneumonia. In a univariate analysis, significant factors ($p<0.05$) associated with increased risk of unexpected readmission were man, smoking history, diabetes mellitus, larger tumor size, positive lymph node, either lobectomy or pneumonectomy, longer operative time, either prolonged air leakage (i.e., more than 5 days) or reoperation for air leakage, longer hospital stay after initial surgery. **Conclusion:** The unexpected readmission rate after lung resection was 4.3% (n=43), with respiratory complications (n=30; 70%) being the most common cause. Four patients (9.3%) died in the hospital due to exacerbation of interstitial pneumonia. Several perioperative factors were identified as risk factors for readmission in this study.

Keywords: Surgery, Readmission

P3.01 ADVANCED NSCLC
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P3.01-103 EFFICACY OF CRIZOTINIB IN CHINESE NON-SMALL CELL LUNG CANCER PATIENTS WITH BRAIN METASTASIS: A MULTICENTER RETROSPECTIVE STUDY

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Background: Brain metastasis in advanced non-small cell lung cancer (NSCLC) patients is often considered as a terminal stage. Crizotinib is a small-molecule tyrosine kinase inhibitor (TKI) for ALK-rearranged NSCLC patients. Herein we conducted a multi-center retrospective study to explore how crizotinib affects the control of brain metastasis and survival outcomes among advanced ALK-rearranged NSCLC patients with brain metastasis in Chinese population. **Method:** We reviewed medical records of 484 unselected ALK-positive NSCLC patients treated with crizotinib at five cancer centers in China from January 2013 to November 2017. Patients developing brain metastasis either before or during the crizotinib treatment were enrolled. Survival outcomes were analyzed with Kaplan-Meier method and prognostic factors were analyzed with multivariate COX analysis. **Result:** A total of 174 patients were enrolled into this study, of whom 95 patients had baseline brain metastasis and 79 patients developed brain metastasis during crizotinib treatment. Among patients with baseline brain metastasis, the median intracranial progression-free survival (PFS) was 15.34 months [95% confidence interval (CI): 10.62-20.07] and median overall survival (OS) was 53.38 months (95%CI: 30.58-76.17). The intracranial objective response rate (ORR) was 17.1%, and the intracranial disease control rate (DCR) was 88.6%. Multivariate COX analysis revealed that patients receiving first-line crizotinib [>first-line vs. first-line, hazard ratio (HR): 2.44, 95%CI: 1.05-5.68, p=0.038], withtout intracranial progression during crizotinib treatment (with vs. without intracranial progression, HR: 18.68, 95%CI: 2.43-143.31, p=0.005) were associated with better OS, while age, sex, number of brain lesions, and operation/radiation therapy for brain metastasis were not significantly associated with OS. Among patients developing brain metastasis during crizotinib treatment, the median OS was 35.64 months (95%CI: not reached). Multivariate COX analysis revealed that brain progression only (brain progression only vs. both brain and extracranial progression, HR: 0.23, 95%CI: 0.08-0.71, p=0.011) was associated with better OS, while age, sex, line of crizotinib treatment, treatment after progression and operation/radiation therapy for brain metastasis were not significantly associated with OS. **Conclusion:** Advanced ALK-rearranged NSCLC patients with baseline brain metastasis could still benefit from crizotinib treatment. However, brain progression during crizotinib treatment may be associated with worse survival outcomes.

Keywords: ALK-rearragement, NSCLC, Brain metastasis

P3.01 ADVANCED NSCLC
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P3.01-104 EGFR-RAD51 FUSION VARIANT IN LUNG ADENOCARCINOMA AND RESPONSE TO ERLOTINIB: A CASE REPORT

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Background: The most frequent epidermal growth factor receptor (EGFR) mutations of lung cancer include exon 19 in deletion and the exon 21 L858R mutation. And EGFR-tyrosine kinase inhibitor (TKI) as the standard first line treatment show good response to classical/sensitizing EGFR mutations. With the development of detection methods, some uncommon genomic mutation events such as exon 18-25 kinase domain duplications (KDD) and EGFR rearrangements (EGFR-RAD51 or EGFR-PURB) are found. We reported a case of EGFR-RAD51 fusion in non-small-cell lung cancer(NSCLC) and the efficacy of erlotinib to this type fusion of NSCLC patients. **Method:** A 48-year-old male diagnosed with adenocarcinoma (IV, T1N2M1), who was shown to have EGFR fusion by next generation sequencing. **Result:** The patient with right lung tumor and multiple brain metastases NSCLC. Histological examination of surgical specimens from the brain tumor showed lung adenocarcinoma metastasis. By using next generation sequencing assay, we found that tumor had EGFR-RAD51 fusion rather than the most common kind of EGFR mutations. Then the patient experienced a remarkable tumor response to erlotinib. Considering this rare EGFR fusion and remarkable response to TKI treatment, we conclude that the incidence of EGFR fusions in NSCLC patients should be attentive. NSCLC patients with EGFR-RAD51 fusion gene response to treatment with EGFR inhibitor. **Conclusion:** With the guidance of precise diagnosis, it is important that we should realize other rare EGFR gene mutations and novel diagnostic method.

Keywords: non-small cell lung cancer, Erlotinib, EGFR fusion

P3.01 ADVANCED NSCLC
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P3.01-105 RETROSPECTIVE ANALYSIS OF EFFICACY AND SAFETY IN CHINESE ELDERLY PATIENTS TREATED WITH NAB-PACLITAXEL

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Background: Albumin-bound paclitaxel (nab-PC) could benefit advanced non-small cell lung cancer (NSCLC) either in first line or second line. However, the safety and efficacy in Chinese elderly population remains unclear. In this study, we retrospectively analyzed the efficacy and safety of nab-pc in Chinese elderly patients (≥65 year old) from a single cancer center. **Method:** We retrospectively collected data from 75 patients who were treated with weekly nab-paclitaxel (125 or 130 mg/m^{2}d1, d8) from Janurary 2010 to December 31, 2017 in Peking University Cancer Hospital. Among which, 33 patients were non-squamous NSCLC, and 42 patients were squamous NSCLC. Twelve of these patients received nab-paclitaxelas first line treatment (7 of which were combined with carboplatin) and 63 patients received single nab-paclitaxel as latter line treatment. **Result:** s: Sixty-eight out of 75 patients were available for efficacy evaluation, the overall objective response rate (ORR) was 13.1 (10/68), disease control rate (DCR) was 69.3%(52/68), median progression free survival (PFS) was 5.2 months and overall survival was 12.2 months in the entire population. For fist-line and latter line setting subgroup, the ORR, DCR, PFS and OS were 18.2% and 14.0%; 90.9% and 73.7%; 6.7 months and 5.0 months; 17.7 months and 12.2 months, respectively. For the patients ≥70 years old, the PFS significantly longer compared with patient <70 years old (6.3 months vs. 3.7 months p=0.021; the same trend was observed in OS, however the difference was not significant (13.3 months vs. 10.0 months, p=0.089). For all grade of adverse events (AEs), the most common AEs were leukopenia (37.3%, n=28), anemia (40%, n=30) fatigue (18.7%, n=14) and Peripheral neuritis (17.3%, n=13) which were all manageable, and the incidence of grade 3 were 13.3% (10/75), no grade 4 AEs were found and no AEs related death. Totally 7 patients discontinued treatment because of AEs. And the incidence of AEs was not different among subgroups of patients defined with age (65≤age <70, 70≤age<75 and age≥75). **Conclusion:** The efficacy of nab-paclitaxel in Chinese elderly patients was desirable. The toxicity was tolerable and manageable. Patients over 70 may benefit more from nab-paclitaxel. Prospective clinical trials are expected to further confirm the results.

Keywords: nab-paclitaxel, elderly, NSCLC

P3.01-106 REAL-WORLD DATA TO EVALUATE THE CLINICAL BENEFIT OF NGS FOR DIRECTING LUNG ADENOCARCINOMA TREATMENT

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Background: Since mid-2017, multiple NGS-based companion diagnostic tests have been approved in NSCLC to select patients eligible for targeted therapy and immunotherapy. Here, we retrospectively analyzed the benefit of NGS for advanced lung adenocarcinoma in routine clinical practice. **Method:** From 2016 to 2018, the samples taken from 9 lung adenocarcinoma patients were sent to Geneplus-Beijing Institute for genetic testing. Mutation profiles were analyzed using hybridization capture based NGS, which enables the simultaneous detection of single-nucleotide variants, insertions/deletions, rearrangements, and copy-number alterations of at least 59 genes (range 59 – 1021 genes). The tumor response was evaluated using RECIST v1.1. **Result:** Six tumor tissue samples, two blood samples and one pleural effusion sample were analyzed (**Table 1**). No actionable mutation was detected in patient 1 and then he left hospital without additional treatment. The *KRAS* mutation present in patient 2 suggested that he might be resistant to EGFR-TKIs. Therefore, he received chemotherapy. According to the genetic testing results, all the other patients received EGFR-TKIs and the disease control rate was 100% at the 2nd month. Apart from *EGFR* T790M mutation, *EGFR* amplification was present in patient 8 with disease progression following gefitinib therapy. She received osimertinib and achieved PR at the 2nd month. The response has maintained for over 7 months up to now, which made us reconsidering the controversial correlation between *EGFR* amplification and EGFR-TKI effectiveness. Rare *EGFR* mutation and *MET* amplification were detected in patient 9, and then he was treated with icotinib.The best response was SD at the 4th month. However, he died of pulmonary embolism or cerebral infarction, making the duration of response 4 months.

Table 1. Clinical and genetic characteristics of 9 patients

Patient No	Age/Gender	Sample	Previous Targeted Therapy	Actionable Mutations	Following Treatment	Response Evaluation (2nd month)	Duration of response (months)
1	72/Male	Blood	No	No	No treatment	Not applicable	Not applicable
2	62/Male	Tissue	No	KRAS p.G12A, STK11 p.D53Gfs*110	Chemotherapy	Not available	Not available
3	62/Male	Tissue	No	EGFR p.L747_T751del (EX19del)	Gefitinib	PR	20+
4	63/Female	Tissue	No	EGFR p.L858R (EX21)	Gefitinib	PR	5+
5	75/Female	Tissue	No	EGFR p.L858R (EX21)	Icotinib	SD	11+
6	63/Male	Blood	Icotinib	EGFR p.L858R (EX21),CHEK2 c.445-1G>A	Combined gefitinib and bevacizumab	SD	6+
7	79/Male	Tissue	No	EGFR p.L747_T751del (EX19), NF1 c.587-1G>C, ATM c.2124+1G>T	Gefitinib	PR	2+
8	80/Female	Pleural effusion	Gefitinib	EGFR p.L858R (EX21), EGFR p.T790M (EX20), EGFR amplification	Osimertinib	PR	7+
9	81/Male	Tissue	No	EGFR p.G719A (EX18), MET amplification, CDK4 amplification	Icotinib	SD	4

Conclusion: NGS-based genetic testing comprehensively predicts the effectiveness of targeted therapy. It can be widely used in routine clinical practice.

Keywords: NGS, lung adenocarcinoma, Real-World Analysis

P3.01-107 CORRELATION STUDY OF BONE METASTASIS AND CHOLESTEROL LEVEL IN PATIENTS WITH LUNG ADENOCARCINOMA

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Background: To explore the correlation between bone metastasis and laboratory examination such as cholesterol level in patients with lung adenocarcinoma. **Method:** Medical records were studied for patients who were admitted into this high-volume institution from Jan 1, 2017 to the present. 114 patients diagnosed and treated as esophageal squamous cell carcinoma with bone metastasis were retrospectively analyzed for the present study. Along with them were 114 patients without bone metastasis in the control group. **Result:** There was no significant statistical difference between groups with respect to neutrophils count, lymphocyte count, monocyte count, bilirubin, calcium ion, phosphorus, or blood sugar. Univariable analysis found that total cholesterol levels (OR: 0.230; 95% CI: 0.064–0.822; P=0.024) and triglyceride levels (OR: 0.001; 95% CI: 0.000–0.201; P=0.012) , and Multivariate analysis indicated that triglyceride levels (OR: 0.001; 95% CI: 0.000–0.327; P=0.020) were independently associated with development of bone metastasis in patients with lung adenocarcinoma. **Conclusion:** Triglyceride levels were independently associated with the development of bone metastasis in patients with lung adenocarcinoma.

Keywords: triglyceride, bone metastasis, lung adenocarcinoma

P3.01-108 ONCOLOGIST TREATMENT CONSIDERATIONS AND SELECTION IN EGFR M+ NSCLC

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Background: The treatment landscape for EGFR M+ stage IIIb/IV NSCLC has significantly changed in the past few years: at the end of 2015, 3rd generation TKI osimertinib was approved for the treatment of EGFR T790M+ NSCLC, and in 2018, osimertinib was approved for the first-line treatment of EGFR M+ patients. As such, there is much debate amongst oncologists around which TKI to prescribe to patients first, now that more targeted treatments are available. The aim of this study was to assess current attitudes towards decision making for TKI sequencing to determine what matters most when selecting a treatment and what challenges oncologists face. **Method:** A representative online survey was conducted with 310 HCPs (Oncologists, Pulmonologists, Respiratory Surgeons and Internal Respiratory Specialists) across four countries (China, Germany, Japan and USA) between April 2018 and May 2018. **Result:** For all four countries and irrespective of treatment line, increasing overall survival (OS), followed by increasing quality of life (QoL) emerged as the most important treatment ambitions when prescribing TKIs. However, examination of treatment goals in the first-line setting revealed that clinically meaningful OS stands out for the US, Germany and Japan. In contrast for China, offering a clinically meaningful progression-free survival (PFS), OS, and improved health related QoL appear to be of equal importance. Predictability of treatment outcome in first-line therapy was also a relevant influence on treatment choice. This included a predictable pattern of resistance to TKIs for the majority of patients, efficacy in specific EGFR M+ subtypes, availability in flexible dose adjustment and if a compound was part of a sequence of targeted treatments which may delay time to chemotherapy. In terms of the sequencing of TKIs, 55% strongly prefer a treatment sequence offering maximum time on targeted therapies. Furthermore, there is a strong need across all countries for information on potential resistance mutations before changing current treatment practice – and over a third (36%) of all HCPs agreed that they do not feel they have all the data required to make informed decisions on how to sequence EGFR M+ NSCLC treatments. **Conclusion:** The study confirms that increasing survival time across treatment lines is the overarching ambition when using TKIs in EGFR M+ NSCLC together with increasing QoL. In order to overcome uncertainties regarding the appropriate treatment decisions for patients EGFR M+ NSCLC, HCPs require more information about the possible impact of treatment sequencing on extending survival.

Keywords: sequencing, treatment, TKIs

P3.01-109 REAL-WORLD PATIENT-REPORTED OUTCOME ASSESSMENT OF PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER

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Background: Patient-Reported Outcomes (PROs) provide information on patient treatment experience. We have established a real-world Advanced Non-Small Cell Lung Holistic Registry (ANCHoR) to understand how the advent of immunotherapy impacts treatment choice, clinical outcomes, and PROs of metastatic non-small cell lung cancer (mNSCLC). The aim of this analysis is to report early results of baseline symptom status and quality of life among mNSCLC patients using the MD Anderson Symptom Inventory lung cancer module (MDASI-LC) and EuroQol-5D 5-level version (EQ-5D-5L). **Method:** During 2017, patients with mNSCLC at a single institution were enrolled in ANCHoR and completed the PRO questionnaires at clinic visits. MDASI-LC consists of thirteen core and three lung cancer-specific symptom severity questions, and six interference items rated on 0-10 scales (0 = no symptom or interference, 10 = worst imaginable symptom or complete interference). EQ-5D-5L captures five health state dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression rated on a five-level scale (1= no problems, 5= extreme problems). A single visual analogue scale (VAS) on EQ-5D-5L records patient self-rated health between "best imaginable" (100) and "worst imaginable" (0) health state. Descriptive statistics for PRO scores at baseline are summarized. **Result:** Forty-two patients completed baseline PROs before the start of therapy. Mean patient age was 63 years and 45% were males. For MDASI-LC, the mean scores for the core symptom, lung cancer-specific symptom, and interference subscales at baseline were 2.2 (standard deviation [SD] = 2.80), 2.1 (SD = 2.80), and 2.8 (SD = 3.10), respectively. Fatigue was the most severe symptom reported at baseline (mean = 4.1, SD = 3.01), followed by shortness of breath (mean = 3.2, SD = 2.81) and pain (mean = 3.19, SD = 3.00). The highest percentages of patients reporting moderate to severe symptom levels (score of ≥5) were 38% for fatigue, 33% for pain, 31% for drowsiness, 29% for shortness of breath and disturbed sleep, and 26% coughing. For EQ-5D-5L, 91% of patient reported problems with self-care, 81% with mobility, 48% with usual activity and anxiety, and 33% with pain. Mean EQ-5D VAS was 73.9 (SD = 18.2). **Conclusion:** Prior to the start of treatment, fatigue, pain, drowsiness, disturbed sleep, and coughing were the most common symptoms with fatigue, shortness of breath, and pain being the most severe. Additional follow up will confirm and expand these findings and will also allow us to examine change in PROs after first-line treatment is administered.

Keywords: NSCLC, Patient-reported outcomes, Observational Registry Study

P3.01-110 DEFINING AGGRESSIVE DISEASE IN PATIENTS WITH ADVANCED NSCLC RECEIVING SECOND-LINE TREATMENT: A SYSTEMATIC REVIEW

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Background: Recent randomized clinical trials (RCTs) have explored survival benefits of second-line treatments (2LTs) in patients who have rapidly progressed and/or are refractory to first-line treatment, and these trials have determined an existing unmet need for these patients with aggressive non-small cell lung cancer (NSCLC). However, specific characterization of aggressive NSCLC is lacking, thus a

systematic literature review was conducted to explore the definitions of aggressive NSCLC. **Method:** We systematically searched Medline, Embase, BioSciences Information Service, the Cochrane Library, and abstracts from scientific meetings (through October 2017) to identify RCTs reporting the efficacy and/or safety of select 2LTs in patients with advanced NSCLC who have characteristics associated with aggressive disease (AD). Six potential overarching categorizations of these characteristics (based on expert clinical opinion) were explored: (1) refractory and/or progressive disease as best response to prior treatment, (2) rapid progression, (3) short duration on previous treatment, (4) high tumor burden or size, (5) short duration since start of last treatment, and (6) high symptom burden. **Result:** The 14 identified studies had one or more subgroups within five of the six categorizations (11, 2, 1, 2, and 4 studies presented subgroups within categories 1-5, respectively). No RCTs presenting a subgroup of patients for category 6 were identified. Within each category, the identified subgroup definitions varied (15, 4, 3, 2, and 7 different definitions within categories 1-5, respectively). Reporting of whether a subgroup was prespecified or not was limited and often unclear; 6 studies indicated that subgroup analyses of patients with AD characteristics were preplanned. Moreover, baseline characteristics for the subgroup of patients with AD were often not reported. **Conclusion:** Definitions of AD varied, both across the identified studies of 2LTs and within the predetermined categorizations, with refractory being the most frequent followed by short duration since start of last treatment. With the emerging clinical importance of AD, more standard use of these definitions within RCTs may allow for greater comparison across 2LTs and will enable indirect treatment comparisons of the results. As with any subgroup, clarity on preplanned versus post hoc analysis is important for interpretation and should be specified. Additional studies powered to assess treatment benefits in advanced NSCLC patients with AD are needed.

Keywords: Second-line treatment, aggressive disease, advanced NSCLC

P3.01 ADVANCED NSCLC
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P3.01-111 EFFICACY AND SAFETY OF CYTOTOXIC DRUG CHEMOTHERAPY AFTER FIRST-LINE EGFR-TKI IN ELDERLY PATIENTS WITH NSCLC HARBORING SENSITIVE EGFR MUTATIONS

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Background: Subsequent therapies confound the ability to discern the effect of firstline chemotherapy on overall survival (OS). Therefore, the objective of our study was to determine the relationships between progression-free survival (PFS) or post-progression survival (PPS) and OS after first-line EGFR-TKI treatment in , using individual level data. **Method:** Between April 2008 and December 2015, we analyzed 68 cases of elderly patients with NSCLC harboring sensitive *EGFR* mutations treated with first-line EGFR-TKI. The relationships between PFS and PPS with OS were analyzed at an individual level. **Result:** PPS was more closely associated with OS (R^2 = 0.54) compared to PFS (R^2 = 0.48), based on linear regression. Best response at first-line treatment, PS at the end of first-line treatment and administration of EGFR-TKI rechallenge were significantly linked to the PPS. **Conclusion:** PPS has a stronger impact on OS than PFS in elderly patients with NSCLC harboring sensitive *EGFR* mutations treated with first-line EGFR-TKI. fluenced by treatments subsequent to first-line chemotherapy; however, this remains to be verified with prospective studies.

Keywords: Advanced Non-Small Cell Lung Cancer, Elderly patients, EGFR-TKIs

P3.01 ADVANCED NSCLC
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P3.01-112 THE PROGNOSIS OF LUNG CANCER PATIENTS WITH UNEXPECTED MALIGNANT PLEURAL EFFUSION AND WITHOUT PLEURAL DISSEMINATION DETECTED AT THORACOTOMY

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Background: Generally, primary lung cancer patients with malignant pleural effusion are not candidate for surgery. But in cases, we have no choice but to perform the surgery for biopsy, prevention for obstructive pneumonitis. We analyzed the surgery for lung cancer patients with unexpected malignant pleural effusion retrospectively. **Method:** We retrospectively reviewed the patients with unexpected malignant pleural effusion and without pleural dissemination detected at thoracotomy underwent surgery in our hospital from 2003 to 2017. Pleural effusion was almost small amount (<50ml), and we included the cases that pleural effusion was malignant in the final report however it was suspicious in intraoperative report. Patient demographics, comorbidity, pathological findings, surgical approach, number of lymph nodes harvested, overall survival were evaluated retrospectively. Overall survivals were analyzed with the Kaplan–Meier method and prognostic factors were analyzed with the Cox proportional hazards model. **Result:** 24 patients underwent resection for NSCLC. The median age was 71 years old (56-79 years old) and 7 cases were male. Pleural effusions of all patients were taken before resection and submitted for rapid diagnosis. The reason we performed surgery was because we judged that we could perform surgery because of pulmonary nodule diagnosis and prevention of obstructive pneumonitis and so on. Surgical procedures were lobectomy in 15 cases, segmentectomy in 1, wedge resection in 8. The median size of resected nodule was 2.7cm (1.1cm-10.0cm). Histological types of lung cancer were adenocarcinoma in 21 cases, squamous cell carcinoma, adenosquamous carcinoma and small cell carcinoma each in 1. There was no surgical-related death or severe complications. The median follow-up time was 40 months and median survival was 66 months. At 5 years after pulmonary resection, 9 patients (38%) were dead. 5-year survival was 59.7% and 70.0% at cT1-2N0 patients, respectively. In a previous report, 5-year survival on resected stage I patients was almost 75%, and it is almost as good prognosis as our cT1-2N0 patients. Univariate analysis of gender, age, lymph node dissection, pathological findings (PL, ly, v, histology), surgical procedure and Brinkman Index were performed. Only PL0 or 1 was revealed as a prognostic factor (HR=0.12, p=0.049). **Conclusion:** The prognosis after surgery of lung cancer patients with unexpected malignant pleural effusion and without pleural dissemination may be better than expected and PL0 or 1 was thought as a prognostic factor. Thus, subsequent analysis should be performed to identify patients who could benefit from surgery.

Keywords: non-small cell lung cancer, malignant pleural effusion, Thoracic Surgery

P3.01 ADVANCED NSCLC
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P3.01-113 A MULTICENTER SURVEY OF ONE YEAR SURVIVAL AMONG CHINESE PATIENTS WITH ADVANCED NONSQUAMOUS NON-SMALL CELL LUNG CANCER (CTONG1506)

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Background: Previous results of CTONG1506 study showed that gene aberration test rate was increasing in Chinese NSCLC patients and first-line treatment was standardized accordingly. This survey further described one year survival of patients with different gene aberration status and under different first-line treatments. **Method:** CTONG1506 was a two-year series cross-sectional study. Patients with advanced nonsquamous NSCLC who were admitted from August 2015 to March 2016 and who received first-line anti-cancer treatment at one of 12 tertiary hospitals across China were included. Data extracted from medical charts were entered into medical record abstraction forms, which were collated for analysis. Survival information was collected one year after patients were admitted to hospital. One year survival rate and its 95% confidence interval were analysed by Kaplan-Meier method. **Result:** A total of 707 patients were analysed, with mean age of 57 years and 56.7% were male. Among the 487 patients who had survival data, 192 were *EGFR*- mutation positive (86 mutated in exon 19 [one year survival rate 0.90, 95% CI: 0.81-0.94] and 88 mutated in exon 21 [one year survival rate 0.84, 95% CI: 0.75-0.90]), 27 patients were *ALK* positive and

164 patients were *EGFR* and *ALK* wild type. Most *EGFR* mutation positive patients (128/192) received tyrosine kinase inhibitors (TKIs) as first-line treatment and most *EGFR* wild type patients (155/175) received first-line chemotherapy (Chemo). Pemetrexed was the most common non-platinum chemotherapy-backbone agent (120/155) in platinum doublet regimens. One year survival rates are shown in the table.

	First line treatment	N	One year survival rate	95% CI of survival rate
Total		487	0.76	0.72, 0.80
	Chemo	331	0.72	0.67, 0.77
	TKIs	148	0.86	0.80, 0.91
EGFR positive		192	0.86	0.80, 0.90
	Chemo	61	0.80	0.68, 0.88
	TKIs	128	0.90	0.83, 0.94
EGFR wild type*		175	0.70	0.63, 0.76
	Chemo	155	0.71	0.63, 0.77
	TKIs	NA	NA	NA
ALK positive		27	0.81	0.61, 0.92
EGFR and *ALK* wild type		164	0.70	0.62, 0.76

*No survival data for *EGFR* wild type patients with TKIs as first line treatment presented due to small number of patients.

Conclusion: This national-wide real world study of tertiary hospitals in China revealed that a majority of (>75%) advanced nonsquamous NSCLC patients survived more than one year and was comparable to well-controlled clinical trial results, indicating survival benefits by gene aberration status guided standard of care. This result may be further validated by our on-going two-year survey.

Keywords: NSCLC, real world, survival

P3.01 ADVANCED NSCLC
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P3.01-114 DISSOCIATION OF HEART AND GREAT VESSELS FOR LONG TRACHEAL TUMORS AND LUNG CANCER INVADED TRACHEA: THE CHINESE EXPERIENCE.

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Background: The length limit of tracheal resection is less than five centimeters. Up to know, there is no any report about resection of more than five centimeters for tracheal tumors. We created a new technique and successfully remove 124 tracheal tumors more than 5 cm in length and 52 lung cancer invaded trachea through dissociation heart and great vessels. Here, we report the results of 176 patients surgically treated in series. **Method:** All patients were given general anesthesia and single cavity endotracheal intubation. After thoracotomy, the right pericardium was totally excised, the heart, inferior vena cava, superior vena cava, ascending aorta and innominate artery were dissociated. Then, thoracic trachea, left and right main bronchus were dissociated; the proximal and distal end of trachea, or left and right main bronchus, or left main bronchus and right middle trunk bronchus were cut off. Fallowing, the distal end of trachea was anastomosed to the proximal end of trachea, or anastomosed to the left and right main bronchus, or anastomosed to the left main bronchus and right middle trunk bronchus with 3-0 micro Joe lines. Finally, the pulmonary artery sleeve reconstruction was performed, and resection and reconstruction of SVC was performed. **Result:** There were 124 patients with tracheal tumor over than 5cm in length and 52 patients with lung cancer invaded trachea. The length of trachea tumor was 5.5 cm to 10.9 cm. 5 tracheal tumor involved SVC and combined with SVCS. The trachea length invaded by the cancer was 4.5cm-7.0cm in the 52 patients with lung cancer. Of the 52 cases, 10 cancer invaded right main pulmonary artery, 22 cancer involved right main pulmonary artery and SVC. The operative procedures included: (1) resection and reconstruction of trachea, or combined with carina in 124 cases, and combined with resection and reconstruction of SVC in 5 cases in the tracheal tumor group; (2) Sleeve right upper lobectomy combined with resection and reconstruction of trachea and carina in 52 cases, combined with sleeve pulmonary artery in 10 cases, combined with sleeve pulmonary artery, and resection and reconstruction of SVC in 32 cases of lung cancer group. There were 5 operative death in this series. The 1-, 3-, 5- and 10-year survival were 71.2%, 54.3%, 33.1% and 22.5%. **Conclusion:** We pioneered a new technique and treated 124 tracheal tumor more than 5 cm in length and 52 lung cancer invaded trachea in the world.

Keywords: tracheal tumor, surgical treatment, heart and vessel dissociation

P3.01 ADVANCED NSCLC
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P3.01-115 LIPOSOMAL PACLITAXEL VERSUS GEMCITABINE: WHICH IS BETTER?

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Background: Lung cancer tends to metastasize to lymph nodes in the early stage.The liposomal Paclitaxel(LP) injection has less side effects and higher uptake.It is also characterized as being able to target to organs with rich reticuloendothelial system and keeping a high concentration for a long time. We assume that LP injection has a better curative effect against NSCLC with regional lymph node metastasis. **Method:** Patients divide to 58 for LP and 56 for Gemcitabine plus cisplatin (GP).Those patients have good comparability in gender,age,ECOG points,pathological pattern,TNM staging and chemotherapy cycles.21 days as a single cycle, each patient finished at least 2 cycles. Estimation was carried on within one week when they have finished the chemotherapy. Chemotherapy Continues if the result turns out CR+PR+SD. surgical treatment would be suggested if the stage of cancer decreases and the lesions of NSCLC turn technically removable. Then continue chemotherapy after surgery, 4 to 6 cycles in total. **Result:** The alleviation rate of lymph nodes metastasis in LP group is significantly higher.The disease control rate of lymph nodes metastasis is 96.551% vs. 92.857%, p=0.38.The alleviation rate of squamous cell carcinoma and the disease control rate is not statistically significant. The alleviation and disease control rate of primary tumor in LP and GP group does not have statistical significance.And among LA patients,it the same trend.

The LP group has a longer period without disease progression and a higher survival rate in 1 year than the GPgroup.The medium PFS of squamous cell carcinoma in 5 LP group is 8 months which is higher than that in GP group (5.5 months) but does not have statistical significance. The survival rate in 1 year of squamous cell is 50% (16/32). The PFS of IIIB stage in LP group is 10 months, significantly higher than GP group(4 months),survival rate in 1 year in LP group is also higher but is not statistically significant. As to side effect, the LP group is significantly lower in the incidence of thrombocytopenia, granulocytopenia, anemia and white blood cell reduction.However, the LP group is higher incidence of alopecia. **Conclusion:** Chemotherapy with LP has higher alleviation rate than chemotherapy with GP in treating advanced NSCLC with regional lymph node metastasis, especially for squamous cell carcinoma. The survival rate and PFS in stage IIIB/IV of LP is also higher than that of GP. Meanwhile, LP is able to reduce the incidence rate of side effects such as hrombocytopenia, granulocytopenia,anemia, white blood cell reduction, nausea and vomiting.

Keywords: Non-small-cell lung carcinoma, lymph node metastasis, liposomal Paclitaxel

P3.01 ADVANCED NSCLC
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P3.01-116 RANDOMIZED CLINICAL TRIAL ON THREE DIFFERENT PLATINUM BASED CHEMOTHERAPY IN ADVANCED NSCLC IN BANGLADESHI POPULATION

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Background: Lung cancer constitutes the major mortality in the world and incidence of the disease varies considerably among different ethnic population throughout the world. Palliative chemotherapy has been a

choice in advance Non-Small Cell Lung Cancer (NSCLC) due to better result. The primary objective of the study was to evaluate the response and toxicity of three different platinum based regimens in Bangladeshi people. **Method:** This Randomized Clinical Trial (RCT) was carried out in the Department of Medical Oncology at National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka. Patients were enrolled from **January 2012** for one year. Total 90 patients with above 18 years of age, both sexes presented with histologically confirmed stage IIIA, IIIB & IV NSCLC were enrolled and randomized (1:1:1) in to three arms. Cumulatively 26 patients were lost to follow up. Chemotherapy was given in 21 days interval (4-6 cycles). Toxicities were measured on Day 1, 7, 21, 28, 42, 3 months and on 6 months. Median follow up period was 6 months. Survival data was estimated by Kaplan-Meier method. **Result:** Significant G-1/2 Hb% was found in Day7 in TP (16.67%) and EP (10.52%) arm and in 6 months EP (31.58%) & TP (29.17%). WBC G-1/2 toxicity was found in EP (31.58%) & TP (20.83%) arm at 6 months. Similarly, in case of neutropenia and thrombocytopenia, GP arm was found to be significantly less toxic than TP and EP arm at 6 months. Response rate and survival data are provided in table 1.

Table 1: Response Rate (RR) and Survival results

Category	TP	EP	GP
Response rate (RR)			
CR (%)	25	10.5	9.5
PR (%)	66.7	68.4	76.2
SD (%)	8.3	10.5	14.3
Survival (months)			
OS	16.07 (95% CI, 13.85 to 18.28)		
Adenocarcinoma	14.09 (95% CI, 10.54 to 17.65)		
	14.1, (95% CI, 2.56 to 25.63)	11.92, (95% CI, 6.88 to 16.97)	13.7 (95% CI, 4.63 to 22.71)
Squamous	17.42 (95% CI, 14.7 to 20.1)		
	15.7, (95% CI, 13.59 to 17.95)	16.28, (95% CI, 0.00 to 36.43)	12.06 (95% CI, 3.76 to 20.36)

Conclusion: In locally advanced or metastatic NSCLC response rate of platinum based combination therapy was satisfactory with increased survival than other reference trials along with lower G1/2 toxicity in GP arm followed by TP and EP in Bangladeshi Ethnic population.

Keywords: Bangladeshi, NSCLC, chemotherapy

P3.03 BIOLOGY
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P3.03-01 BRAF V600 AND NON-V600 MUTATIONS IN CHINESE LUNG CANCER

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Background: *BRAF* gene mutation, especially V600E, was frequently mutated in cancer. Vemurafenib and dabrafenib has already been approved in melanoma as well as NSCLC and preclinical studies have demonstrated promising results in non-V600 NSCLC. But the landscape of *BRAF* non-V600 mutation in Chinsese lung cancer was rarely descripted. **Method:** 7,417 normal-paired samples from lung cancer patients were analyzed using hybridization capture-based next generation sequencing and alterations including single nucleotide variants (SNVs), short insertions/deletions (indels), copy number variations (CNVs) and structural variations (SV) were analyzed. **Result:** *BRAF* was altered in 1.8% (133 of 7,417) of all tumors. *BRAF* V600 (gain of function, GOF) and non-V600 mutations (GOF: G469V/R/E/A, K601N/E, L597V/R, T599dup/T599R, N486_P490del, L525R, and loss of function/ LOF: D594N/G, N581S/I, G466V/A, K483E, G596R), has previously been reported to increase MEK/ERK activation, were detected in 52.3% (58/111) and 47.7% (53/111) of *BRAF* functional mutation patients. CNVs and SVs were both observed at a frequency of 0.9% (1/111). Two patients have two GOF mutations (V600E/T599R). We also found that 82.0% (91/111) of the *BRAF* functional mutation carriers also owned the other actionable or driver mutation, the most frequent one was *TP53* (68.1%), then was *EGFR* (18.7%), *KRAS/NRAS* (14.3%), *PIK3CA* (11.0%) as well as *CDKN2A/B* (9.9%). **Conclusion:** *BRAF* gene mutations, non-V600 especially, was extensively mutated in Chinese lung cancer. This work supports a broad profiling approach in lung cancers and suggests that non-V600E *BRAF* alterations represent a subgroup of lung cancers in which targeted therapy should be considered.

Keywords: non-V600 mutations, BRAF, Chinese Lung Cancer

P3.03 BIOLOGY
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P3.03-02 SINGLE-CELL RNA-SEQ IN HUMAN LUNG CANCER

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Background: Lung cancer has the highest mortality rate amongst cancers primarily due to delay of diagnosis. Until recently, the focus on genomic and transcriptomic characterization of lung cancers has guided to the diagnosis and treatments of the cancers. Although RNA sequencing (RNA-seq) has been used for transcriptome profiling in cancer research, few studies have employed single cell (sc) RNA-seq approaches to investigation of the heterogeneity among individual cells directly isolated from resected surgical human lung cancer tissues. The aim of our work is to identify new biomarkers indicating early stage versus late stage of lung cancers. As an initiative step, the current study presents a profile of differentially expressed genes (DEG) of single cells of lung cancer tissues collected from diverse lung cancer patients. **Method:** Tumours resected from lung cancer patients were prepared for scRNA-seq. Microfluidic system, C1 (Fluidigm), was used to capture individual cells, and full-length cDNAs (FL-cDNA) were synthesized in the system. Next-generation sequencing (Illumina) of FL-cDNA libraries generated sequence reads from transcriptomes of single and bulk cells, respectively. Following read mapping, DEGs were selected by >2x fold-change difference in normalized expression values. qPCR was employed to validate transcriptional changes in selected DEGs comparing expression values resulted from scRNA-seq and bulk RNA-seq. Both gene set enrichment and signaling pathway analyses were used to identify mechanism of action for validated DEG-encoding molecules. **Result:** Raw scRNA-seq datasets were processed for read mapping. More than 1 million processed reads per single-cell FL-cDNA library were used for DEG selection. We examined standard deviation of normalized expression value per selected DEG to characterize transcriptomic features of individual tumour cells. We identified a minimum of a dozen DEGs showing certain fold-change differences in each stage of lung cancers. Selected DEGs were validated by qPCR whereby unique patterns of gene expression at specific stages were confirmed. **Conclusion:** The heterogeneity of lung cancers coupled with late stage diagnosis contributes to poor outcomes. The advent of scRNA-seq allows for the identification of differential gene expression and stage-specific markers that can be used to improve our understanding of highly complex intratumour heterogeneity in lung cancers. In the future, our discoveries will lead to the development of targeted therapies based on validated DEGs, ultimately allowing for early diagnosis, treatment and improved lung cancer survivorship. PAM is supported by CCSRI-i2I and DMRF.

Keywords: Lung cancers, gene expression profiling, Single cell RNA sequencing

P3.03 BIOLOGY
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P3.03-03 DIFFERENTIAL MICROBIOTA FEATURES IN LUNG TUMOR AND ADJACENT NORMAL TISSUES IN LUNG CANCER PATIENTS

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Background: Emerging evidence has demonstrated the link between the host microbiota and varied malignancies, including colorectal, gastric, hepatocellular, and pancreatic cancers. However, for lung cancer, one of the leading cause of the cancer-related morbidity and mortality worldwide, the interplay between the lung cancer and the lung microbiome has yet not been well investigated. In this study, we surveyed and compared the microbiota composition and diversity in paired tumor and adjacent normal tissues to test whether any tumor specific microbial features can be identified in tumor tissues. **Method:** We surveyed the microbiota composition of 55 lung tumor and 55 paired adjacent normal tissue samples using bacterial 16S sequencing protocol. The microbial diversity was further analyzed using QIIME pipeline. The differential taxa feature by tumor status was selected using LefSe method. **Result:** We observed diversified microbiota in lung tissue samples. The dominant phyla include *Proteobacteria*, *Firmicutes*, *Bacteroidetes* and *Actinobacteria*. The overall microbiota similarity in paired tumor and adjacent tissues was significantly higher than unpaired ($p<0.01$). Compared to adjacent normal tissues, the lung tumors showed significantly lower alpha diversity ($p=0.05$) but no difference in beta diversity (PERMANOVA test, p-value=0.27). At taxa level, tumor samples showed increased *Modestobacter* and decreased *Propionibacterium*, and *Enterobacteriaceae*. **Conclusion:** In conclusion, our study demonstrated

and compared the lung microbiota diversity and composition in paired tumor and adjacent normal tissues. Compared to non-tumor tissues, the reduction of potential pro-inflammatory microbial families/genera in tumor tissues suggest the possible link between the tumor microbiota to the immunosuppression tumor microenvironment.

Keywords: NSCLC, microbiome, 16S RNA

P3.03 BIOLOGY
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P3.03-04 IS THE CILIARY FUNCTION OF THE LESION BRONCHUS MAINTAINED IN PATIENTS WITH LUNG CANCER?

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Background: In patients with lung cancer, infections of the lower respiratory tract are often complicated, while It is not known whether ciliary function will be maintained in lung cancer lesion bronchus. We reported the newly developed simple method to evaluate patients bronchial mucoculliary movement using bronchoscopic sample. To evaluate human bronchial ciliary movement in the patients with lung cancer, the ciliary beat frequency (CBF) and amplitude (CBA) and drug reaction of bronchodilator were examined by our method using bronchoscope sample which collected in the transbronchial biopsy for the diagnosis. **Method:** Objective: Fifty eight patients with lung cancer were enrolled who had met the following eligibility criteria. 1) necessity of bronchoscopic biopy by the medical reason, 2) Adult and written informed consent, 3) tolerable organ function to perfume bronchoscopy. Method: When the bronchoscopy was performed in the patients with respiratory disease, bronchial lavage to the transbronchial biopsy site was examined to collect peripheral bronchial epithelial cells. After ciliary motion were observed to identify with microscopy, the cilliary beat were captured at 240 frames per second using a high-speed photographing function of the general-purpose digital video camera on the market. After inhalation of clinical dose of bronchodilator (tiotropium ± Olodaterol or Fluticasone / Formoterol) the cilliary beat were captured again. By software analysis, frequency and amplitude of the ciliary movement was measured. **Result:** There were cases in which epithelial cells could not be collected, 50 of 58 cases were able to analyze ciliary function. Ciliary epithelium in the patients with lung cancer was confirmed in the amplitude of 4 ~ 8μm and frequency of 5 ~ 20bps. It was observed that ciliary movement is significantly. activated by inhale bronchodilater, from 6.6 to 8.4 beat per second as frequency, and from 6.0 to 6.5 micrometer as amplitude. **Conclusion:** Even in lung cancer lesion bronchus of the patients, ciliary function was maintained and it was shown that ciliary function will be activated by drug stimulation.

Keywords: bronchodilater, mucoculliary movement, airway clearance

P3.03 BIOLOGY
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P3.03-05 COMPARATIVE TRANSCRIPTOMIC ANALYSIS OF LUNG-IPSC, NSCLC, AND SCLC: POTENTIAL IMPLICATIONS FOR IPSC MODELING OF LUNG CANCER

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Background: In addition to having broad applicability as cellular therapies in regenerative medicine, transplantation and oncology, induced pluripotent stem cells (iPSC) may be useful models for studying a variety of benign and malignant diseases. Presently, limited information is available pertaining to the potential utility of iPSC for investigating epigenetic mechanisms of pulmonary carcinogenesis. **Method:** In the present study, RNA- seq techniques were used to examine gene expression profiles in 2 lung-iPSC (Lu-iPSC) clonesderived from normal human small airway epithelial cells (SAEC), 10 SCLC lines, and 10 NSCLC lines relative to SAEC. **Result:** Using criteria of 2 fold change and FDR< 0.05, 6318, 12051, and 6504 genes were differentially expressed in Lu-iPSC, SCLC, and NSCLC lines, respectively. A substantial number of differentially expressed genes (44% total) in Lu-iPSC were unique to these cells. Approximately 1/3rdof genes differentially regulated in Lu-iPSC were modulated in a histology specific manner. 1515 genes representing 24%, 12%, and 23% of differentially expressed genes in Lu-iPSC, SCLC, and NSCLC lines, respectively, were commonly regulated across Lu-iPSC, SCLC and NSCLC. Top canonical pathways included cell cycle control of chromosomal replication and mitotic roles of Polo-like kinases (up-regulated), and granulocyte adhesion and role of cytokines in mediating communication between immune cells (down-regulated). 3499 genes were uniquely regulated in SCLC and NSCLC. 1937 genes were uniquely modulated in SCLC and Lu-iPSC; top canonical pathways included GABA receptor signaling and CREB signaling in neurons (up-regulated), and TREM1 signaling and IL-15 production (down-regulated). Only 102 genes were uniquely modulated in Lu-iPSC and NSCLC; top canonical pathways included tight junction signaling and hepatic fibrosis/hepatic stellate cell activation (up-regulated) and neurotrophin/TRK signaling and PTEN signaling (down-regulated). Differential gene expression signatures and associated pathways suggested that Lu-iPSC more closely reflect SCLC rather than NSCLC. To further examine similarities in epigenetic regulation of gene expression in Lu-iPSC and lung cancers, RNA-seq was performed on Lu-iPSC grown in the presence or absence of Decitabine (0.1μM x 72h). Expression levels of 885 genes were significantly altered by DAC; inflammatory cascades predominated the top canonical pathways. Additional pathways included nuclear excision repair, cell cycle control, DNA methylation and transcriptional repression, and transcriptional regulation of stem cells.DAC-mediated gene signatures in Lu-iPSC did not appear to overlap with SCLC or NSCLC signatures. **Conclusion:** Collectively, these findings have potential implications regarding the use of Lu-iPSC models for examining lung cancer associated epigenetic events, and the development of epigenetic regimens for lung cancer therapy.

Keywords: Small Cell Lung Cancer, Induced Pluripotency, Transcriptomic

P3.03 BIOLOGY
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P3.03-06 DIFFERENTIALLY EXPRESSED MICRORNAS IN LUNG ADENOCARCINOMA INVERT EFFECTS OF COPY NUMBER ABERRATIONS OF PROGNOSTIC GENES

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Background: Significant associations between chromosomal copy number aberrations (CNAs) and differential gene expression have been found across many cancers. However, significantly downregulated genes have been often found to reside within chromosomal regions with increased number of copies and *vice versa*, creating a paradoxical signal. This phenomenon was usually ignored as a noise, but can potentially be a consequence of interference of other regulatory mechanisms controlling mRNA transcription. **Method:** To explore existence of such paradoxes in lung adenocarcinoma (LUAD), we performed integrative analysis of 1,937 tumour and normal tissue samples, comprising copy number aberrations, gene expression and microRNA expressions data and conducted meta-analysis of 9 microRNA expression studies. **Result:** We identified and validated 75 "paradoxical" genes whose differential expression consistently contrasted with aberrations of their copy numbers. Of these, 41 genes ($p < 0.001$) are prognostic and form a clinically relevant signature. Interestingly, differential expression of 19 microRNAs that are frequently deregulated in LUAD, explains observed paradoxes. **Conclusion:** Our results show that deregulation of paradoxical genes is crucial in LUAD and their expression pattern is maintained epigenetically, defying gene copy number status. Our work highlights importance of large integrative analysis of diverse biological data and the need to examine phenomena that contrast the established knowledge.

Keywords: lung adenocarcinoma, microRNA, Copy number aberrations

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P3.03-07 CO-OCCURRING GENOMIC ALTERATIONS IN EGFR ALTERED CHINESE LUNG ADENOCARCINOMA PATIENTS

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Background: *EGFR* mutation is one of the most common driver gene mutations in non-small cell lung cancer (NSCLC) patients, especially in adenocarcinoma. Increasing numbers of rare alterations of *EGFR* such as kinase domain duplication and fusion have been identified with the clinical applications of next generation sequencing (NGS). However, co-occurring genomic alterations of *EGFR* have not been fully understood in Chinese lung adenocarcinoma patients. **Method:** FFPE tumor and matched blood samples of 989 Chinese patients with confirmed histology subtype of adenocarcinoma, consisting of 503 males and 486 females with a median age of 60 years, were collected for NGS-based 450 cancer genes panel assay. Genomic alterations including single nucleotide variations (SNV), short and long insertions/deletions (Indel), copy number variations (CNV) and gene rearrangements in selected genes were assessed. **Result:** About 57% of Chinese lung adenocarcinoma patients harbored at least one *EGFR* genomic alteration, which was mainly composed of patient with SNVs and Indels (74%), both gene amplifications and SNVs/Indels (23%), gene amplifications only (2.7%) and gene rearrangements (0.5%). 20% of the patients with SNVs and Indels in *EGFR* carried more than one *EGFR* mutations. Moreover, *EGFR* gene rearrangement was mutually exclusive with other types of genomic alterations. Exon 19 deletions and L858R substitution were the most common *EGFR* mutations, which accounted for 37.9% and 33.7% of all *EGFR* alterations, respectively. Exon 20 insertions, the mostly insensitive variant to *EGFR*-TKIs, amounted to 3.7%, and the most common resistant alteration T790M accounted for 5.9%. Uncommon *EGFR* mutations including L861Q, G719X, S768I and others were identified in 18.9% of patients with *EGFR* mutations. Further analysis of co-occurring *EGFR* mutations and kinase receptor fusions revealed that 1.1% (6 of 559) of *EGFR* mutated Chinese NSCLC patients harbored both *EGFR* mutations and known druggable kinase receptor fusions including *ROS1, RET* and *NTRK*. Three of the six patients received *EGFR*-TKI as the standard treatment. One patient achieved partial response for 10 months and two achieved stable disease for 5 and 4 months, respectively. **Conclusion:** About 38% of Chinese lung adenocarcinoma patients harbored more than one *EGFR* genomic alterations, and 19% of *EGFR* mutations identified in Chinese lung adenocarcinoma patients were uncommon mutations. In addition, 1.1% of *EGFR* mutated patients also harbored known druggable kinase receptor fusions. Though our preliminary data showed that the co-existence of *EGFR* mutations and kinase receptor fusions might be associated with shorter response time to *EGFR*-TKIs, further large cohort study is needed to validate this finding.

Keywords: EGFR co-occuring genomic alterations, lung adenocarcinoma, NGS

P3.03 BIOLOGY
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P3.03-08 ANALYSIS OF ESR1 MUTATION SPECTRUM FROM NON-SMALL-CELL LUNG CANCER IN CHINESE PATIENTS

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Background: A number of studies have documented that estrogen receptor alpha (*ESR1*) may play an important role in the development and progression of breast cancer. While the genetic variability of *ESR1* mutation NSCLC patients is unclear. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *ESR1* mutations. **Method:** A total of 501 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *ESR1* mutation and other genes were detected by next generation sequencing. **Result:** *ESR1* gene mutation rate was 1.60% (8/501) in non-small cell lung cancer, including V392I (1 patient), H373Y (1 patient), E22K (1 patient), E589Q (1 patient), Q375R (1 patient), N304S (1 patient), G457V (1 patient) and M437I plus M421I (1 patient), and median overall survival (OS) for these patients was 14.0 months. Among them, all patients were *ESR1* gene with co-occurring mutation. Briefly, patients with (n=3) or without (n=5) co-occurring *EGFR* mutations had a median OS of 19.0 months and 6.0 months respectively (P=0.36); patients with (n=4) or without (n=4) co-occurring *TP53* mutations had a median OS of 11.0 months and 14.0 months respectively (P=0.45); patients with (n=2) or without (n=6) co-occurring *BCRA2* mutations had a median OS of 4.0 months and 19.0 months respectively (P=0.03); patients with (n=3) or without (n=5) co-occurring *RB1* mutations had a median OS of 19.0 months and 9.0 months respectively (P=0.47). **Conclusion:** Our results demonstrated that decreased *ESR1* gene mutation correlated with poor overall survival in non-small-cell lung cancer patients. *ESR1* gene mutation may define a subset of patients with lung cancer appropriate for investigational therapeutic strategies.

Keywords: Non-small-cell lung cancer, Prognosis, ESR1 mutation

P3.03 BIOLOGY
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P3.03-09 MOLECULAR SPECTRUM OF KIT MUTATIONS DETECTION IN CHINESE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: The *KIT* gene activation of the gene depends on ligand binding with stem cell factor, which enables the phosphorylation of substrate proteins. Subsequently, certain signal transduction pathways are activated, which stimulate important cellular functions, such as proliferation and apoptosis. Mutations in *KIT* that cause autophosphorylation without the presence of the ligand lead to uncontrolled cell proliferation, which eventually induces tumor development. The aim of this study is to investigate mutations and prognosis of NSCLC harboring *KIT* mutations. **Method:** A total of 402 patients with non-small-cell lung cancer were recruited between July 2012 and December 2015. The status of *KIT* mutation and other genes were detected by next generation sequencing. **Result:** *KIT* gene mutation rate was 3.48% (14/402) in non-small cell lung cancer, including T84M (3 patients), K918Nfs*6 (1 patient), E849Q (1 patient), G961S (1 patient), I748T (1 patient), S741Y (1 patient), S712F (1 patient), D816Y (1 patient), T304A (1 patient), H180N (1 patient), R19C (1 patient) and A736D plus T734N (1 patient), and median overall survival (OS) for these patients was 23.0 months. Among them, all patients were *KIT* gene with co-occurring mutation. Briefly, patients with (n=4) or without (n=10) co-occurring *EGFR* mutations had a median OS of 23.5 months and 23.0 months respectively (P=0.63); patients with (n=6) or without (n=8) co-occurring *TP53* mutations had a median OS of 15.0 months and 23.0 months respectively (P=0.47); patients with (n=2) or without (n=12) co-occurring *HER2* mutations had a median OS of 4.5 months and 23.0 months respectively (P=0.01); patients with (n=2) or without (n=12) co-occurring *RB1* mutations had a median OS of 14.5 months and 23.0 months respectively (P=0.26). **Conclusion:** *HER2* accompanied mutations might play a worse prognosis in *KIT* gene mutation NSCLC. We report different mutations than those previously reported, which emphasizes the importance of personalized medicine that could be empowered by the use of bioinformatics tools in the diagnostic process and therapeutic approaches.

Keywords: KIT mutation, Non-small-cell lung cancer, Prognosis

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P3.03-10 TRANSCRIPTOMIC DIFFERENCES BETWEEN EARLY AND LATE STAGE LUNG ADENOCARCINOMA

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Background: Early and late stage lung adenocarcinoma patients differ significantly in overall survival. The tumor progression to advanced stage is driven by tumor genomic variation and the resulted abnormal gene expression profiles. A thorough study of molecular expression profiles between early and late stage lung adenocarcinoma will greatly contribute to the understanding of progression mechanism and biomarker discovery. **Method:** We used RNA-seq to investigate the gene expression differences of 17 fresh frozen tissue samples, which were collected from 7 early (IA) and 10 late stage (IIIA, 3; IIIB, 2; IV, 5) lung adenocarcinoma patients. **Result:** In total, 232 protein coding genes show differential expression levels between early and late stage subgroups. Gene functional

annotations show that the differentially expressed (DE) protein coding genes are enriched in multiple KEGG pathways: pancreatic secretion, nicotine addiction, neuroactive ligand-receptor interaction, circadian entrainment, amphetamine addiction, and serotonergic synapse. The majority of pathway enriched DE genes (16 of 24) are translated into transmembrane proteins, such as ADCY2 (high in early) and GRIN2B (high in late) etc., with no correlation between expression level and certain stage. For cancer driver genes, ALK and NTRK2 show higher expression levels in late stage than in early stage. ERBB4 shows lower expression level in the late stage We also identified a group of keratin family genes (KRT2, KRT6A, KRT6B, KRT14, and KRT16) with higher expression levels in the late stage lung adenocarcinomas; Interestingly, keratin expression level distinguishes the subgroups of solid tumors in other cancer types. Though ERBB2, PIK3CA, and TP53 were not identified as differentially expressed genes, their expression variations in the late-stage samples are significantly larger than those in the early stage,which could be a result of regulatory network change along the progression of tumor. Furthermore, 79 non-coding RNA were identified as DE "genes". Among them, four previously studied ncRNA prognostic markers: MIR31HG, DRAIC, LUCAT1, and LINC00261 were also identified as DE "genes" with consistent expression-stage relationship comparing with the previous report. Two other ncRNA, VLDLR-AS1 and LINC01919, are highly expressed in early stage samples and may serve as potential prognostic markers for lung adenocarcinoma. **Conclusion:** This study investigated the gene expression differences between early and late stage lung adenocarcinomas and identified differential expressed coding genes and non-coding genes, which will provide potential target information for the diagnosis and clinical intervention of lung adenocarcinoma patients.

Keywords: lung adenocarcinoma, transcriptome, Gene Expression

P3.03 BIOLOGY
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P3.03-11 LUNG CANCER STEM CELLS ON IMMUNE MODULATION IN TUMOROUS MICROENVIRONMENT

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Background: Cancer immunotherapy has made a big advance on benefit for cure the patients from malignancy. Recent hypothesis indicates that the crosstalk between cancer cells and tumor microenvironment can regulate the innate and adaptive immune system drives immunosuppressive condition for the immune escape of cancer cells. **Method:** Using genome-wide microarray and RNA-sequencing analysis, the immune-related gene profiling has been identified in the lung cancer stem cells (CSCs). The CSCs-condition medium was collected from the CSCs or CSCs/CAFs co-culture system to treat and analyze the functional responses of the tumor-associated macrophage (TAMs)/M2 macrophage and T cells populations. The flow cytometry and Q-PCR were used to validate the markers and related gene expression. **Result:** We found that the tumor microenvironment is crucial to support the tumor malignancy and cancer stemness through paracrine networks (e.g., IGFII, HGF, LIF, IL-4/6/17, BMP-1/2, and CXCL6); as well as, the niche showed the impacts on the immune regulation. According to the genome-wide microarray and RNA-sequencing transcriptomic analysis of the lung cancer stem cells (CSCs), we have identified a cluster of genes and signaling involved in the immune modulation under the tumor microenvironment. Such CSCs-condition medium could significantly induce the interferon signaling, and immune checkpoints, CD274 and CD273 (PDL1 and PDL2), expression in CSCs. The population of tumor-associated macrophage (M2 population) from the malignant pleural effusion could be maintained via the CSCs-condition medium concentration-dependently. Most importantly, the population of the regulatory T cells (Treg) and the TAMs could be increased via the condition medium from CSCs; whereas, the CD8+ T-cells was significantly reduced. According to the transcriptomic/proteomic analysis of the CSCs and the niche, we have identified several important immune modulating signaling; affecting the paracrine and cytosine networks, which modulate the T cells population and may correlate with the immune escape of lung CSCs. **Conclusion:** Our results have identified the roles of CSCs on the immune modulation in the tumorous microenvironment, targeting on CSCs and related immune modulating signaling could be benefit for improving the antigen presentation and inhibit the immune checkpoints PDL1 and PDL2 expression in the combinatory anti-cancer immunotherapy.

Keywords: Immunotherapy, Cancer Stem Cells, tumor microenvironment

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P3.03-12 CYCLIC MECHANICAL STRAIN AND MYOFERLIN MODULATES LUNG ADENOCARCINOMA CELL PROLIFERATION AND ERLOTINIB RESISTANCE

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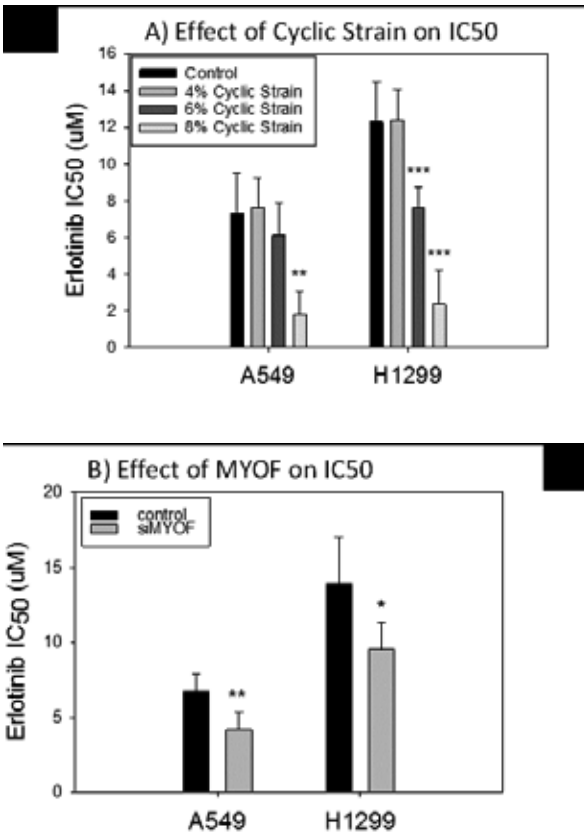
Background: Lung cancer patients with mutations in the epithelial growth factor receptor (EGFR) are treated with tyrosine kinase inhibitors (TKI) such as Erlotinib. Although resistance to EGFR-TKI is common, it is not known how biomechanical factors in the lung tumor microenvironment alters resistance. Alveolar epithelial cells experience 15% cyclic strain while increased tumor stiffness result in 40-fold decrease in cyclic strain. However, it is not known if cyclic mechanical strain alters the sensitivity of lung adenocarcinoma cells to EGFR-TKI. Mechanical stretch and silencing a membrane repair protein, myoferlin (MYOF), results in fluidization of the actin cytoskeleton. In this study we investigated how cyclic strain and silencing MYOF modulates EGFR expression and Erlotinib sensitivity in lung adenocarcinoma cells. **Method:** A Flexcell system was used expose human lung adenocarcinoma cells (A549 and H1299) to 0.2Hz cyclic strain (0-15%) for 72h. To knockdown MYOF expression, cells were treated with 30uM siRNA for 24h. Cells were expose to a range of Eroltinib concentrations and a MTT cell proliferation assay was used to determine the concentration require to reduce proliferation by 50% (*i.e.* IC50). Western blots and immunohistochemistry were used to quantify EGFR expression and localization. **Result:** Increasing the magnitude of cyclic strain caused a dramatic decrease in IC50 for A549 and H1299 cells. Similarly, silencing MYOF lead to a dramatic decrease in IC50 in A549 and H1299 cells. Cyclic strain and MYOF knockdown resulted in both increased EGFR expression and internalization.

Figure 1. (A) Effect of cyclic strain on Erlotinib sensitivity as measured by IC50. Data is mean +/- stderr. **p<0.01 and ***p<0.001 with respect to control (n=4-6, ANOVA). (B) Effect of MYOF expression of Erlotinib IC50. Data is mean +/- stderr, *p<0.05 and **p<0.01 with respect to control (n=3-6, ANOVA).



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Conclusion: Low levels of cyclic strain in the lung tumor microenvironment lead to increased Erlotinib resistance and exposure to physiologic levels of cyclic strain initiates EGFR signaling and increases Erlotinib sensitivity. This highlights the need for modeling and characterizing the mechanics of the lung tumor microenvironment to investigate how cyclic strain and MYOF expression influence chemosensitivity to other cancer therapeutics.

Keywords: NSCLC, drug resistance, tumor microenvironment

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P3.03-13 DOWNREGULATION OF MIRNA-506 MEDIATES EGFR-TKI RESISTANCE THROUGH INDUCING SONIC HEDGEHOG SIGNALING IN NON-SMALL-CELL LUNG CANCER CELL LINES

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Background: Lung cancer is the leading cause of cancer related mortality among both women and men in the United States and worldwide. Epidermal Growth Factor Receptor (EGFR) mutation predicts response to a tyrosine kinase inhibitor (TKI) of EGFR in approximately 25% of patients. All ANSCLC patients with EGFR mutation eventually develop resistance to EGFR-TKI. The mechanism of resistance is not fully elucidated but majority of the cases is related to emergence of clones with T790M mutation in EGFR, and amplification of MET. Recently, increasing numbers of miRNAs, non-coding RNAs are correlated with the drug resistance indicating that miRNAs may serve as novel targets and/or promising predictive biomarkers for anti-EGFR therapy. In this study, we investigated the role of miRNA-506 in the regulation of Sonic Hedgehog (SHh) in TKI-resistant lung cancer cell lines. **Method:** To generate cell lines resistant to EGFR TKI, HCC4006 cells were exposed to increasing concentrations of erlotinib over 6 months with increasing concentration upto 20 μM. The resultant clones (designated HCC4006 ER1 to HCC4006 ER4), following expansion from single cell. Cell viability was measured by crystal violet staining assay. The expression of miRNA in parental and resistant clones was checked by real-time qRT-PCR. The mRNA and protein expression level of SHh was determined by real-time qRT-PCR and Western blot. Invasive/migratory ability of parental and resistant clones was measured by Boyden chamber assays. EMT and stemness markers were evaluated by Western blot. Single-cell suspensions from pre-treated cells were re-suspended at a density of 500 cells/ml mammocult media in ultralow attachment dishes. Number as well as the size of the tumorosphere/spheroids in specified experimental set-up was monitored and recorded alternate day for 8-10 days. **Result:** The studies demonstrated that miR-506 was downregulated in resistant clone as compared to parental cell lines which promotes significantly the invasive/migratory ability and EMT phenotypes of lung cancer cells through induction of SHh. Interestingly, ectopic expression of miRNA-506 in these resistant cells inhibits SHh signaling and thus reprograms EMT, EGFR-TKI resistance and stemness. **Conclusion:** Our data suggest that miR-506 downregulation and induction of SHh are associated with resistance to EGFR-TKI. miR-506 interference and inhibition of SHh pathway are potential therapeutic strategy to reverse resistance to EGFR-TKI in NSCLC with EGFR mutation.

Keywords: EGFR-TKI, NSCLC, Sonic Hedgehog

P3.03 BIOLOGY
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P3.03-14 DOWNREGULATION OF FOXM1 INHIBITS TUMOR PROLIFERATION, COLONY FORMATION AND SPHEROID FORMATION OF NON-SMALL CELL LUNG CANCER

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Background: Forkhead box protein M1 (FOXM1) is a member of the forkhead superfamily of transcription factors. It plays numerous critical roles in cancer development and progression, such as the regulation of G2/M transitions of cell cycle, anti-apoptosis, DNA damage repair, invasion, and drug resistance. In a pan-cancer meta-analysis of mRNA expression signatures from ~18,000 human tumors with overall survival outcomes across 39 malignancies, over expression of the FOXM1 was a major predictor of adverse outcomes and appeared anti-correlated with tumor immune cell populations (Nat Med. 2015;21(8):938-945). Thus, we examined the prognostic and biological role of FOXM1 in non-small cell lung cancer (NSCLC). **Method:** We examined the prognostic impact of FOXM1 expression in lung cancer patients using a genomic database (UTSW – "Lung Cancer Explorer" and KM-Plotter). We also assessed the expression of *FOXM1* in NSCLC lines, and human bronchial epithelial cells (HBECs), and assessed the association between *FOXM1* and cell cycle related genes in RNA-seq data. We examined the effect of the downregulation of FOXM1 on tumor proliferation and colony formation of lung adenocarcinoma cell lines by short hairpin RNA (Tet-pLKO-FOXM1-shRNA), and the effect of the downregulation of FOXM1 on tumor 3D spheroid formation in spheroid-forming cell lines using Nunclon Sphera. **Result:** High *FOXM1* expression correlated with poor prognosis in NSCLC patients who underwent surgical resection, especially adenocarcinoma. *FOXM1* expression in lung cancer cell lines was also much higher than in HBECs. The expression level of *FOXM1* was significantly correlated with cell cycle regulator genes such as *CCNB1*, *CCNA2*, and *PLK1* in both tissue samples (Lung cancer explorer) and cell lines (our data). shRNA mediated reduction of FOXM1 expression significantly inhibited tumor cell proliferation and colony formation of NSCLC cells. Additionally, in the 3D spheroid formation assay, FOXM1 knockdown altered spheroid morphology. **Conclusion:** FOXM1 was over expressed in NSCLC compared to normal lung epithelial cells, and high tumor FOXM1 expression was prognostic of poor survival in patients with NSCLC who underwent surgical resection, especially in patients with adenocarcinoma. FOXM1 expression correlated with the expression of regulators of the G2/M transition, and functional knockdown studies demonstrate an important role in tumor proliferation, colony formation, and 3D spheroid formation. Overall, our results suggest that FOXM1 has important roles in NSCLC growth, while data from other groups using "CIBERSORT" analyses suggest a possible role for FOXM1 in tumor immune cells infiltration, collectively indicating that FOXM1 is a potential target for the treatment of lung cancer adenocarcinoma.

Keywords: FOXM1, Cell cycle, non-small cell lung cancer

P3.03 BIOLOGY
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P3.03-15 LUNG CANCER REGULATION OF GLUCOSE METABOLIC STRESS RESPONSE

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Background: Cancer cells have altered metabolism in order to accommodate for the increased metabolic needs required for oncogenic transformation, proliferation, development and survival. The metabolic profile observed in cancer cells often includes increased consumption of glucose and glutamine, increased glycolysis, changes in the use of metabolic enzyme isoforms, and increased secretion of lactate. In order to better understand this hallmark of cancer, we studied the regulation of pathways by microRNAs (miRNA) expression profile under normal or deprived glucose condition in different lung cancer cell lines. **Method:** Two different NSCLC adenocarcinoma cell lines were tested in the study, A549, which is highly glycolytic (HG) and H358, which is low glycolytic (LG). Sequencing was performed using Illumina TruSeq RNA library preparation kit v2 with Illumina HiSeq 2500 sequencer using single-end 50bp protocol. Cell were analysed in two different conditions, under 24h of normal glucose concentration and under 24h glucose starvation. Samples were prepared in duplicates from the initial step of cell culturing summarizing to a total of eight samples. Differential expression analysis was performed using EdgeR algorithm with an adjusted p-value >0.05 and a log2 fold > 1.5. **Result:** An opposite regulation profile was observed for miRNA of cells that are highly glycolytic (HG), A549, in comparison with low glycolytic, H358 cells. The formers presented 42 downregulated miRNAs from which 39 miRNAs were unique. Only 2 upregulated miRNAs, miR324 and miR616, were found significant in this cohort but they are also upregulated in the latter group. In comparison, from the 20 upregulated miRNAs found in high-glycolygic group from which 18 were unique to lower glycolytic cell line. Lower glycolytic cell lines show 4 downregulated miRNAs from which only one miRNA, miR205 was significantly uniquely downregulated, moreover, MIR205HG, which is miR205 host gene, is also found significantly downregulated, suggesting the strong involvement of miR205 in glucose metabolic stress response. **Conclusion:** Under glucose metabolic stress, miR205 and MIR205HG are uniquely downregulated in low glycolytic NSCLC adenocarcinoma cell line.

Keywords: Glucose stress, Metabolic, miRNA

P3.03 BIOLOGY
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P3.03-16 3D MORPHOMETRIC DETECTION OF MISMATCH REPAIR DEFICIENCY IN HUMAN LUNG ADENOCARCINOMA CELL LINES USING THE CELL-CT® PLATFORM

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Background: Mismatch repair protein deficiency (MMR-D) is proving to be a predictive biomarker for the efficacy of immune checkpoint inhibitor therapy for many malignant neoplasms. MMR-D leads to microsatellite instability and high tumor mutational burden (TMB) and ultimately results in the generation of neoantigens. While multiple molecular tests are available today for the detection of MMR-D, including immunohistochemistry staining for mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2), PCR to evaluate MSI, MLH1 promoter methylation analysis, and targeted next-generation sequencing, they require invasive biopsy and are often not applicable for early stage disease. Studies have demonstrated that MMR-D results in histological and morphological changes. The automated Cell-CT® platform produces isometric, high-resolution 3D images of cells in liquid biopsies, such as sputum, where published studies have demonstrated 92% sensitivity to biopsy-confirmed lung cancer with 95% specificity. This new study reports the development of morphology-based classifiers for lung cancer cells that have been engineered to exhibit MMR-D. **Method:** Two human lung cancer adenocarcinoma cell lines, NCI-H23 and NCI-H1650, were transduced with lentiviral particles expressing either scrambled or MLH1 shRNAs and selected for puromycin resistance. Individual clones were isolated and screened for MLH1 expression. Several scrambled shRNA clones, with parental levels of MLH1, and several shMLH1 clones, with a range of 86 to 97% suppression of MLH1, were expanded, fixed, and analyzed using the Cell-CT® platform. Over 1,000 cells from several harvests of each cell line were used to measure 845 different 3D structural biomarkers for each cell. **Result:** A classifier to test the degree to which the features discriminate between control scrambled shRNA and shMLH1 cell lines was developed and its performance was characterized by the area under the ROC curve (aROC). MLH1-knockdown specific differences for both the H23 and H1650 line clones as compared to pooled shRNA clone data were observed. The aROC's for 4 different H23 shMLH1 clones were 0.86, 0.81, 0.81, and 0.84, while those for 3 H1650 shMLH1 clones were 0.83, 0.80, and 0.90. **Conclusion:** This study demonstrates the feasibility of using the Cell-CT® platform for morphometric detection of MMR-D. Discriminatory features assessed from both cell lines will be presented as well as possible correlation to TMB level.

Keywords: morphology, mismatch repair deficiency, tumor mutational burden

P3.03 BIOLOGY
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P3.03-17 ROLES OF α7NACHR SIGNALING IN LUNG CANCER

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Background: Lung cancer is the leading cause of cancer-related mortality worldwide. Cigarette smoking is the leading risk factor driving lung cancer. Nicotine, as the major addictive component in cigarettes, can stimulate the progression of lung cancer cells through nicotinic acetylcholine receptors (nAChRs). The nAChR α7 subunit has been found to be pivotal in growth signal transduction induced by nicotine binding to nAChRs in lung cancer cells. Nevertheless, its clinical roles remain unclear. **Method:** We firstly used the bioinformatics platform to analyze whether the messenger RNA (mRNA) expression of various nAChRs might contribute to patient survival. The immunohistochemistry was additionally applied to analyze the distribution patterns of α7nAchR protein in lung cancer. Complementary DNA (cDNA) microarray, immunoblotting analysis, and Cell Proliferation Kit II (XTT) assay were used to explore the potential effects and mechanisms. **Result:** We found that patient groups with high CHRNA7 mRNA levels had an improved overall survival rate in 1926 lung cancer cases (p<0.001). Furthermore, increased CHRNA7 mRNA expression improved overall survival of squamous cell, but not adenocarcinoma, lung cancer patients (p=0.043). In addition, high CHRNA7 mRNA expression predicted better overall survival only in female patient group (P=0.001). Nuclear and cytoplasmic α7nAChR staining were significantly increased in cancerous and metastatic lesions as compared with adjacent non-cancerous tissues. Membranous α7nAChR staining was present only in cancerous lesions and was low in metastatic lesions. Notably, H157N cells have been harvested with nicotine for 2 years and had an increased α7nAChR expression. In addition, nicotine was able to increase α7nAChR expression in both H157 and H157N cells. Anti-α7nAChR antibody suppressed cell grow in only H157N cells despite of nicotine treatment with or without. Long term nicotine exposure might change the dependence of α7nAChR signaling in squamous lung cancer cells. **Conclusion:** Our results suggested that α7nAChR might play roles in squamous lung cancer and in female lung cancer. mRNA and protein levels of α7nAChR appear to represent a tumor suppressive or an oncogenic role, respectively. The exact roles and underlying mechanisms of the α7nAChR related signaling demand further investigations in particular squamous lung cancer patients with smoking history.

Keywords: nicotinic acetylcholine receptors, lung cancer, smoking

P3.03 BIOLOGY
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P3.03-18 COLLAGEN TYPE XI PROMOTES LUNG ADENOCARCINOMA DISSEMINATION VIA INTEGRIN α2 AND DDR1

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Background: Our previous studies showed that non-small cell lung cancer (NSCLC) stroma is an important actor of lung tumorigenesis. We found integrin α11, a fibrillar collagen receptor expressed on cancer-associated fibroblasts (CAF), to be strongly up-regulated in NSCLC stroma and to promote NSCLC growth *in vivo*. Collagen XI is a fibrillar collagen that expression is increased in NSCLC and is correlated with integrin α11 expression. The purpose of the present study is to determine whether integrin α11-mediated lung tumorigenesis is induced via collagen XI and how that collagen may affect lung carcinoma cell invasion. **Method:** To study the effects of collagen XI, collagen XI has been incorporated in a matrix of collagen I at a ratio 1:3 (collagen I/XI). For tumor cell invasion, lung adenocarcinoma H1975 cells were allowed to form spheroids before being embedded in a collagen I or a mix of collagen I/XI matrix. Area of dissemination and migration pattern has been analyzed 48 hours later. In order to identify the collagen receptor interacting with collagen XI, we used cell attachment and ELISA assay. Knockout of integrin α2 and DDR1 has been performed using the CRISPR-Cas9 strategy in H1975 cell line. **Result:** We showed that high collagen XI expression is associated with high risk of recurrence in the UHN cohort of 165 NSCLC patients (hazard ratio= 1.97, 95% confidence interval 1.09-3.56, P<0.026). Surprisingly, CAF embedded in a mix of collagen I/XI matrix failed to reorganize the collagen matrix as efficient as embedded CAFs in only collagen I matrix and displayed inhibition of migration in presence of collagen XI. In contrast, collagen XI greatly enhanced invasion of lung adenocarcinoma H1975 cells in a mix collagen matrix with a different invasion pattern compared to H1975 cell invasion in collagen I. Although integrin α11 expression correlates with collagen XI expression in NSCLC, this integrin bound poorly to collagen XI. Instead we found integrin α2 and DDR1 to interact with collagen type XI (Kd=5nM and Kd=24nM, respectively). Knockout of integrin α2 or DDR1 in H1975 cells suppressed collagen XI-increased invasion in a collagen I/XI matrix, indicating that both collagen receptors are required to mediate collagen XI effect on lung adenocarcinoma dissemination. **Conclusion:** We showed that the presence of collagen XI in NSCLC stroma could enhance lung adenocarcinoma dissemination via integrin α2 and DDR1. Thus, targeting these two collagen receptors may be a new strategy to improve the outcome of lung cancer.

Keywords: NSCLC, tumor stroma, tumor dissemination

P3.03 BIOLOGY
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P3.03-19 THE LYSYL OXIDASE LIKE-1 PROMOTES NSCLC TUMORIGENECITY THROUGH INCREASED MATRIX REORGANIZATION AND STIFFNESS

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Background: The importance of the stroma in tumorigenicity has been increasingly recognized in the past few years and targeting tumor stroma has become a new strategy for the development of new therapies. The lysyl oxidase like-1 (LOXL1) is a matrix cross-linking enzyme, essentially secreted by cancer-associated fibroblasts (CAFs) in the stroma. We previously showed that LOXL1 expression strongly correlated with integrin α11 expression, a collagen receptor that promotes NSCLC tumorigenecity, suggesting that LOXL1 may also contribute to lung

tumor growth and metastasis by modifying the stromal collagen matrix. **Method:** Primary CAFs (CAF094) isolated from a NSCLC resection specimen and immortalized with hTERT were infected with full length LOXL1 (LOXL1 overexpression), LOXL1 shRNA (LOXL1 knockdown) or with their respective controls, using a lentiviral system. To investigate the impact of LOXL1 on collagen matrix reorganization, we allowed CAFs expressing different levels of LOXL1 to contract collagen matrices. Contracted collagen matrices have then been submitted to second harmonic generation to analyze collagen fibers. We established the role of LOXL1 in lung carcinoma invasion and growth using an *in vitro* organotypic model and an *in vivo* xenograft model, respectively. **Result:** LOXL1-overexpressing CAFs embedded in collagen lattices displayed greater ability to reorganize the collagen matrix than those with lower LOXL1 expression. Furthermore, analysis of the collagen matrix demonstrated that LOXL1 contributed to more linear and dense collagen fibers organization. As a consequence of collagen matrix reorganization, invasion of the lung carcinoma H661 cell line significantly increased in an organotypic model in presence of LOXL1-overexpressing CAFs. Moreover, we showed that loss of Loxl1 in mice inhibited subcutaneous growth of the lung adenocarcinoma H4006 cell line compared to the mouse wild-type counterparts. **Conclusion:** We demonstrated that overexpression of LOXL1 in NSCLC tumor stroma results in an increased of tumor growth and invasion, due to a change in the matrix reorganization. Thus, LOXL1 appears as an interesting target to improve the outcome of lung cancer.

Keywords: NSCLC, tumor stroma, matrix reorganization

P3.03 BIOLOGY
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P3.03-20 CIRCULATING TUMOR CELL CLUSTERING IN VITRO SHORT-TERM CULTURE CORRELATES WITH POOR SURVIVAL AND ALLOWS MONITORING RESPONSE TO TREATMENT

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Background: Circulating tumor cells (CTCs) are putative markers for tumor prognosis and may serve to evaluate patient's response to chemotherapy. CTCs are often detected as single cells but infrequently as clusters indicative of worse prognosis. **Method:** Blood samples were obtained from the 86 breast cancer patients, 52 lung cancer patients. The nucleated cells were cultured in ellipsoidal microwells The microwells were prepared by placing a cover slip (22mm X 22mm) on a 35mm culture dish. Molten agar (3%) was poured on the top of the cover slip enough to cover it (500µl approx). The ellipsoidal microwell in PDMS (polydimethylsiloxane) was then placed on the top of the cover slip containing the molten agar and allowed it to solidify. The culture conditions were carried at 37°C, 5% CO_2 and humidified hypoxic conditions (1% O_2). The culture medium was replaced every 48-72 hrs with nominal disturbances to the microwells. Cultures were maintained for 3 weeks and imaged on day 7, 14, 21 with bright field microscope and analyzed the images using (Olympus IX71). **Result:** To correlate cluster formation with survival, samples were obtained from 31 patients with lung cancer. These patients were enrolled, when they were presented with progressive disease since their last treatment regimen but before commencing a new treatment regimen. Blood was collected before and on 9th, 12th week after the treatment. It is interesting to note that tight cluster formation correlated with patient survival. The Kaplan-Meier survival analysis showed that cluster formation in patients who have undergone neoadjuvant therapy correlated with shorter overall survival Our culture system enabled us to successfully expand the CTCs without any prior enrichment. The method requires 2.5 ml of blood per 35-mm dish to expand CTCs. Microwells were easy to establish and replicate with minimal set-up in a laboratory. **Conclusion:** To the best of our knowledge, this study is one of the few, which suggest the possible role of cluster formation in patient survival in Lung cancer patients.

Keywords: NSCLC, CTC

P3.03 BIOLOGY
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P3.03-21 CXCR4 OVEREXPRESSION IS ASSOCIATED WITH POOR SURVIVAL OUTCOME AFTER RECURRENCE IN EARLY STAGE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Overexpression of CXCR4 is associated with poor outcomes for patients with advanced non-small cell lung cancer (NSCLC). Studies suggest a gender specific difference in outcomes of stage IV NSCLC patients, with shorter survival in females with high expression of CXCR4. The current study evaluates the association between CXCR4 expression and gender, time to recurrence, and survival in early stage NSCLC patients. **Method:** Patient characteristics, clinical variables and outcome data were obtained from the Glans-Look Lung Cancer database for stage I-III NSCLC patients diagnosed between 2003-2006 at the Tom Baker Cancer Centre. Tissue microarrays were created from surgical or biopsy specimens, and CXCR4 expression was evaluated using quantitative fluorescent immunohistochemistry. CXCR4 expression and outcome data were analyzed using a Cox proportional hazards and multi-state model. **Result:** 230 patients with stage I-III NSCLC were identified, and 181 patients had corresponding tissue for CXCR4 analysis. Early stage NSCLC patients with CXCR4 overexpression had worse overall survival compared to those with low CXCR4 expression ($p<0.05$). No gender specific difference was observed. Time to recurrence did not correlate with CXCR4 expression, and there was no association with the site of recurrence (local versus distant). However, high CXCR4 expression was associated with increased risk of death after recurrence ($p<0.05$). **Conclusion:** Early stage lung cancer patients with high CXCR4 expression have worse survival outcomes, particularly after recurrence of disease. The role of CXCR4 as a prognostic marker in NSCLC patients who have recurred should be further elucidated.

Keywords: CXCR4, recurrence, survival

P3.03 BIOLOGY
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P3.03-22 IL-1β AS A NEW EARLY PREDICTIVE BIOMARKER FOR NON-SMALL CELL LUNG CANCERS OUTCOME

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Background: Lung cancer is the first cause of cancer mortality worldwide. Patients diagnosed with early stage disease (stage I) have been considered to have a reasonably favourable prognosis. Unfortunately, up to 40% early stage cases of all non-small cell lung cancers (NSCLCs) have a poor prognosis. Recent studies have suggested that combined modality treatment of NSCLC may improve survival in selected patients. One of the most critical questions in choosing the appropriate use of combined therapy is determining which patients might benefit from the more aggressive treatment. Recent data have enhanced the idea that inflammation is a critical component of tumour progression. It is now becoming clear that the tumour microenvironment is largely orchestrated by inflammatory cells and it is an indispensable participant in the carcinogenesis. In particular, IL-1b is a pleiotropic pro-inflammatory cytokine and its up-regulation is closely associated with various cancers. Chronic inflammation (sustained by overactivation of IL-1b system) is a crucial event in carcinogenesis and tumor progression and there is evidence that plasma IL-1b level is higher in patients with advanced cancers. Our goal is to determine whether IL-1b expression might be associated with NSCLCs patients' clinical outcome. **Method:** Patients diagnosed with lung cancer stage I and treated with potentially curative resection during 2012 were recruited for this study. Tissue samples (tumor masses including peri-tumoral stroma and lungs) were collected during surgery, embedded in paraffin and processed for immunohistochemistry (IHC). IHC was performed by ABC-peroxidase. Adjacent sections were incubated for 1 h at room temperature with monoclonal antibody against human IL-1b. **Result:** In our randomized experiment 35 patients with NSCLC whose tumor was resected or biopsied were enrolled during 2012 and followed up for 5 years through 2017. Our preliminary results showed that patients with high levels of IL-1b in the peritumoral area, revealed by IHC, present a poor prognosis and a reduced overall survival. **Conclusion:** This retrospective analysis of

patients with stage I NSCLCs who had received standard surgery resulted in statistically significant improvement in overall survival in patients with a low release of IL-1b in the tumor microenvironment. This data define a new role for IL-1β as a predictive biomarker of NSCLCs tumor behavior that can be used to better profile the use of treatments and improve patients' outcome.

Keywords: tumor microenvironment, NSCLC, IL-1b

P3.03 BIOLOGY
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P3.03-23 A PROPENSITY SCORE MATCHING COHORT STUDY ON PROGNOSIS OF THE DIVERSITY OF MUC1 EXPRESSION IN PATIENTS WITH LUNG ADENOCARCINOMA

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Background: To probe the expression of MUC1 (Mucin-1) in lung adenocarcinoma tissues, and estimate the relationship between the expression level of MUC1 and prognosis or clinical pathological factors in patients with lung adenocarcinoma simultaneously, so as to establish personal therapeutic strategies and forecast prognosis. **Method:** A retrospective analysis was originally conducted on 182 lung adenocarcinoma patients who underwent surgical resection collected from July 2007 and September 2010 at the First Affiliated Hospital of Dalian Medical University. None of the patients received neoadjuvant therapy. Each tumor was reevaluated according to the current adenocarcinoma classification based on HE stains. Additional immunohistochemical staining for MUC1(Mucin-1) was used in selected cases. Cox proportional hazard regression model was used for univariate analysis. The confounding parameters were compromised by propensity score matching (PSM). **Result:** Among 182 patients with lung adenocarcinoma, 107 patients were MUC1 low expressed, 44 patients were MUC1 moderate expressed 33 patients were MUC1 high expressed. We found the expression of MUC1 was significantly different in gender (p=0.014), smoking history (p=0.009), T stage (p=0.019), N stage (p=0.015), clinical stage (p=0.024) and the WHO classification of tumors of the lung adenocarcinoma (p=0.002). But we found all above differences among groups were no significance after PSM. Lung adenocarcinoma patients with high MUC1 expression, poorly differentiated and high pTNM stage had early relapse than the other (P≤0.05), no matter took PSM.

Univariate analysis of clinical pathologic factors on disease-free survival risk.

Clinical Factor	HR	95%CI	P value
Gender			
male	1.000		
fmale	0.732	0.437-1.226	0.236
Age			
≤67	1.000		
>67	0.928	0.562 -1.534	0.772
History of smoking			
Out	1.000		
Without	1.756	0.981 -3.140	0.058
Tumor size			
≤2cm	1.000		
>2cm	2.100	1.067- 4.135	0.032
Differentiation			
Poor	1.000		
Moderate	10.929	4.734- 25.232	<0.001
Well	3.151	1.376- 7.218	0.007
T stage			
T1	1.000		
T2	1.483	0.798- 2.757	0.213
T3	3.831	2.083- 7.048	<0.001
N stage			
N0	1.000		
N1	2.247	0.879- 5.744	0.091
N2	3.506	2.047- 6.006	<0.001
TNM stage			
I	1.000		
II	2.310	0.810- 6.591	0.118
III	3.823	2.272- 6.432	<0.001
Pathological subgroups			
MIA	1.000		
AP	3.414	1.146- 10.174	0.028
PA	1.486	0.600- 3.683	0.392
MPA	2.245	0.918- 5.494	0.076
SOP	5.566	1.116- 27.754	0.036
MU	5.148	0.617- 42.923	0.130
Lep	0.748	0.090- 6.210	0.788
MUC1 expression			
Low	1.000		
Moderate	1.235	0.604- 2.527	0.563
High	2.289	1.318- 3.974	0.003
MUC1 expression (PSM)			
Low	1.000		
Moderate	1.289	0.557- 2.985	0.553
High	2.462	1.142- 5.312	0.022

Conclusion: High expression of MUC1 can be a significant independent risk factors for predicting the prognosis of lung adenocarcinoma.

Keywords: propensity score matching, lung adenocarcinoma, MUC1

P3.03 BIOLOGY
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P3.03-24 INCORPORATION OF A MOLECULAR PROGNOSTIC CLASSIFIER IMPROVES CONVENTIONAL NON-SMALL CELL LUNG CANCER STAGING

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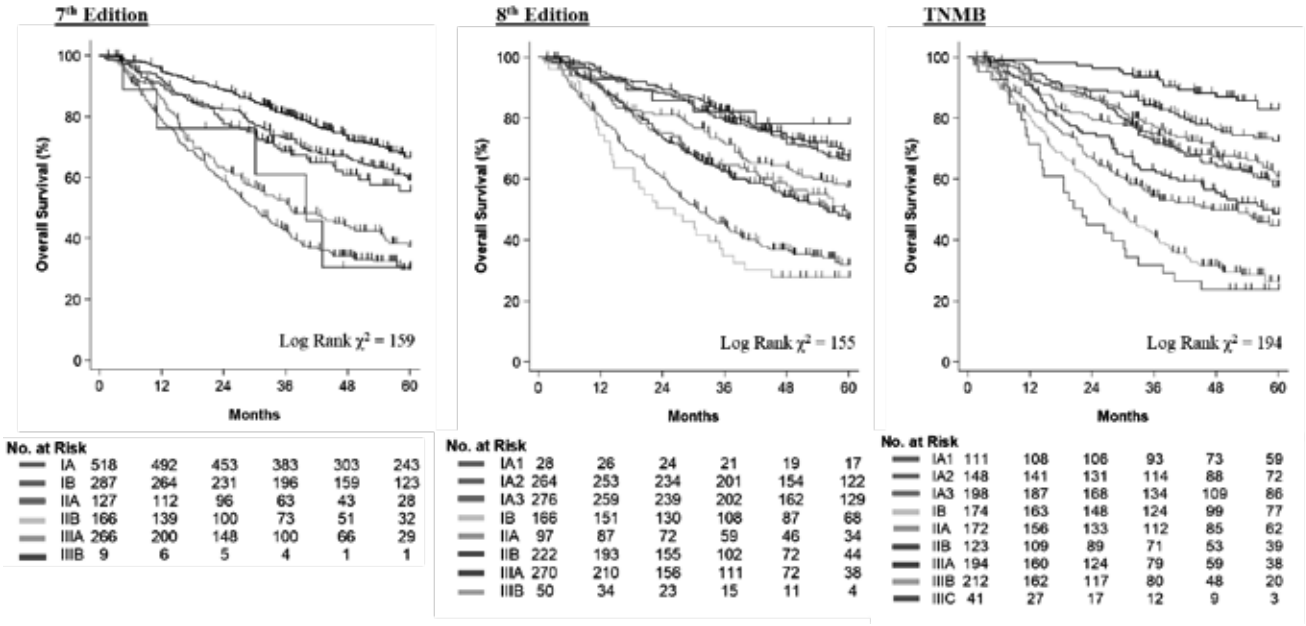
Background: Despite significant advancements in the understanding of the molecular genetics of tumor biology, the 8th Edition of Non-Small Cell Lung Cancer (NSCLC) staging adopted in 2018 remains dependent upon tumor size, nodal spread, and metastasis. The survival of patients with early stage NSCLC remains poor and further improvement in staging is needed to better inform adjuvant therapy. In this study, we explored the integration of a clinically validated, molecular prognostic classifier into conventional staging.

Method: A novel staging system, TNMB ("B" indicating Biology), that integrates a 14-gene molecular prognostic classifier with the 8th Edition, was developed using 332 patients with non-squamous NSCLC resected at the University of California, San Francisco (UCSF). TNMB was subsequently validated on a separate multi-institutional international cohort of 1,373 patients. Reclassification metrics were evaluated from adoption of TNMB and the 8th Edition. **Result:** Adoption of TNMB improved prognostication of overall survival significantly more than adoption of the 8th Edition. TNMB resulted in Net Reclassification Improvement of 0.33 (95% CI 0.24-0.41), relative Integrated Discrimination Improvement of 22.1% (95% CI 8.8-35.3%), and Reclassification Calibration Statistic from 36 to 18 (P-Value 0.03 to 0.73). In contrast, the 8th Edition resulted in no change in Net Reclassification Improvement 0.03 (95% CI -0.00-0.06) or relative Integrated Discrimination Improvement -2.5% (95% CI -17.6-12.4%) and resulted in Reclassification Calibration Statistic from 134 to 22 (P-Value <0.01

to 0.27). **Conclusion:** Incorporation of a molecular prognostic classifier offers substantial improvement to conventional staging of NSCLC and may lead to a significant impact on clinical decision-making in early stage disease where identification of high risk patients is needed to guide adjuvant therapy. Our findings may encourage application of molecular prognostic classifiers into the refinement of conventional staging for other solid tumors.

Overall Survival of Non-Small Cell Lung Cancer Patients Following Surgical Resection by 7th Edition, 8th Edition, and TNMB Staging. TNMB had distinct separation of survival by stage and larger range of survival between early and late stages compared to conventional staging.



P3.03 BIOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.03-25 SQUAMOUS CELL CARCINOMA-ASSOCIATED BRONCHIAL DYSPLASIAS DEMONSTRATE ALTERED T-HELPER LYMPHOCYTE DIFFERENTIATION

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Background: Persistent bronchial dysplasia (BD) is associated with an increased risk for development of invasive squamous cell carcinoma and demonstrates altered polarization of inflammatory cell subsets by gene expression analysis as compared to BD that regresses. We hypothesized that a decrease in the T-helper 1 (Th1) to T-helper 2 (Th2) lymphocyte ratio would be associated with progression to invasive squamous cell carcinoma (SCC). **Method:** VECTRA 7-color multispectral staining was applied to formalin fixed paraffin embedded (FFPE) persistent (N=12) and regressive (N=10) BD that also included four biopsies from patients that subsequently developed SCC (3 persistent and 1 regressive, 2 from the actual site of progression). inForm (Perkin-Elmer) image analysis software was used to enumerate cells that showed double positivity for Tbet-CD4 (Th1) and GATA3-CD4 (Th2) and the ratios of the percentage of Th1 and Th2 cells amongst all CD4 positive cells were calculated from multiple lesional fields for each BD (dysplastic epithelium and underlying stroma). DNA extracted from the full remaining FFPE tissue of four of these cases were sequenced employing the Oncomine Comprehensive v3 NGS panel (ThermoFisher) and the number of somatic mutations and variant allele frequencies (VAF) were determined using a threshold of at least 200 total reads and 25 variant reads per variant identified. **Result:** A decreased Th1:Th2 ratio was seen in SCC-associated BD as compared to BD from patients that did not develop lung cancer (p=0.04; ratio = 0.04 vs. 0.68, respectively). No significant difference was seen in persistent versus regressive BD groups. There was an inverse correlation between Th1:Th2 ratios and mutational load (r^2=0.21) and VAF (r^2=0.28) although the small number of specimens precluded identification of a statistically significant relationship. **Conclusion:** A decreased Th1:Th2 ratio is associated with BD from subjects that progress to SCC suggesting that alterations in T-helper lymphocyte differentiation may contribute to progression. A potential inverse relationship between Th1:Th2 ratios and mutational load or mutant clonal expansion (increased VAF) will require further study.

Keywords: Immunoprevention, bronchial dysplasia, progression of premalignancy

P3.03 BIOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.03-26 TUMOR IMMUNE MICROENVIRONMENT IN NSCLC IS PREDICTIVE OF PROGNOSIS AFTER SURGERY

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Background: To investigate the tumor microenvironment in NSCLC and try to understand more about how, and why, it differs in histological and expression subtypes of NSCLC . **Method:** Samples were collected from 399 patients who underwent surgery for stage I-IV NSCLC at Oslo university hospital 2006-16. Gene expression was assessed by using Agilent microarray on samples from adenocarcinomas (n=184) and squamous cell carcinomas (n=183) separately. RNA sequencing was performed of 32 samples. Of these 53 % (n=17) were adenocarcinomas (AD) and 47 % (n=15) were squamous cell carcinomas (SCC). Xcell(1) was used to find the proportion of different cells in the tumor microenvironment and to calculate an immunescore. All samples were assigned a gene expression subtype by using previously described nearest centroid classifiers for AD and SCC respectively (2, 3) **Result:** For AD we found significant differences in progression free survival (PFS)

between the three expression subtypes with better prognosis for TRU versus non-TRU and worse for PP versus non-PP, adjusted for stage. We found no differences in prognosis between SCC expression subtypes. Higher immune score was associated with better PFS in AD but not in SCC. **Conclusion:** The composition of both stromal and immune cells in the tumor microenvironment will be further investigated. Differential gene expression analysis will be preformed to better understand what differentiates immunologically active from immunologically silent tumors.

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Keywords: tumor immune microenvironment, immune score, Prognostic

P3.03 BIOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.03-27 SOMATIC BRCA1/2 MUTATIONS IN ADVANCED NSCLC PATIENTS: DESCRIPTION OF A SUB-POPULATION FROM THE ONGOING UNICANCER SAFIR02-LUNG / IFCT-1301 TRIAL

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Background: Molecular profiling is considered standard of care in advanced NSCLC. Identification of druggable molecular alterations may enhance the percentage of patients suitable for personalized treatment. **Method:** From 04/2014 to 03/2017, 602 newly diagnosed,advanced NSCLC patients (pts) were enrolled in SAFIR02-Lung trial (NCT02117167). Molecular profile provided information on copy number alterations and mutations on 71 oncogenes and tumor suppressor genes. The profile was performed for 420 pts (70%) on archival tissue or frozen tissue collected from a new biopsy performed before the 3rd cycle (tissue or liquid) of chemotherapy. The frequency of *BRCA* mutation (mut) was assessed and clinicopathologic data collected. A homologous recombinant deficiency (HRD) score was performed on the copy number variations (CNV) data and the germline status was based on blood analysis. The BRCAshare database was the reference for the variants classification. **Result:** 18 pts were identified with BRCA alterations. BRCA variants of unknown significance were detected in 11 pts (2.6%). Response to chemotherapy according to RECIST 1.1 by investigator was: 6 stable disease (SD), 1 partial response, and 4 progressive disease (PD). CNV profile was evaluable for HRD in 6 out of 11 pts, with 50% positive. Seven pts (1.7%) were identified with deleterious BRCA-mut. 2 pts (0.5%) harboured germline BRCA2-mut (1 with breast cancer familiar history). Both pts had SD to chemotherapy. Somatic BRCA-mut was identified in 5 pts (1.2%, 2 BRCA1- and 3 BRCA2-mut). All were male, 100% adenocarcinoma, 75% smokers of 40 pack/year, 1 pt with familial cancer history, and 80% of pts had bone metastases. Response to chemotherapy was: 4 SD, and 1 PD. Three of 7 corresponding CNV profiles were evaluable for HRD score analysis with 100% positive.

N=420	BRCA alterations (N=18)	
	BRCA VUS N=11	BRCA deleterious N=7
Somatic	6	5
Germline	5	2
HRD positive- Somatic Germline	3/6* 2 1	3/3* 3 0
VUS: variants of unknown significance *Amongst patients with available samples for analysis		

Conclusion: Pathogenic *BRCA1/2* mutations occur in 1.7% of advanced NSCLC with 71% of somatic mutations suggesting its value for exploring new therapeutic strategies in this population

Keywords: BRCAness, advanced NSCLC, BRCA 1/2 mutation

P3.03 BIOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.03-28 LKB1 MUTATION STATUS IS ASSOCIATED WITH POOR RADIATION OUTCOME IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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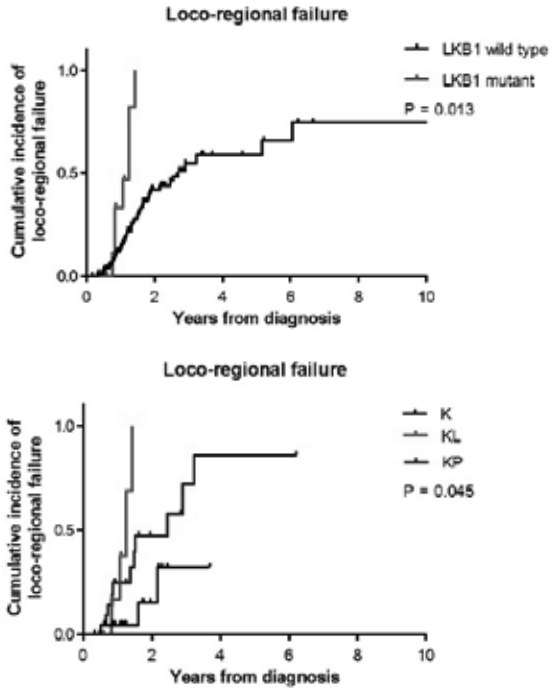
Background: Previously, we reported that the upregulation of the NRF2/KEAP1 pathway in non-small cell lung cancers (NSCLC) bearing co-mutations in KRAS and LKB1 is critical to maintain redox homeostasis which contribute to radiation resistance in these tumors. Here, we explore the role of the LKB1 mutation as a potential predictor radiation outcome in NSCLC. **Method:** We retrospectively analyzed the patients undergoing definitive treatment for newly diagnosed NSCLC who were enrolled in the prospectively collected MD Anderson Lung Cancer Moon Shot GEMINI database according to LKB1 mutation status. Cox regression analysis and log-rank tests were used to correlate with radiation outcomes according to LKB1 mutation status and/or KRAS mutation subgroup. We then investigated the mechanisms of radiation resistance in these tumors in preclinical models. **Result:** Of the 173 patients with stage III NSCLC treated with definitive radiotherapy, with or without chemotherapy were analyzed according to LKB1 mutation status demonstrated that LKB1 mutation had statistically significantly higher rate of loco-regional recurrence, and shorter disease-free survival than in patients with wild type LKB1 (P = 0.013 and P = 0.037, respectively). Moreover, additional loss of either LKB1 or TP53 in KRAS-mutant tumors renders these tumors higher loco-regional recurrence after radiation (P interaction = 0.045). We identified that LKB1 loss is associated with radio-resistance in part by KEAP1/NRF2 pathway activation. Re-expression of LKB1 or NRF2 pathway suppression (via KEAP1 expression) enhanced radiotherapy sensitivity *in vivo*.

Figure 1. LKB1 mutation status predicts loco-regional failure after radiation in patients with stage III NSCLC.



Conclusion: Our results suggest that LKB1 mutation is a potential predictive impact on radiation outcome of patients with NSCLC. The upregulation of the KEAP1/NRF2 pathway in NSCLC bearing co-mutations in KRAS and LKB1 is critical to maintain redox homeostasis and determine the sensitivity for radiation.

Keywords: Liver Kinase B1, Kelch-like ECH-Associated Protein 1, Radio-resistance

P3.03 BIOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.03-29 THE PROGNOSTIC EFFECT OF TUMOR MUTATION BURDEN AND SMOKING HISTORY IN RESECTED EGFR MUTANT NON-SMALL CELL LUNG CANCER

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Background: Although *EGFR*m NSCLC occurs mainly in non-smoking patients, most series report 20%-35% of cases in current or previous smokers. Broad molecular profiling of *EGFR*m NSCLC in smokers has not been reported. **Method:** Surgically resected primary *EGFR* exon 19, 20 and 21 mutated NSCLC tumors from 106 patients were molecularly profiled by whole exome sequencing using the Illumina HiSeq2000 platform. Alignment and variant discovery analysis was performed according to GATK best practices workflow; 74 sequenced to a mean coverage of 65.1x. Demographics and outcomes were compared for smokers and non-smokers (non-S), and by mutation profile. **Result:** Among 53 non-smokers and 21 smokers (5 current/recent within 10 years), 70% were female, 51% non-Asian, 40.5% >65 years of age and 58.1% had *EGFR* exon 19. Of the 74 patients, 51% were stage I, 19% stage II and 30% stage III+. Smoking was associated with male sex (p= **0.011**) and non-Asian ethnicity (p=0.00002) but not age, stage or *EGFR* exon 19/20/21 subtype. Multiple "driver" mutations occurred in tumors of 23.8% smokers and 26.4% non-S. *TP53/EGFR* co-mutation occurred in 52.4% smokers and 47.2% non-S. There was no significant difference seen for TMB in smokers: median TMB in smokers 3(1.4-7.46) versus 2.7(0.96-3.95) in non-S (p=0.11). The strongest prognostic factor for OS and DFS was stage (I, II, III+) (p<0.0001 for each compared to stage I). Smoking history did not have a significant effect on survival: HR 1.61 (CI 0.78-3.32, p=0.2) or probability of relapse: HR 0.9 (CI 0.46-1.77, p=0.77). Smoking within 10 years of NSCLC diagnosis was not associated with shorter OS/DFS. Neither *EGFR*m subtype nor *TP53/EGFR* co-mutation was associated with probability of relapse or OS. High TMB was significantly associated with shorter survival: HR above *vs* below the median 2.37 (CI 1.12-5.01, p=0.024), but not probability of relapse: HR 1.67 (CI 0.88-3.19, p=0.12). A subset analysis found the effect of TMB on survival was significant in patients >65 years (p=0.004), but not in patients ≤65 years (p=0.95). **Conclusion:** Stage remains the strongest prognostic factor for survival and probability of relapse in completely resected *EGFR*m NSCLC. TMB appears to have an effect on survival outcomes, unlike smoking status, and this effect may be greater in patients older than 65 years.

Keywords: EGFR, NSCLC, TMB

P3.03 BIOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.03-30 CLINICAL SIGNIFICANCE OF UROTHELIAL CARCINOMA ASSOCIATED 1 IN LUNG CANCER

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Background: Lung cancer is a leading cause of death worldwide. Long non-coding RNAs have been documented aberrantly expressed and exerted crucial role in variety of cancers. Urothelial carcinoma associated 1 (UCA1) is a potential new type of biomarkers for tumor diagnosis and exerts oncogenic effect on various human cancers. In previous work of our lab, we demonstrated that UCA1 exerts oncogenes activity in lung cancer, acting mechanistically by up-regulating HMGB1 expression through 'sponging' miR-193a. However, the contributions of this pathway in lung cancer remain largely unknown. **Method:** In this study, we sought to dissect the role of UCA1/miR-193a/HMGB1 pathway in progression of lung cancer. Firstly, we detected the expression profile of UCA1/miR-193a/ HMGB1 pathway in 50 pairs of lung cancer and adjacent normal tissues and meanwhile, plasma samples from 50 healthy controls, 50 lung cancer patients before and after tumor removal. **Result:** We found that UCA1 and HMGB1 were up-regulated and miR-193a down-regulated in cancer sample from tissues and plasma. Then, the relationships between UCA1/miR-193a/ HMGB1 pathway and clinical features and overall survival were analyzed. The results demonstrated that high expression of UCA1, HMGB1 and low expression of miR-193a were associated with LMN, higher pT category, advanced TNM stages ($P < 0.01$) and worse survival time than those with low expression of UCA1, HMGB1 and high expression of miR-193a ($P = 0.038$). Furthermore, plasma levels of UCA1 and HMGB1 in lung cancer patients were significantly higher than those of controls ($P = 0.017$). In addition, we displayed the significant difference in plasma level of UCA1, miR-193a and HMGB1 between samples taken before and after surgery ($P = 0.048$). **Conclusion:** The expression profile of UCA1/miR-193a/ HMGB1 pathway is related to prognosis in lung cancer and served as a potential biomarker for early diagnosis and disease monitoring of lung cancer patients.

Keywords: lung cancer, Long non-coding RNA UCA1, miR193a/HMGB1

P3.04 IMMUNOONCOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.04-01 COMBINED PLASMA CFDNA MUTATIONS AND A SERUM PROTEOMIC SIGNATURE MAY IDENTIFY NON-RESPONDERS TO ANTI PD-1 TREATMENT IN NSCLC

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Background: Predictive scoring systems, for example the status of programmed death-ligand 1 (PD-L1), provide physicians a tool to prescribe immune checkpoint inhibitors for patients diagnosed with non-small cell lung cancer (NSCLC). However, a significant percentage of patients do not respond to these therapies. Additional predictive biomarkers, which further define subpopulations that will benefit from these drugs, are needed. **Method:** Serum/plasma samples, clinical and survival data were available for 20 patients with NSCLC that received anti PD-1 therapy either in first (n=1) or second line or later (n=19). Serum/plasma samples were acquired on the day when immunotherapy was administered the first time and at the timepoint of first staging, following initiation of therapy. Plasma samples were analysed for circulating KRAS (G12C, G12D, G12V) and EGFR (ΔE746-A750, L858R, T790M) mutation status by droplet digital PCR (the GeneStrat test). Furthermore, matrix assisted laser desorption/ionization (MALDI) mass spectra were acquired from the matched serum samples using a proteomic test (the VeriStrat test). VeriStrat creates a profile of eight protein features and uses a supervised machine learning algorithm to define outcome subgroups. **Result:** Four patients were found to harbour either EGFR or KRAS mutations or a combination of both in circulation. Two patients displayed a mutation in KRAS G12D and EGFR del19 simultaneously. The other two patients exhibited only a mutation in KRAS (either G12V or G12C). Interestingly, three patients harbouring driver mutations displayed a VeriStrat status of poor at first staging and did not benefit from anti PD-1 therapy. The two patients harbouring both EGFR and KRAS mutations had VeriStrat good labels before start of treatment, which switched to poor results at first staging. Only one patient, displaying a single KRAS mutation and a VeriStrat good status before start of treatment showed a partial response at first staging. Of the 16 patients for whom no circulating mutation was present we found no change in VeriStrat status from before start of treatment to first staging. **Conclusion:** Integrated analysis of circulating genomic and proteomic markers for patients that will receive therapy aimed at the inhibition of anti-PD1 and anti-PD-L1 axis may further define patient cohorts that will not respond to immunotherapy.

Keywords: NSCLC, Immunotherapy, liquid biopsies

P3.04 IMMUNOONCOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.04-02 EARLY PLASMA CTDNA RESPONSE ANTICIPATES CLINICAL RESPONSE TO FIRST-LINE IMMUNOTHERAPY IN ADVANCED NSCLC

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Background: Shedding of circulating tumor DNA (ctDNA) into plasma can be an independent prognostic indicator in lung cancer, and changes in plasma ctDNA levels correlate with response to targeted therapy. We hypothesized that serial assessment of plasma ctDNA by next generation sequencing (NGS) would enable early detection of response to immunotherapy in NSCLC. **Method:** Patients with advanced NSCLC who

received first-line treatment with pembrolizumab alone or in combination with platinum doublet chemotherapy at the Dana-Farber Cancer Institute were enrolled in this study. Plasma collected from patients prior to starting therapy and again at 3 and 3 weeks after starting therapy was analyzed by NGS using enhanced tagged-amplicon sequencing of hotspots and coding regions from 36 genes (InVisionSeq). The trends of the ctDNA allele frequency were correlated with radiographic responses to therapy. **Result:** Serial plasma samples were collected on 21 patients with the following characteristics: 67% female, median age 62, 90% adenocarcinoma, 10% squamous cell carcinoma. Pembrolizumab was administered as monotherapy to 18 (86%) patients and in combination with platinum/pemetrexed in 3 (14%) patients for a median of 6 cycles. Among the 8 (38%) patients with no detectable ctDNA at baseline, 5 patients who maintained no detectable ctDNA during serial analyses responded to treatment, and 3 patients with emergence of ctDNA within the first 6 weeks of treatment initiation experienced progressive disease. In the 13 (62%) patients with detectable ctDNA at baseline, radiographic responses were preceded by earlier changes in ctDNA allele frequency. Six of 7 patients with >50% decreases in ctDNA allele fraction responded to treatment while 4 of 6 patients with progressive disease had increases in ctDNA within 6 weeks. **Conclusion:** In advanced NSCLC treated with first-line immunotherapy, rapid decreases and clearance of ctDNA correlated with clinical benefit, while increasing or newly detectable ctDNA was a harbinger of progressive disease. These results suggest a potential role for ctDNA as an early pharmacodynamic biomarker of response or resistance to immunotherapies.

Keywords: Immunotherapy, ctDNA, plasma

P3.04 IMMUNOONCOLOGY
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P3.04-03 ASSOCIATION OF FUNCTIONAL POLYMORPHISM IN CTLA-4 GENE WITH SURVIVAL IN NON-SMALL CELL LUNG CANCER: A BRAZILIAN STUDY

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Background: Blockade of immune checkpoints with monoclonal antibodies has recently emerged as a novel therapy against cancer. Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) is a potent immunoregulatory molecule which regulate T- cell activation and proliferation. The most studied +49A/G polymorphism (rs231775) of the *CTLA-4* gene has been associated with several autoimmune diseases and cancer.This study aimed to investigate the relationship between +49A/G polymorphism can predict the prognosis of patients with early stage non-small cell lung cancer (NSCLC) after surgical resection in Brazilian population. **Method:** Genomic DNA (gDNA) was extracted from fresh-frozen NSCLC tissue using the QIAamp DNA Mini Kit (Qiagen, Valencia, USA) following the manufacturer's recommendations. The *CTLA-4* gene was customized in a amplicon-based assay for targeted resequencing by TruSeq Custom Amplicon v1.5kit (TSCA, Illumina) on an Illumina MiSeq instrument (Illumina, San Diego, CA, USA). SNPs with minor allele frequency (MAF) of 0.05 or higher were included. X^2 test was used to assess the association between *CTLA-4* 49A/G SNP and categorical clinicopathologic parameters. The overall survival (OS) estimates were calculated using the Kaplan-Meier method. p <0.05 was considered as statistically significant. **Result:** Seventy-five patients with diagnosed NSCLC have been enrolled into this study. According to the pathological reports, the samples included adenocarcinoma (AC,n=52), adenosquamous carcinoma (ASC,n=5), squamous cell carcinoma (SCC,n=15) and large cell carcinoma (LCC, n=3). The *CTLA-4* +49A/G genotype frequencies in NSCLC patients were detected with the following disposition: the frequencies of AA, AG and GG genotype were 53,3% (40/75), 33,3% (25/75) and 13.4% (10/75), respectively. We observed that patients with the GG-genotype of *CTLA-4* rs231775 had longer OS compared with patients with an AG or AA genotype. **Conclusion:** This study suggests that CTLA-4 rs231775 could potentially be used as a prognostic biomarker.

Keywords: CTLA-4 Polymorphism, immune checkpoint, non-small cell lung cancer

P3.04 IMMUNOONCOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.04-04 PROGNOSTIC VALUE OF MHC-I, PD-L1 AND CD8+ TILS EXPRESSIONS IN PATIENTS WITH SURGICALLY RESECTED NON-SMALL CELL LUNG CANCER

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Background: Lung cancer is the most commonly diagnosed cancer and also the leading cause of cancer death globally. Chemotherapy showed limited improvement in the survival of surgically resected non-small cell lung cancer (NSCLC) patients. There was no effective prognostic indicators in surgically resected NSCLC. The expression levels of tumor surface molecules, such as major histocompatibility complex class I (MHC-I), programmed cell death-ligand 1 (PD-L1) and CD8+ tumor infiltrating lymphocytes (TILs) were detected in this study to investigate the potential prognostic markers in the patients with surgically resected NSCLC. **Method:** Tissue of 125 patients with surgically resected NSCLC were obtained from the First Hospital of Jilin Universtiy. MHC-I, PD-L1 and CD8+ TILs expressions were detected with immunohistochemistry. The association between their expression levels and patients' prognosis was analyzed by SPSS 17.0 software (SPSS, Chicago, IL). **Result:** MHC-I was down-expressed, PD-L1 was up-regulated in NSCLC compared with the adjacent tissues. CD8+ TILs could be seen in tumor stroma and nest. With univariate analysis, we found that the down-expression of MHC-I had an association with poor relapse-free survival (RFS) and overall survival (OS) in NSCLC patients (P = 0.007 and P = 0.001). RFS and OS in PD-L1− group tended to be longer than that of PD-L1+ group, but the difference was not significant (P > 0.05). Based on the distribution of CD8+ TILs, patients were divided into three groups: immune-inflamed group, immune-excluded group and immune-desert group. RFS and OS of patients with the immune-inflamed phenotype ($CD8^{inflamed}$) were longer than patients with the immune-excluded and immune-desert phenotype ($CD8^{non\text{-}inflamed}$) (P = 0.013 and P = 0.015). Besides, patients were divided into four subgroups based on the PD-L1 and CD8+ TILs expression: PD-L1+/$CD8^{inflamed}$, PD-L1+/$CD8^{non\text{-}inflamed}$, PD-L1−/$CD8^{inflamed}$, and PD-L1−/$CD8^{non\text{-}inflamed}$. Statistical differences were achieved both in RFS and OS (P = 0.012 and P = 0.032). RFS and OS in patients with PD-L1+/$CD8^{inflamed}$ and PD-L1−/$CD8^{inflamed}$ were longer than patients with PD-L1+/$CD8^{non\text{-}inflamed}$ and PD-L1−/$CD8^{non\text{-}inflamed}$. Patients with PD-L1+/$CD8^{non\text{-}inflamed}$ experienced the worst RFS and OS. With multivariate analysis, we found that MHC-I and CD8+ TILs might be independent prognostic factors in surgically resected NSCLC. **Conclusion:** MHC-I and CD8+ TILs expression had a close association with patients prognosis in this study. The combination of PD-L1 and CD8+ TILs, instead of PD-L1 alone, suggested impressive prognostic values in NSCLC patients. It worth further study to confirm the clinical value of MHC-I, PD-L1 and CD8 TILs expressions in the patients with surgically resected NSCLC.

Keywords: tumor infiltrating lymphocyte, non-small cell lung cancer, programmed cell death ligand-1

P3.04 IMMUNOONCOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.04-05 PROGRAMMED DEATH-LIGAND 1 OF CYTOLOGY SPECIMENS AS A PROMISING METHOD FOR MAKER EVALUATION IN PATIENTS OF NON-SMALL CELL LUNG CANCER

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Background: Measuring programmed death-ligand 1 (PD-L1) expression has been commonly used to classify the promising patients for immunotherapy. PD-L1 heterogeneous expression has been elucidated within the tumor. Therefore, we questioned whether small tissue samples, such as cytology samples, sufficiently represented PD-L1 expression in non-small cell lung cancer(NSCLC). **Method:** Paired cytological cell block and surgical resection before systemic therapy was assessed. PD-L1 expression was quantified by using both 28-8 and SP142 assays. Feasibility of PD-L1 expression in cell blocks was compared with that in matched surgical resection with various cutoffs. **Result:** A total of 112 pairs of specimens were collected at the time of initial diagnosis, including 79(63.2%) adenocarcinomas and 28(25.0%) squamous cell carcinomas. PD-L1 expression showed fair to substantial concordance between cytology specimens and surgical resection for both antibodies' staining (**Conclusion:** PD-L1 expression of cytology specimens with high tumor cells showed concordance with surgical resection. These findings suggested that cytology specimens might be adequate representative for PD-L1 expression of patients with NSCLC.

Keywords: cell block, NSCLC, PD-L1

P3.04-06 PROGNOSTIC SIGNIFICANCE OF SERUM CXCL12 LEVEL IN PATIENTS WITH SURGICAL RESECTED LUNG ADENOCARCINOMA

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Background: Lung cancer is the leading cause of cancer-related death in the world. Cytokines are a heterogeneous group of soluble small polypeptides or glycoproteins. The tumor microenvironment is rich in cytokines and other inflammatory mediators that influence immunosuppression, cancer cells growth, tissue remodeling and angiogenesis. In this study, we determined the prognostic value of selected cytokines or chemokines in patients with lung adenocarcinoma. **Method:** Sixty-three patients undergoing surgical resection for lung adenocarcinoma were enrolled in this study. A total of 63 serum samples from these patients were used for study. The levels of cytokines/chemokines in these serum samples were determined by cytometric bead array according to manufacture's instruction. The following cytokines/chemokines have been examined, including interleukin-1b (IL-1b), IL-6, IL-8, IL-10, CXCL9, CXCL10, CXCL12, CCL19, CCL21, and CCL25. **Result:** With a median follow-up time of 62.3 months (range, 0.7 to 94.1 months), the 5-year overall survival rate was 88.1%. To determine the expression of cytokines/chemokines in lung adenocarcinoma serum samples, cytometric bead array was performed in 63 lung adenocarcinoma serum samples. Univariate analysis indicated that stage II and III (vs. stage I) (P = 0.016) was a significant prognostic factor for worse overall survival. Poor differentiation (P = 0.062) and CXCL12 overexpression (P = 0.052) tended to be significant prognostic factors for worse overall survival. IL-1b, IL-6, IL-8, IL-10, CXCL9, CXCL10, CCL19, CCL21, and CCL25 were not significant prognostic factors for overall survival. The advanced stage (II and III vs. I) (hazard ratio [HR], 7.775; 95% confidence interval [CI], 1.243 to 48.618; P = 0.028), poor differentiation (HR, 7.995; 95% CI, 1.092 to 58.547; P = 0.041) and CXCL12 overexpression (HR, 7.307; 95% CI, 1.163 to 45.899; P = 0.034) were still significant prognostic factors for worse overall survival in multivariate analysis. Male sex (P = 0.007) was significantly associated with CXCL12 overexpression. **Conclusion:** CXCL12 overexpression was a significant prognostic factor for worse overall survival in patients with surgical resected lung adenocarcinoma. Male sex was significantly associated with CXCL12 overexpression. CXCL12 overexpression has the potential to be used as a predictor of worse outcome in lung adenocarcinoma patients after surgical resection.

Keywords: chemokine, lung adenocarcinoma, Prognosis

P3.04-07 CORRELATION BETWEEN PD-L1 EXPRESSION AND EXPRESSION OF CDK4 AND SPOP IN NON-SMALL CELL LUNG CANCER

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Background: Immunotherapy that targets programmed cell death protein 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) has emerged as a novel treatment modality for cancers. Clinical trials have reported durable responses and long-term remissions using PD-1/PD-L1 inhibitors, and the expression level of PD-L1 at the tumor cells was correlated with a response to PD-1/ PD-L1 inhibitors. However these inhibitors are only effective in a subset of lung cancer patients, and the underlying molecular mechanisms are not well understood. Recently, it has been reported that PD-L1 expression can be regulated at both transcriptional and post-translational levels, such as cyclinD-CDK4 and the cullin 3-SPOP (phosphorylation of speckle-type POZ protein) E3 ligase. In this study, we focus on the regulation of PD-L1 expression in lung cancer, and we investigated the association between the expression of PD-L1 and biomarkers in regard to clinical outcomes. **Method:** We invested CDK4, CDK6 and SPOP expression of lung cancer, and CD4 and CD8 expression of tumor-infiltrating lymphocytes (TILs) by immunohistochemistry of 36 non-small cell lung cancers, those had undertaken an operation or chemotherapy from March 2007 to January 2018 and analyzed PD-L1 expression (negative:0%, low expression:1-49%, high expression:≥50%). The staining intensity of CDK4, CDK6 and SPOP was scored as 0 (negative), 1 (weak), 2 (medium), and 3 (strong). Extent of staining was scored as 0 (0-10%), 1 (11-25%), 2 (26-50%), 3 (51-75%), and 4 (76-100%) according to the percentages of the positive staining areas in relation to the whole cancer area. For CD4+ and CD8+ cells, a maximum numbers of stained cell were counted semi-quantitatively in high-powered fields for the scoring as 1-4. The observed protein expression levels and TILs counts were analyzed for correlation to PD-L1 expression, clinicopathological parameters and the responses of PD-1 inhibitors. **Result:** PD-L1 expression was observed in 15 (48%) patients of lung cancer, 8 (26%) of low expression and 7 (23%) of high expression. Positive expression rates of SPOP were 56.3% of negative expression of DP-L1, 50.0% of low expression and 28.6% of high expression. That of CDK4 and CDK6 was 43.8%, 25.0%, 16.6%, and 43.8%, 62.5%, 51.7%, respectively. The positive rate of SPOP (p=0.67), CDK4 (p=0.16) and CDK6 (p=0.37) in PD-L1 positive group was lower than that of PD-L1 negative group, but significant. CD8+ cell count was positive relation to PD-L1 expression. **Conclusion:** Our data supported previous findings that inhibition of CDK4 and CDK6 increases PD-L1 protein levels and SPOP-deficiency correlated with increased PD-L1 protein abundance.

Keywords: PD-L1, SPOP, CDK4

P3.04-08 IDENTIFYING RESISTANCE TO IMMUNE CHECKPOINT INHIBITORS BY SCREENING FOR PD-L1 AND MHC I EXPRESSION ON CTCS IN PTS WITH NSCLC

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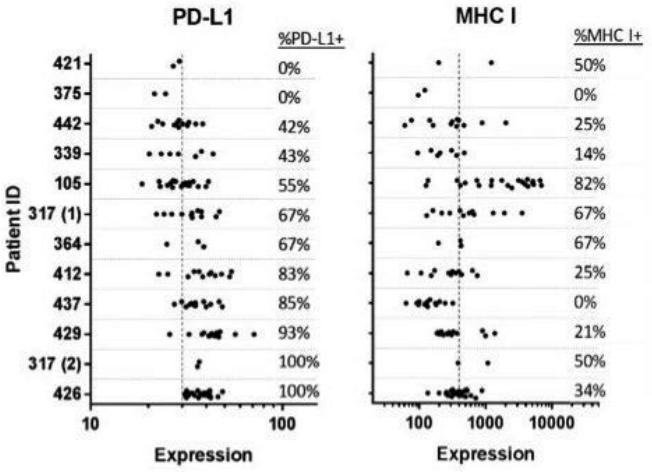
Background: PD-L1 expression on tumor predicts benefit to immune checkpoint inhibitors (ICIs) in patients with advanced NSCLC. However, there are a significant number of patients whose tumor test positive for PD-L1 expression that do not derive benefit from ICIs, suggesting the existence of intrinsic resistance mechanisms. PD-L1 blockade aims to trigger tumor cell recognition and lysis by CD8+ T cells, but this process requires concordant expression of MHC I by tumor cells. Recently, MHC I negativity was observed in 49% of patients with lung carcinoma, and correlated with a lack of CD8+ T cell infiltration, emphasizing the importance of screening for MHC I in combination with PD-L1. **Method:** For the purposes of both screening and the detection of acquired resistance, we developed a minimally invasive diagnostic test using Circulating Tumor Cells (CTCs). CTCs were captured and stained on the ExtractMax system (Gilson, Inc.) with Exclusion-Based Sample Processing (ESP) technology (Salus Discovery, LLC). With automation, the ExtractMax simplifies complex multi-step procedures, reduces variability, and ensures gentle manipulation of rare cell targets for optimal yield and viability. **Result:** A range of PD-L1 and MHC I expression levels were detected on CTCs captured from a cohort of patients with NSCLC, with two patients showing no MHC 1 expression and all others with heterogeneous expression of MHC 1. PD-L1 expression was variable across all samples tested with subset of patients with PD-L1 positive CTCs but MHC I negative, suggesting intrinsic resistance to PD-L1 targeted therapies.



Conclusion: This data supports the feasibility of using an automated CTC processing system to detect and monitor PD-L1 and MHC I expression in patients with NSCLC. Ongoing efforts include expanding this patient cohort in larger clinical trials and transitioning this test into a clinical laboratory testing facility for regulatory approval and use as a clinically actionable diagnostic tool.

Keywords: Circulating tumor cells, PD-L1, MHC I

P3.04-09 ANALYSIS OF REPERTOIRE FEATURES OF T CELL RECEPTOR IN TREAT-NAÏVE EGFR WILD-TYPE LUNG CANCER PATIENTS BY HIGH-THROUGHPUT SEQUENCING

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Background: T cells can recognize peptides encoded by mutated genes. Assessment of the repertoire features of TCR is vital for us to deeper understand of immune behavior and immune response. However, detailed characterization of the peripheral blood T cell receptor (TCR) repertoire and its interaction with treat-naïve EGFR wild-type lung cancer patients have not been systemically studied. **Method:** We used ultra-deep sequencing of rearranged genes in TCR β-chain (TCRβ) to profile the basic characteristics of T cells in peripheral blood samples of 27 treat-naïve EGFR wild-type lung cancer patients received chemotherapy as well as age- and gender-matched healthy donors without any history of cancer. **Result:** Data showed that healthy donors had more TCR clonotypes and higher diversity while patients represented with restricted TCR repertoire. Interestingly, TCR repertoire was associated with TP53 mutation status, tumor volume, rapid progression and squamous cell carcinoma antigen (SCC) level in patients, but not with metastasis. Patients with TP53 mutation had fewer clonotypes (p=0.011), lower diversity (p=0.006) and higher clonality (p=0.054), while those with larger tumor volume and rapid progression following chemotherapy had fewer clonotypes (p=0.046 and p=0.011, respectively) in peripheral blood. peripheral blood TCR repertoire was not significant correlated with brain metastasis or bone metastasis. In addition, clonality was positive correlation with SCC Concentration (p=0.024,R=0.48,n=22). **Conclusion:** Our study promote a better knowledge about the T cells among treat-naïve EGFR wild-type lung cancer patients and provides new insight into the TCR repertoire associated with clinical presentation in lung cancer patients. And the TCR repertoire in peripheral blood samples before treatment may be used as a predictor of rapid progression in lung cancer patients treated with chemotherapy.

Keywords: lung cancer, High-Throughput Sequencing, TCR

P3.04-10 MONOCYTES AND NEUTROPHILS AS PREDICTIVE MARKERS OF RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN METASTATIC NON-SMALL CELL LUNG CANCER

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Background: PD-L1 expression and mutational load in tumor cells have been found to predict response to immune checkpoint inhibitors (ICI) in patients with metastatic non-small cell lung cancer (mNSCLC). These parameters, however, are not readily available clinically. Identification of parameters easily measured in the clinics will help select NSCLC patients most likely to benefit from ICI. **Method:** A retrospective cohort study was carried out on patients with mNSCLC to identify clinical and laboratory factors associated with response to ICI. **Result:** Of the 37 consecutive patients identified, only 32 patients were analyzed as 5 patients were not evaluable for response. There were 17 males and 15 females. Their median age was 64.5 years (range 20-84). History of smoking was present in 25/32 (78%) patients. Non-squamous cell tumors were by far the commonest histologic subtype (27/32, 84%). 12 patients received pembrolizumab, 19 patients nivolumab, and one patient received nivolumab followed by pembrolizumab. Responses were observed in 19 (59%) of these 32 patients. All 19 patients had partial response. There was no difference in the distribution of sex, age, smoking status, and histologic subtypes between responders and non-responders. The median time to response (TTR) in this cohort of patients was 12 weeks (range 6-24) and the median duration of response (DoR) was 24 weeks (range 7-112). Higher pre-therapy absolute monocyte counts (AMC) were correlated to shorter TTR (R = -0.50; 95% CI -0.79 – -0.05) (p = 0.03) but not DoR. Patients with AMC > 700/mm^3 had a significantly shorter median TTR than those with AMC $\leq$ 700/mm^3 (8 weeks vs 12 weeks; p = 0.048). Lower absolute neutrophil counts (ANC) after dose #1 predicted response to ICI (p = 0.02). Patients with ANC < 4200/mm^3 after dose #1 were more likely to respond than those with ANC >4200/mm^3 (OR = 6.8; 95% CI 1.1 – 41.8) (p = 0.05). Pre- and post-therapy lymphocyte counts, platelet counts, or hemoglobin did not predict responses or DoR. **Conclusion:** Higher pre-therapy AMC and lower post-dose #1 ANC in mNSCLC treated with ICI were correlated to improved probability of response. Analysis of AMC and ANC before and during therapy may provide an easy method to identify those mNSCLC patients most likely to respond to ICI.

P3.04-11 THE INFLUENCE OF CIRCULATING TUMOR DNA ANALYSIS ON RESPONSE TO IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: In advanced NSCLC, immunotherapy has demonstrated good response rates with some responses being remarkably durable, however emerging biomarkers predictive of response (or lack thereof) include PD-L1 expression, tumor mutation burden (TMB), genomic alterations in *EGFR/ALK/ROS1* and *KRAS/TP53/STK11* mutations, all competing for limited tissue biopsy samples. Therefore, we investigated whether these biomarkers can be detected from a non-invasive plasma sample. In particular, challenges to assessment of TMB with cell-free DNA next-generation sequencing (NGS) include the limited size of liquid biopsy gene panels and the fact that low shedding of tumor DNA into circulation may fail to detect hypermutated tumors. We previously reported, in a modest 27 advanced NSCLC cohort, that TMB can be ascertained with a 73-gene cfDNA NGS panel that adjusts for the degree of tumor shedding, and here investigate whether detection of TMB and the above genomic mutations can be used to predict immune checkpoint inhibitor response in a larger cohort. **Method:** In this retrospective study, data were collected on NSCLC patients treated in multiple medical centers in Israel between 2014 and 2017. We used NGS on cell-free circulating tumor DNA (ctDNA) to evaluate whether mutational burden and specific genomic alterations influence the response to immunotherapy in these patients. **Result:** Overall, 336 NSCLC patients underwent NGS on ctDNA. Of these 336 patients, 192 (57%) were females and 144 (43%) were males. The average age (range) was 64 (23-103) years. Clinical treatment information is currently available for 117 patients, of whom 50 (43%) received immune check-point inhibitors. Rates of stable disease, partial and complete responses (RECIST criteria), as well as progression-free survival and overall survival will be reported. In addition, to unravel the genomic determinants of response to immunotherapy we will use the blood-derived ctDNA to understand if hypermutated ctDNA is a predictive biomarker of response to immunotherapy. **Conclusion:** ctDNA collection was feasible in 336 patients. A prediction model to associate the ctDNA signature with response to immunotherapy based on plasma will be presented.

Keywords: TMB, Immunotherapy, ctDNA

P3.04-12 PROGNOSTIC AND PREDICTIVE ROLE OF PERIPHERAL BLOOD BIOMARKERS IN NSCLC PATIENTS TREATED WITH CHECKPOINT, A SINGLE-CENTER EXPERIENCE.

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Background: Tumor characteristics and host immune system play a crucial role for the immune response. As reported in preclinical studies, a sustain immune cell proliferation in the periphery is necessary for the immune response and tumor destruction. More evidence in melanoma patients (pts) and less evidence are available in non small cell lung cancer (NSCLC). Aim of this study is to demonstrate the role of the peripheral blood as biomarkers in NSCLC patients treated with checkpoint inhibitors (CPIs). **Method:** 94 evaluable patients from one institution NSCLC pts, treated with at least one course immunotherapy (IO) (nivolumab and pembrolizumab) in 2nd or further line, were considered for analysis. Baseline peripheral blood, at week 2 and 4 were collected for each patients. Univariate analysis were performed and correlation between biomarkers and progression free-survival (PFS) and overall survival (OS) are reported. **Result:** median age was 67 years (31-86 years), most pts were male (80%), 35 pts were S and 59 NS. 75,5% of pts were smokers and Eastern Cooperative Oncology Group (ECOG) pre-IO were: 0 (5,3%),

1 (58,5%) and 2 (36,2%). Overall median (m) PFS and mOS were 3,93 months (mo) and 20,7 mo respectively. Baseline absolute neutrophil count (ANC) ≥ 7500/μL and neutrophil to lymphocyte ratio (NLR) >5 correlate with worse PFS (3.3 mo vs 5.5 mo, p=0.04 and 2.8 mo vs 5.4 mo, p=0.006 respectively) and OS (15.6 mo vs 34.9 mo p=0.02 and 16.7 vs 34.9 mo p=0.004, respectively). Poor OS and PFS were persist at week 2 in pts with NLR ≥5 (HR=0.3, p<0.0001 for OS and PFS), this was not significant at week 4. Also, baseline derived neutrophil to lymphocyte ratio (dNLR) >3 correlate with worse PFS (p=0.01) and OS (p=0.016). Absolute lymphocyte count (ALC) ≥1000/μL at baseline and week 2 confer higher PFS (5.3 mo vs 3.1 mo, p=0.05) and a tred in OS. Interestingly, week-4 absolute monocytic count (AMC)≥ 1000/μL imply a poor PFS and this was not observed at baseline and week 2. Low, absolute eosinophil count (AEC) <50/ μL correlate with worse PFS (p=0.031). Finally, pts with lymphocyte monocyte ratio (LMR)≥ 1.5 at baseline, week 2 and 4 correlate with better survival. *Table. 1 Univariate analysis of peripheral blood biomarker and survival outcome in NSCLC patients treated with immunotherapy*

NSCLC non-small cell lung cancer, ALC absolute lymphocyte count, ANC absolute neutrophil count, NLR neutrophil to lymphocyte ratio, dNLR absolute neutrophil count/(white blood cell count-absolute neutrophil count), AEC absolute eosinophil count, AMC absolute monocyte count, LMR lymphocyte monocyte count, OS overall survival, PFS progression free survival, RR response rate, HR hazard ratio, **Conclusion:** Despite the retrospective nature, in our knowledge, this is the first study to demonstrate the role of AMC in NSCLC pts. Also, LMR could probably reflect the peripheral immune-fitness. However, prospective sudies are needed to confirm their role.

Keywords: biomarker, Immunotherapy, NSCLC

Biomarker	Outcome	Survival (months)	Impact (HR CI95%, p-value)	Results
Baseline ANC≥ 7500/μL	OS	15.6 mo vs 34.9 mo	HR= 0.43, p=0.002	Poor OS Poor PFS
	PFS	3.3 mo vs 5.5 mo	HR= 0.61, p=0.04	
Baseline NLR ≥ 5	OS	16.7 mo vs 34.9 mo	HR=0.45, p=0.004	Poor OS Poor PFS
	PFS	2.8 mo vs 5.4 mo	HR=0.50, p=0.006	
2 weeks NLR≥ 5	OS	11.9 mo vs 35 mo	HR=0.32, p<0.0001	Poor OS Poor PFS
	PFS	2.6 mo vs 6.1 mo	HR=0.31, p<0.0001	
Baseline dNLR> 3	OS	16.7 mo vs 34.8 mo	HR= 0.51, p=0.016	Poor OS Poor PFS
	PFS	2.8 mo vs 5.4 mo	HR= 0.52, p= 0.01	
Baseline ALC≥ 1000/μL	OS	31.7 mo vs 26.4 mo	HR=1.23, p=0.54	Same OS Good PFS
	PFS	5.3 mo vs 3.1 mo	HR= 1.8, p=0.05	
2 weeks ALC≥ 1000/μL	OS	34.8 vs 18 mo	HR=1.4, p=0.14	Same OS Good PFS
	PFS	8.1 mo vs 3.3 mo	HR=1.8 , p=0.007	
4 weeks AMC≥ 1000/ μL	OS	34.8 mo vs 31.7 mo	HR=1.0, p=0.91	Same OS Poor PFS
	PFS	3.3 mo vs 8.0 mo	HR=0.43, p=0.003	
Baseline LMR≥ 1.5	OS	34.8 mo vs 15.0 mo	HR=2.1, p=0.007	Good OS Good PFS
	PFS	5.3 mo vs 2.6 mo	HR=1.8, p=0.025	
2 weeks LMR≥ 1.5	OS	34.9 mo vs 15.0 mo	HR=1.92, p=0.025	Good OS Good PFS
	PFS	6.1 mo vs 2.8 mo	HR=3.4, p<0.001	
4 weeks LMR≥ 1.5	OS	35.1 mo vs 16.7 mo	HR=2.7, p=0.003	Good OS Good PFS
	PFS	5.9 mo vs 3 mo	HR=2, p=0.017	
Baseline (AEC) <50/ μL	OS	26.4 mo vs 24.6 mo	HR=0.83, p=0.55	Same OS Poor PFS
	PFS	3.4 mo vs 5.6 mo	HR=0.55, p=0.034	

P3.04-13 PD-L1-GENE EXPRESSION BY NCOUNTER CORRELATES WITH PD-L1 PROTEIN EXPRESSION IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: PD-L1 immunohistochemistry (IHC) staining is a Food and Drug Administration-approved marker to identify patients for immunotherapy treatment in advanced non-small cell lung cancer (NSCLC). However, several antibodies and cut-off criteria have been used and pathological evaluation involves a certain degree of subjectivity. Multiplexed technologies can be of help in this setting and provide an objective measurement of PD-L1 levels. **Method:** A 7-gene 'immune signature' comprising *CD4, CD8, PD-1, PD-L1*, *IFNG*, *GZMM* and *FOXP3* was incorporated into our routine clinical practice as part of a customized nCounter panel (NanoString Technologies), which simultaneously screens for gene fusions (*ALK*, *ROS1*, *RET* and *NTRK1),* MET overexpression and *MET* exon 14-skipping mutations. Formalin-fixed paraffin embedded (FFPE) samples from advanced NSCLC patients were analyzed with the panel and compared with PD-L1 IHC evaluation on tumor cells, using 22C3 clone antibody. **Result:** Since 2017, a total of 296 FFPE samples have been analyzed with the nCounter panel. PDL-1 IHC has been performed in 113 FFPE samples, as requested by the oncologist. All samples were evaluable for nCounter and IHC (100%). By IHC, 48/113samples (42.5%) were scored as negative for PD-L1 protein expression, whereas 65/113 (57.5%) were evaluated as positive. Of those, 39 presented moderate (≥1-49%) and 26 (23%) high PD-L1 staining (≥50%). Using an appropriate cut-off value, the levels of PD-L1 mRNA, as determined by the nCounter panel, closely correlated the PD-L1 IHC evaluation, with a 78% of concordance and a 0.554 Cohen's kappa (confidence interval 95% 0.400- 0.709). **Conclusion:** PD-L1 mRNA expression closely correlates with PD-L1 protein expression. Clinical validation is warranted to determine if nCounter can be an alternative to IHC for PD-L1 evaluation.

Keywords: IHC, nCounter, PD-L1

P3.04 IMMUNOONCOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.04-14 TMB AND IMMUNE CHECKPOINT INHIBITOR GENE EXPRESSION ARE UNRELATED IN NSCLC PATIENTS

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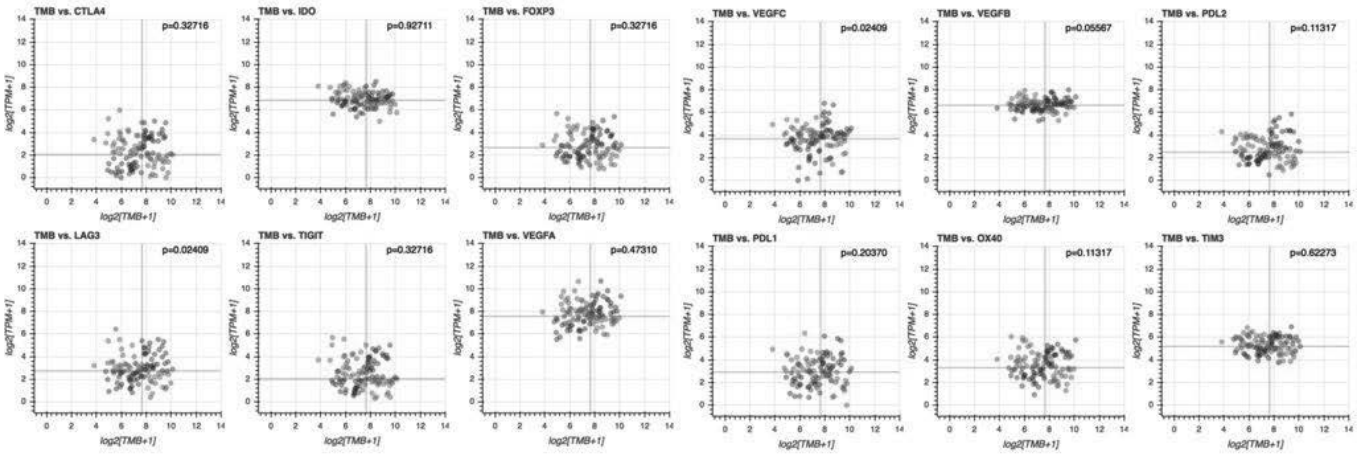
Background: Tumor Mutation Burden (TMB) is an emerging biomarker for response to immune checkpoint inhibitor therapy (ICT). PDL1 is still the only companion diagnostic test for ICT. We sought to examine the relationship between TMB based on whole exome sequencing (WES) data and ICT gene expression. **Method:** Retrospective analysis of a database from a commercial DNA tumor:normal and RNAseq platform was carried out. 112 samples were identified with tumor and normal DNA sequencing (WGS or WES) and RNA sequencing. A "high" vs "low" mutation burden was defined with a threshold of 200 exonic non-synonymous mutations. ICT gene expression of 12 checkpoint markers (CTLA4,IDO,FOXP3,LAG3,TIGIT,VEGFA,VEGFC,VEGFB,PDL2,PDL1,OX40, & TIM3) were analyzed for tissue-specific enrichment and within the TMB high and low categories. Immune-cell infiltration was estimated using RNA deconvolution based on known immune cell marker genes (Bindea et al 2013). **Result:** 52 of the 112 patients had high TMB based on the defined threshold. ICT gene expression was not significantly different in the TMB high and low groups and none of the 12 ICT markers showed a significant correlation with TMB. Age and gender did not affect TMB. **Conclusion:** Quantitative TMB may be a marker of ICT efficacy independent of ICT gene expression.

Keywords: immuno-oncology, checkpoints, TMB



X-axis is log2(TMB+1), 200 cutoff marked with a vertical red line. Y-axis is log2(TPM+1) for the various checkpoint markers, median line marked with a horizontal red line. Red points are 'discordant' (i.e. high checkpoint & low TMB, or low checkpoint & high TMB), blue are concordant. P-values in top-right are one-sided Fisher's exact probabilities of seeing the observed enrichment for concordance.

P3.04-15 IDO AND TIM3 GENE EXPRESSION IS CORRELATED IN NSCLC PATIENTS WITH LOW PDL1 GENE EXPRESSION

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Background: Tumor cells evade immunosurveillance by expression of immune checkpoint proteins *PD-L1, IDO, and TIM3*, even when tumor-infiltrating lymphocytes (TILs) are present. Combination of checkpoint inhibitors Pembrolizumab(*PD-1*i) and Epacadostat (IDOi) failed to show synergy in melanoma. Yet there are several candidate targets for checkpoint inhibition and rational selection of which combinations to explore is lacking. In particular, which checkpoints to target when *PD-L1* is not expressed is largely unexplored. The purpose of this study was to assess the expression of 12 immune checkpoint genes in lung cancer patients with high and low expression of PD-L1. **Method:** Retrospective review of deep whole transcriptomic sequencing (RNA-Seq) (~200x10^6 reads per tumor) on 1467 unselected clinical cases from NantHealth. 112 NSCLC cases were categorized as *PD-L1*-low and *PD-L1*-high by median splitting. Expression and co-expression of 12 checkpoint markers (CTLA4,IDO,FOXP3,LAG3,TIGIT,VEGFA,VEGFC,VEGFB,PDL2,PDL1,OX40, & TIM3) were analyzed for tissue-specific enrichment and within *PD-L1*-defined categories. Immune-cell infiltration was estimated using RNA deconvolution based on known immune cell marker genes (Bindea et al 2013). **Result:** CTLA, TIGIT and FOXP3 showed high correlations across all 112 samples as well within the PD-L1 low and high expression groups and differential expression across the two groups, with higher expression of the markers among the PD-L1 high expression group versus the low group. Within the PD-L1 high expression group, the expression of markers LAG3, TIM3, OX40, FOXP3, CTLA4 and TIGIT was both higher and more highly correlated than in the PD-L1 low group. Within the *PD-L1*-low category, *IDO1* and *TIM3* have relatively high expression and are highly correlated with each other (R=0.72, p=3.85x10^-10). **Conclusion:** *PD-L1* is a primary driver of immune suppression, however when *PD-L1* is low there may be some differential role for *IDO* or *TIM3*. Combination IDOi and Tim3i should be considered in *PD-L1* low patients.

P3.04-16 A SEVEN-GENE EXPRESSION SIGNATURE REVEALS UNIQUE IMMUNE-PHENOTYPES RELATED TO MAJOR ONCOGENIC-DRIVERS IN NSCLC

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Background: In oncogenic-driven non-small cell lung cancer (NSCLC), programmed death ligand 1 (PD-L1) expression is the result of a constitutive oncogenic activation leading to an immunosuppressive microenvironment. However, the relationship between the major driver mutations (KRAS, EGFR and ALK) and PD-L1 and other immune markers remains unclear. Gene expression signatures incorporating not only PD-L1 but also other components of the stroma might better capture the immune-context of these oncogenic subgroups. **Method:** A 7-gene 'immune signature' comprising *CD4, CD8, PD-1, PD-L1*, *IFNG*, *GZMM* and *FOXP3* was included in a customized nCounter panel (NanoString Technologies), used in our clinical institution on a routine basis and designed to simultaneously screen for gene fusion drivers (*ALK*, *ROS1*, *RET* and *NTRK1),* MET overexpression and *MET* exon 14-skipping mutations in formalin-fixed paraffin embedded (FFPE) samples. A total of 296 advanced NSCLC patients from two different institutions were analyzed by the panel. Among them, 115 patients (38.9%) were also submitted to next-generation sequencing (NGS, Ion Torrent PGM® or GeneReader) . Analyses of variance (ANOVA) were used to describe statistical significance between immune response genes in the two major oncogenic groups: *KRAS* mutant (n=33) and*ALK* rearranged (n=44), compared to wild-type (WT) tumor samples (n=38). **Result:** Oncogenic genes (*ALK, KRAS*) were mutually exclusive. The analysis of the 7-gene signature revealed distinct expression patterns in the oncogenic biomarker groups. A significantly higher mRNA expression of CD4 and PD-L1 was found in ALK rearranged tumors compared to the KRAS mutant, and WT groups (p=0.0014 and p=0.0467, respectively). In addition, a trend was observed between GZMM mRNA levels and the oncogenic groups (p= 0.0665) whereas no association was found with the other immune genes (CD8, PD-1, IFNG, FOXP3). There was a significant linear correlation between CD4 and PD-L1 in ALK positive patients (p= 0.0214), but not in KRAS mutant samples (p= 0. 112). Unsupervised clustering across mRNA expression data from 296 samples using 7-immune-related genes showed two clusters, high expression for ALK-rearranged patients and low expression for KRAS mutant patients. The correlation between each of the immune genes was performed and a high correlation was found between PD-1 and FOXP3 (r=0.9) and PD-1 with GZMM (r=0.8). **Conclusion:** NSCLC tumors with *ALK* alterations show a distinct CD4 and PD-L1 immune profile when compared to KRAS and WT samples.

Keywords: nCounter, PD-L1, Immune genes

P3.04-17 COST-EFFECTIVENESS OF ATEZOLIZUMAB FOR PREVIOUSLY TREATED ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) IN CANADA

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Background: Atezolizumab is a humanized monoclonal antibody targeting PD-L1 that enhances tumour-specific T-lymphocyte responses. The efficacy and safety of atezolizumab versus docetaxel was demonstrated in patients with advanced NSCLC previously treated with chemotherapy in the phase III OAK trial (NCT02008227). Here, we report the cost-effectiveness in Canada of atezolizumab compared with docetaxel and nivolumab in previously-treated advanced NSCLC. **Method:** A cost-utility analysis was performed to estimate the cost per quality-adjusted life-year (QALY) associated with atezolizumab treatment compared to docetaxel and nivolumab in previously-treated advanced NSCLC. A three-state partitioned-survival model was developed, and the target population reflected patients in the OAK study. The analysis was conducted using a 10-year time horizon from the perspective of the Canadian publicly-funded healthcare system. Treatment efficacy was informed by the OAK trial (data cut-off date of January 23, 2017), with crossover adjustment. Overall survival (OS), progression-free survival (PFS), and time to treatment discontinuation (TTD) for atezolizumab were estimated by parametric extrapolation of Kaplan-Meier (KM) data from OAK. For OS, a cure modelling approach was used with an assumed cure fraction of 1% for atezolizumab to represent long-term survivorship as seen with cancer immunotherapy. OS, PFS and TTD for docetaxel and nivolumab were estimated through network meta-analysis of randomized controlled trials. A discount rate of 1.5% was applied in the base case to costs and effects. Costs considered in the analysis included treatments and administration, supportive care, adverse events management, subsequent treatments, and terminal care. Most costs were obtained from publicly-available sources. Health-related quality of life was estimated using EQ-5D-3L data from OAK. All analyses were performed probabilistically, and several scenario analyses were performed to assess the robustness of results. **Result:** The base-case incremental cost per QALY for atezolizumab versus docetaxel was $142,074 (2017 CAD). Atezolizumab resulted in more QALYs and less costs compared to nivolumab; however, differences were small. Docetaxel had the highest probability of being cost effective at a willingness-to-pay (WTP) threshold below $125,000/QALY; the probability that atezolizumab was cost effective approached 40% at WTP thresholds beyond $125,000/QALY. Results were generally consistent in scenario analyses. **Conclusion:** The ICER of atezolizumab vs. docetaxel used as second-line treatment for advanced NSCLC was $142,074/QALY. Atezolizumab dominated nivolumab; however, differences were small. The results of our analysis, as well as the added convenience of a fixed-dose regimen administered every three weeks, support the use of atezolizumab for patients in Canada with advanced NSCLC after progression on chemotherapy.

Keywords: NSCLC, Immunotherapy, Cost-effectiveness

P3.04-18 THE EFFICACY AND SAFETY OF SOLID TUMORS COMBINATION THERAPY WITH IMMUNE CHECKPOINT INHIBITOR: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The value of combination therapy with immune checkpoint inhibitor (ICI) for patients with solid tumors remains unclear. We conducted a meta-analysis to evaluated the combination therapy with immune checkpoint inhibitor (ICI) for patients with solid tumors. **Method:** Pub-med, EMBASE, Cochrane Library and ClinicalTrials.gov website were searched for eligible randomized controlled trails (RCTs). The selection criteria were defined according to the PICOS (population, intervention, comparison, outcome and study design) framework. We assessed overall response rate (ORR), progression free survival (PFS), overall survival (OS) and grade 3 or 4 adverse effects (AEs). Pooled hazard ratio (HR) for survival outcomes (PFS and OS) and pooled risk ratio (RR) for dichotomous data (ORR and AEs) with 95% CI were calculated. **Result:** 17 RCTs with 6,616 patients were included in this meta-analysis. The combination therapy of ICI was signifcantly associated with improvement of ORR (RR = 1.56 [95% CI 1.24, 1.96], P = 0.0001), PFS (HR = 0.69 [95% CI 0.59, 0.81], P < 0.00001) and OS (HR = 0.76 [95% CI 0.67, 0.87], P < 0.0001) in solid tumor. In subgroup analyses, combination ICI therapy obviously prolonged OS in melanoma patients (HR = 0.64 [95% CI 0.57, 0.72], p<0.00001), but not in SCLC (HR = 0.94 [95% CI 0.82, 1.08], P = 0.40) and NSCLC (HR = 0.92 [95% CI 0.79, 1.07], P = 0.26) patients. As for toxicity, there was an increased risk of fatigue, rash, diarrhoea and increased transaminases with combination ICI therapy. **Conclusion:** In conclusion, our meta-analysis found that combination ICI therapy showed significant benefits in ORR, PFS and OS for patients with solid tumors. Both of combination of ICI with chemoradiotherapy and dual ICI were effective and relatively safe. Melanoma patients got definite survival benefit from combinaiton ICI therapy. There was also a tendency of improvement of survival for SCLC and NSCLC patients.

Keywords: chemoraidotherapy, immune checkpoint inhibitor, combination therapy

P3.04-19 DO ADVANCED LUNG CANCER PATIENTS DERIVE SIMILAR SURVIVAL BENEFITS FROM IMMUNOTHERAPY? A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Checkpoint inhibitors targeting the programmed death-1 (PD-1)/PD-ligand 1 (L1) pathway have become a standard treatment in advanced non-small cell lung cancer (NSCLC) in the first and second line setting. Yet, subgroup analyses from randomized trials have shown inconsistent results regarding survival benefit in elderly patients (> 65 years old), never-smokers and patients with PD-L1 (-) expressing tumors (<1%). We conducted a systematic review and meta-analysis to assess the efficacy of checkpoint inhibitors in these pre-defined subgroups of patients. **Method:** The electronic databases PubMed and EMBASE, were searched for relevant randomized trials between January 2005 and December 2017. Pooled hazard ratios (HR) for overall survival (OS) and progression free survival (PFS) were meta-analyzed using the generic inverse variance method. To account for between-studies heterogeneity, random-effect models were used to compute pooled estimates. Subgroup analyses compared patients treated in the first versus second line setting. **Result:** Seven studies were included. Compared to chemotherapy, a significant reduction in the risk of death was seen with the use of checkpoint inhibitors in the second line independent of PD-L1 expression (4 studies, 2,364 participants, HR=0.79, 95%CI 0.66-0.96 and HR=0.66, 95%CI 0.57-0.78 in PD-L1 (–) and (+) patients respectively). Yet, a PFS benefit was only seen in patients with PD-L1 (+) tumors (2 studies, 852 participants, HR=0.69, 95%CI 0.55-0.88). Similarly, an OS benefit was seen in patients independent of age (5 studies, 3,651 participants, HR=0.77, 95%CI 0.64-0.92 and HR=0.75, 95%CI 0.6-0.94 in elderly and non-elderly patients respectively). Conversely, an OS benefit was only seen in ever-smokers (5 studies, 2,905 participants, HR=0.76, 95%CI 0.63-0.92 in ever-smokers and HR=0.83, 95%CI 0.64-1.08 in never-smokers) and a detrimental effect on PFS in never-smokers (3 studies, 1,426 participants, HR=1.68, 95%CI 1.07-2.63). In subgroup analyses, with the use of checkpoint inhibitors, elderly patients derived an OS benefit only in the second line setting (HR=0.69, 95%CI 0.59-0.81). Furthermore, never-smokers had no OS benefit in the first or second line (HR=1.02, 95%CI 0.54-1.93 and HR=0.79, 95%CI 0.59-1.07 respectively) and worse PFS particularly in the first line (HR=2.3, 95%CI 1.23-4.3). **Conclusion:** In the second line setting, patients with advanced NSCLC derive a survival benefit from checkpoint inhibitors independent of tumor PD-L1 expression and age. However, never-smokers do not benefit from these drugs particularly in the first line. Caution should be exercised when offering checkpoint inhibitors to elderly patients with advanced NSCLC in the first line and further research is needed to define their role in never-smokers.

Keywords: Systematic review, Checkpoint inhibitors, survival benefit

P3.04-20 CORRELATION OF IMMUNE-RELATED ADVERSE EVENTS AND RESPONSE FROM IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH ADVANCED NSCLC

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Background: Immune checkpoint inhibitors (ICIs) are associated with a unique set of toxicities termed immune-related adverse events (irAEs). The association between response to ICI therapy and development of irAEs has been documented in various cancer types. **Method:** Stage IV non-small cell lung cancer (NSCLC) patients treated with ICIs at the Princess Margaret Cancer Centre between 2013 and 2016 were followed for treatment response, treatment duration, survival, and toxicity. The relationship between treatment outcomes and occurrence of irAEs was examined. **Result:** A total of 97 advanced NSCLC patients were followed. Most patients (81%) received anti-PD-1 agents, 17% received anti-PD-L1 agents, and 2% received combination anti-PD-L1 plus anti-CTLA-4 therapy. Median follow up for the cohort was 5.1 months (0.3-38.1 months) from treatment start. Demographic and tumour characteristics were balanced between the groups. IrAEs occurred in half of patients (51%) on ICIs and grade≥3 irAEs in 7%. The most commonly observed irAEs were arthralgia (13%), diarrhea/colitis (12%), and skin rash (11%). Discontinuation of treatment due to irAEs occurred in 10% of patients, half of whom experienced grade≥3 irAEs. The overall response rate to ICIs was 23%, with the majority occurring by week 8 of treatment (16/22). Response was non-evaluable in one patient and this was excluded from response analysis. Patients with grade≥3 irAEs were more likely to have response to treatment compared to those with grade I/II irAEs and no irAEs (67% vs 17% vs 23%, p=0.035), Table 1. Smoking status was not associated with response rate or frequency of irAEs. Median survival was not reached in those with grade≥3 irAEs, 15.7 months in those with grade I/II irAEs, and 7.4 months in those with no irAE (p=0.16). Duration of treatment did not differ significantly among the groups.

Table 1. Relationship between Immune-Related Adverse Events (irAE) and Response to Treatment

	All Patients N (%)	Progression or Stable Disease N (%)	Partial Response N (%)	p-value
irAE				
Total	96 (100)	74 (77)	22 (23)	
None	48 (50)	37 (77)	11 (23)	
Grade 1/2	42 (44)	35 (83)	7 (17)	0.035
Grade ≥3	6 (6)	2 (33)	4 (67)	

Conclusion: The occurrence of grade≥3 irAEs may be associated with treatment response in advanced NSCLC patients undergoing ICI therapy.

Keywords: immune related Adverse event, immune checkpoint inhibitor, lung cancer

P3.04-21 ANTIBIOTICS ATTENUATE THE CLINICAL BENEFIT OF ANTI-PD-(L)1 IMMUNOTHERAPIES IN CHINESE PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Immune checkpoint inhibitors (ICIs) targeting PD-(L)1 have shifted the treatment paradigm of advanced non-small cell lung cancer (NSCLC), but responses are often heterogeneous and temporary. Several landmark publications have confirmed the dominant role of gut microbiome in modulating tumor responses to ICIs, suggesting the predictive value of antibiotics (ATB) in patients treated with anti-PD-(L)1 antibody. However, more evidence is needed to comprehensively reveal the association between ATB usage and ICIs therapeutic response in NSCLC, especially in Chinese populations. **Method:** We retrospectively reviewed the medical records of patients with advanced/metastatic NSCLC received anti-PD-(L)1 based therapies at our hospital. Detailed clinicopathologic characteristics, response data and ATB usage were collected for all patients. The patients receiving ATB within one month around the first administration of ICIs (defined as ATB-treated) were compared to those without (ATB-untreated). **Result:** 109 cases receiving anti-PD-(L)1 based therapies and underwent response evaluation were identified. 65 (59.3%) of them received monotherapy and 44 received combination therapies including anti-PD-(L)1 plus anti-angiogenesis/chemotherapy. 35 (32.1%) patients had been prescribed ATB 60 days before or during the course of ICIs treatment, and 20 (18.3%) were categorized as ATB-treated group. The most commonly administered ATB were β-lactam inhibitors, fluoroquinolones and macrolides. No major statistical differences in baseline clinicopathologic features were observed between ATB-treated and -untreated groups. The objective response rates (ORR) to ICIs in two groups were 65% and 82%, respectively. ATB treatment was significantly associated with shorter progression-free survival (PFS) (median 3.73 vs 9.3 m, $p<0.001$), and also tended to be associated with primary disease progression (35% vs 18%, $p=0.087$). The overall survival (OS) (median 31.9 vs 37.6 m, p=0.74) was similar in two groups, but ATB appeared to be related to decreased duration of survival from ICI treatment start to death (median 6.07 vs 26.9 m, p=0.002). In multivariable analysis, ATB treatment was markedly associated with poorer ORR and survival to ICIs after adjusting for prior line treatment setting, ICI regimens, numbers of ICI-related toxicity and clinical characteristics. **Conclusion:** ATB usage was a predictor for decreased clinical benefit from anti-PD-(L)1immunotherapies in Chinese NSCLC patients. More comprehensive understanding of the interaction between gut microbiome and ATB is still in urgent need. Furthermore, modulating ATB-related gut microbiome dysbiosis may enhance response to anti-PD-(L)1 immunotherapies.

Keywords: Antibiotics, non-small cell lung cancer, anti-PD(L1) immunotherapy

P3.04-22 RESPONSE OF BRAIN METASTASES IN PATIENTS WITH NON-SMALL CELL LUNG CANCER TREATED WITH IMMUNOTHERAPY AND BRAIN DIRECTED RADIOTHERAPY

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Background: The phase III trials of nivolumab, pembrolizumab or atezolizumab in comparison to standard chemotherapy for advanced non-small cell lung cancer (NSCLC) included a small number of patients with brain metastases. The aim of this study was to evaluate the radiological features of brain metastases after treatment with radiotherapy (RT) and immunotherapy (IT) in combination, as IT may synergize with RT. **Method:** We retrospectively reviewed the clinical data and radiological findings from 27 patients with NSCLC receiving IT (nivolumab or pembrolizumab) and RT of brain metastases from June 2015 until August 2017 at the University Hospital of Zürich. Response to RT was assessed with magnetic resonance imaging in all patients and in case of non-unequivocal findings with 18F-Fluorethyltyrosin PET (FET-PET) in 6 patients. **Result:** A total of 33 treatments with RT were applied (22 patients received one treatment, 4 patients 2, and 1 patient 3 treatments) of which 16 consisted of radiosurgery, 7 of hypofractionated stereotactic radiotherapy and 10 of whole brain radiotherapy. 23(85.2%) patients received nivolumab and 4 (11.1%) pembrolizumab. RT was performed in 36% of the cases (12 out of 33) during IT, in 61% (20 out of 33) before, and 3% (1 out of 33) after IT. In cases where RT was performed before, the median time to IT was 6.5 months. 22 (81.5%) patients had an adenocarcinoma and 5(18.5%) sqamous cell histology. Response of brain metastases was assessed after completion of treatment: in 6 out of 33 treatments (18.2%) a complete response was achieved, in 14 (42.4%) a partial response, in 2(6.1%) a mixed response, in 2 patients (6.1%) a progression of disease and in 4 (12.1%) a pseudoprogression was observed. FET-PET was performed when pseudoprogression was suspected (6 patients) and perfusion curves helped differentiating between pseudoprogression (4 out of 6 patients) and true progression (2 out of 6 patients). Median overall survival was 17.8 months (95%CI: 2.9-32.6). **Conclusion:** Peudoprogression of brain metastases, defined as initial enlargement of tumor lesions and then decrease in size, should be considered in patients treated with immunotherapy and radiotherapy of brain metastases from NSCLC. Dynamic FET-PET patterns may help differentiating pseudoprogression and true progression. In cases of pseudoprogression, immunotherapy can be safely continued without additional interventions on brain metastases.

Keywords: Immunotherapy, pseudoprogression, brain metastases

P3.04-23 PHASE 1B/2 STUDY TO EVALUATE NOVEL COMBINATIONS WITH OLECLUMAB (MEDI9447) IN PREVIOUSLY TREATED ADVANCED EGFRM NSCLC

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Background: Patients with mutant EGFR (EGFRm) non–small cell lung cancer (NSCLC) have a limited chance of benefiting from treatment with programmed death-1 inhibitors. EGFR activation leads to overexpression of CD73 and may provide a mechanism of immune evasion. CD73 overexpression has also led to worse outcomes in multiple tumor types, including NSCLC. Recent studies demonstrated that an orthogonal therapeutic approach to cancer, such as combining tyrosine kinase inhibitors (TKIs) with immunotherapy, may result in synergistic clinical activity. Oleclumab is a human monoclonal antibody (mAb) that selectively binds to CD73 and inhibits the enzymatic production of adenosine. Adenosine exerts its immunosuppressive effects on various immune cells via the adenosine 2A receptor (A_2AR). AZD4635 is a potent, selective A_2AR antagonist that inhibits this signaling pathway. Osimertinib is a potent and selective inhibitor of EGFRm, including the T790M resistance mutation. We hypothesize that novel combinations of targeted and immunotherapeutic agents targeting the adenosine pathway will be well tolerated and lead to increased antitumor activity in subjects with EGFRm NSCLC. **Method:** This is a multi-arm, open-label, multicenter, phase 1b/2 study (NCT03381274) consisting of 2 parts. In Part 1, the safety and tolerability of oleclumab in combination with either osimertinib (Arm A) or AZD4635 (Arm B) will be evaluated, and a recommended phase 2 dose for each combination will be identified. In Part 2, the safety, tolerability, and preliminary antitumor activity will be evaluated. In both parts, patients will be allocated to treatment arms based upon their EGFRm status and their prior therapy. For Part 2, the primary objective of antitumor activity will be assessed by objective response according to RECIST v1.1. Key secondary objectives include additional evaluation of clinical activity, the pharmacokinetic profiles of oleclumab, osimertinib, and AZD4635, and the evaluation of oleclumab immunogenicity. Additional treatment arms may be added as the study progresses. The study is open for enrollment and recruitment is ongoing, with a planned enrollment of up to approximately 98 patients. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: adenosine, CD73, EGFR mutant

P3.04-24 EMPOWER-LUNG 2: CEMIPLIMAB AND IPILIMUMAB 4 CHEMOTHERAPY VS PEMBROLIZUMAB IN ADVANCED NSCLC WITH PD-L1 ≥50%, A PHASE 3 STUDY

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Background: Immune checkpoint inhibitors have shown clinical activity in multiple tumor types, including NSCLC, which accounts for 80–85% of all lung cancers. Median progression-free survival (PFS) with platinum-based doublet chemotherapy ranges from 2.7–6.4 months. Cemiplimab (REGN2810), a human monoclonal antibody to PD-1, has exhibited antitumor activity and safety in a phase 1 trial of advanced malignancies including NSCLC. Recognizing that NSCLC tumors express PD-L1, combining cemiplimab with other immunotherapies and/or chemotherapy has the potential for a synergistic effect in patients with advanced NSCLC **Method:** EMPOWER-lung 2 (16111) is a randomized (1:1:1), open-label, global, phase 3 study on the efficacy and safety of combinations of cemiplimab, ipilimumab, and platinum-based doublet chemotherapy vs pembrolizumab monotherapy in the firstline treatment of patients with stage IIIB or stage IV squamous or non-squamous NSCLC with tumors expressing PD-L1 ≥50% (EudraCT 2017-001041-27). Patients who have received prior systemic treatment for their advanced disease will be excluded. Patients will be stratified by histology and randomized into three study arms: Arm A: standard of care pembrolizumab monotherapy for 108 weeks; Arm B: cemiplimab every 3 weeks (Q3W) for up to 108 weeks plus ipilimumab 50mg every 6 weeks (Q6W) (4 doses); Arm C: cemiplimab Q3W for up to 108 weeks plus platinumdoublet Q3W (2 doses) and ipilimumab 50mg Q6W (4 doses). The primary objective is to evaluate PFS. Key secondary objectives include overall survival and overall response rates. Assuming a median PFS of 10 months for patients treated with pembrolizumab monotherapy and a median PFS of 15 months for patients treated with each of the cemiplimab combination therapies, 585 patients are needed to obtain sufficient PFS events for the analysis of PFS with 90% power to detect statistical significance for each of cemiplimab combination vs pembrolizumab monotherapy comparison. This study is open for enrollment with the first patient's first visit planned for Q2 2018 and last patient's last visit planned for Q1 2023. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: cemiplimab, Anti-PD-1, REGN2810

P3.04-25 EMPOWER-LUNG 3: A PHASE 3 STUDY OF CEMIPLIMAB, IPILIMUMAB AND CHEMOTHERAPY IN ADVANCED NSCLC WITH PD-L1 <50%

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Background: Immune checkpoint inhibitors have shown activity in NSCLC, but the benefit is mostly seen in patients with tumor proportion score (TPS) ≥50%. Patients with TPS <50% will likely require a combination therapy approach. Cemiplimab (REGN2810), a human monoclonal antibody to PD-1, has exhibited antitumor activity and safety in a phase 1 trial of advanced malignancies including NSCLC. Based on their unique modes of action, combining cemiplimab with ipilimumab, an antiCTLA4, and modified platinumbased chemotherapy has the potential for a synergistic effect in patients with advanced NSCLC with PD-L1 <50%. **Method:** EMPOWER-lung 3 (16113) is a randomized (1:1:1), open-label, global, phase 3 study of the efficacy and safety of combinations of cemiplimab, ipilimumab, and platinum-based doublet chemotherapy in the first-line treatment of patients with advanced or metastatic NSCLC with tumors expressing PD-L1 <50% (NCT03409614). Patients will be stratified by histology and PD-L1 expression level (<1% vs 1–24% vs 25–49%). Treatment arms: Arm A: standard of care platinumbased doublet chemotherapy every 3 weeks (Q3W) for 4–6 cycles; Arm B: cemiplimab Q3W (up to 108 weeks) plus standard of care platinum-based doublet chemotherapy Q3W for 4–6 cycles; Arm C: cemiplimab Q3W (up to 108 weeks) plus standard of care platinum-based doublet chemotherapy Q3W for two cycles and ipilimumab 50 mg every 6 weeks (up to 4 doses). The primary objective is to evaluate progression-free survival (PFS). Key secondary objectives include overall survival and overall response rate. A total of 690 patients are planned. This assumes a median PFS of 6 months for patients treated with chemotherapy alone and 10 months for patients treated with each of the cemiplimab combination therapies, corresponding to a 66.7% increase in median PFS and a hazard ratio of 0.6. Under these assumptions, the planned enrollment will generate sufficient PFS events for analysis of PFS with 90% power to detect a statistical significant difference for each of cemiplimab combination vs standard of care platinum-based doublet chemotherapy comparison. Enrollment has begun for this study. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Anti-PD-1, cemiplimab, REGN2810

P3.04-26 EMPOWER-LUNG 4: A PHASE 2 STUDY OF CEMIPLIMAB PLUS IPILIMUMAB IN THE SECOND-LINE TREATMENT OF ADVANCED NSCLC WITH PD-L1 <50%

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Background: Immunotherapies have been investigated as potential therapeutic approaches to improve survival and quality of life in patients with advanced NSCLC. With monotherapy PD-1 blockade, the greatest benefit was seen in patients with tumor proportion score (TPS) of PD-L1 immunoreactivity of ≥50%. Patients with TPS <50% will likely require a combination approach. Cemiplimab (REGN2810), a human monoclonal antibody to PD-1, has exhibited antitumor activity and safety in a phase 1 trial of advanced malignancies including NSCLC. Combination of cemiplimab with other therapies may improve overall response rate (ORR) in patients with advanced NSCLC whose tumor have TPS <50%. **Method:** EMPOWER-lung 4 (1763) is a randomized (1:1:1), open-label, global, phase 2 trial of the efficacy and safety of high-dose (HD) vs standard-dose (SD) cemiplimab in combination with ipilimumab vs SD cemiplimab in the second-line treatment of patients ≥18 years old with advanced NSCLC with tumors expressing PD-L1 <50% (NCT03430063). Patients will be stratified by histology and PD-L1 expression level (<1% vs 1–49%), and randomized to Arm A: SD cemiplimab every 3 weeks (Q3W); Arm B: SD cemiplimab Q3W in combination ipilimumab 50 mg every 6 weeks (up to 4 doses); or Arm C: HD cemiplimab Q3W. Patients will receive cemiplimab for up to 108 weeks or until progression. The primary objective is to evaluate ORR (complete response + partial response) based on RECIST v1.1 assessed by blinded independent review committee. Key secondary objectives include the assessment of overall survival, progression-free survival, and safety/tolerability of the study drugs. Assuming an ORR of 10% in Arm A and 30% in each of Arm B and Arm C, 201 patients (67 per Arm) will yield an 80% power to detect a statistically significant difference for HD or SD cemiplimab in combination with ipilumimab vs SD cemiplimab. This study is open for enrollment with the first patient's first visit planned for Q2 2018 and the last patient's last visit planned for Q4 2021. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Anti-PD-1, cemiplimab, REGN2810

P3.04-27 AN ALLOGENEIC TUMOR CELL LYSATE VACCINE INDUCES IMMUNE RESPONSES TO LUNG CANCER ASSOCIATED ANTIGENS: PRELIMINARY RESULTS OF A PHASE II STUDY

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Background: Whereas lung cancers often express cancer-germline (CG) protein as well as onco-fetal carbohydrate antigens, immune responses to these antigens are limited in lung cancer patients. This trial was performed to examine if a tumor cell lysate vaccine could induce broad immunity to CG and oncofetal antigens, and to ascertain if metronomic cyclophosphamide and celecoxib (cy/cel) enhances vaccine-induced immune responses. **Method:** Freeze-thaw lysates were prepared from H1299 lung cancer cells exhibiting high level CG and oncofetal antigen expression. 11 patients with primary thoracic malignancies (6 NSCLC, 2 SCLC, 2 esophageal cancer, 1 thymoma; median age = 61 y) and 10 patients with extrathoracic neoplasms metastatic to the chest (8 sarcoma, 1 melanoma, 1 RCC; median age = 36 y) rendered NED by conventional therapy were randomized to receive lysate (10 mg protein/vaccine) with Iscomatrix™ adjuvant via deep intradermal injection q

month x 6 with or without daily oral metronomic cy/cel. The primary endpoint was serologic response to a panel of purified CG as well as carbohydrate antigens assessed in a blinded manner by ELISA or glycan array techniques, respectively, 1 month after the 6th vaccination. Immune subsets were assessed in peripheral blood (p-values uncorrected for multiple comparisons). Standard of care imaging studies were obtained at baseline and 1 month after the 3rd and 6th vaccinations unless otherwise clinically indicated. **Result:** All patients exhibited local inflammatory responses and flu-like symptoms lasting 72-96 hours following vaccinations. There were no dose limiting treatment related toxicities. 14 patients (67%) completed all six vaccinations; 7 patients were removed from study early due to disease recurrence. 8 of 14 patients (4: vaccine alone and 4: vaccine and cy/cel; 57%) exhibited serologic responses to NY-ESO-1. One patient developed antibodies to GAGE7; several patients exhibited reactivity to XAGE and MAGE-C2. Additional serologic responses were observed against Muc1, Muc1Tn, and LSTc. Vaccine therapy decreased percent Tregs (p=0.067), PD-1 expression on Tregs (p=0.023), PD-L1 expression on $CD14^+$ monocytes (p=0.0089), PD-L1 expression on classical monocytes (p=0.0159), and PD-L1 expression on intermediate monocytes (p= 0.0031). Cy/cel did not increase immune responses or enhance vaccine-induced alterations in peripheral immune subsets. **Conclusion: :** H1299 lysate vaccines with Iscomatrix™ induce immune responses to CG and oncofetal antigens commonly expressed in lung cancers, and modulate peripheral immune subsets in a manner that may enhance antitumor immunity. These findings support further evaluation of the vaccine in combination with epigenetic agents and immune checkpoint inhibitors for lung cancer therapy.

Keywords: Tumor Cell Lysate Vaccine, phase II study

P3.04 IMMUNOONCOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.04-28 CAN IPILIMUMAB RESTORE IMMUNE RESPONSE IN ADVANCED NSCLC AFTER PROGRESSION ON ANTI PD1/PDL1 AGENTS?

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Background: Anti PD1/PDL1 agents play a crucial part in the treatment of NSCLC demonstrating improved overall response rate (ORR) and overall survival. While anti CTLA4 alone did not show significant single agent activity, a phase 1 study evaluating the combination with anti PD1 suggests improved ORR. Evidence is scarce regarding subsequent treatment with immune checkpoint inhibitors (ICI) after progression on anti PD1/PDL1. A recent study in melanoma patients reported lack of benefit from the addition of Ipilimumab after progression on anti PD1. **Method:** All off-label Ipilimumab administrations in a single tertiary center were retrieved through the institutional review board records. 21 patients with advanced NSCLC were allocated during 2017. Clinical data were retrieved retrospectively. Disease control was define as partial response (PR) or stable disease (SD).

Result: Of 21 patients who were treated with a combination of anti PD1 agent and Ipilimumab, in 15 Ipilimumab was initiated after confirmed progression on anti PD1/PDL1 alone. Patients' characteristics are described in table 1. The overall disease control rate was 33.3% (n-5); 3 patients with PR and 2 patients with SD, 3 of them had previously responded to anti PD1. Immune related AE rate was 40% (n-6); 2 patients had grade 3 AE and one patient died of pneumonitis. While the median time to progression was 2 months, 4 of the 5 responding patients are still stable after median 4 months follow up (range 1-15).

Table 1 - Patients' characteristics

	N-15 (%)	
Sex	**M-15, F-0**	
Median age (range)	67 (53-87)	
Histology	Adenocarcinoma	12 (80%)
	Squamous	1 (6.7%)
	Adenosquamous	1 (6.7%)
	NSCLC-NOS	**1 (6.7%)**
PD-L1 expression	>50%	2 (13.3%)
	1-50%	4 (26.7%)
	<1%	2 (13.3%)
	Unknown	**7 (46.7%)**
Line of Tx with anti PD1/PDL1	1st	2 (13.3%)
	2nd	12 (80%)
	3rd	**1 (6.7%)**
Best response to anti PD1/PDL1	**PR**	5 (33.3%)
	SD	2 (13.3%)
	PD	**8 (53.4%)**
Median time to progression on anti PD1 (range)	**9 mon. (6-17)**	

Conclusion: This small retrospective cohort suggests Ipilimumab might re-boost immune response in patients with advanced NSCLC progressing on anti PD1 therapy, while delaying exposure to the higher rates of AE associated with upfront combination therapy. This strategy should be explored prospectively.

Keywords: combination immunotherapy, NSCLC

P3.04 IMMUNOONCOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.04-29 EFFICACY OF RE-TREATMENT WITH IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH PRETREATED ADVANCED NON-SMALL CELL LUNG CARCINOMA

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Background: The majority of NSCLC patients treated with immune-checkpoint inhibitors (ICI) develop acquired resistance. Conventional cytotoxic chemotherapy remains the treatment of choice for those patients. There are case reports on re-administration of ICIs for advanced NSCLC; however, these case series are difficult to draw definitive conclusions. We therefore retrospectively reviewed the efficacy of retreatment with ICI in our hospital. **Method:** Patients with pathologically confirmed advanced NSCLC who were treated with ICI in Kindai University hospital were retrospectively reviewed from December 2015 to July 2017. Among 212 NSCLC patients treated with ICIs, 10 patients (4.7 %) were retreated with ICI. **Result:** Number of patients treated with Nivolumab, Pembrolizumab and Atezolizumab were four, five and one, respectively. The best response of initial treatment with ICIs among 10 patients were five partial response (PR), two stable disease (SD) and three progressive disease (PD). Whereas, three patients (30%) showed SD and the others (70%) had PD to ICI retreatment. No severe adverse events attributable to the ICIs were noted. **Conclusion:** In the limited number of retrospective study, we could not find good responders for retreatment with ICIs. Best

overall response during the previous treatment period is not related to the efficacy of retreatment with ICIs. At present, former responder to ICI therapy may not be the proper candidate for ICI re-challenge treatment strategy. Further biomarker analysis and treatment strategy is warranted for the patients and physicians to retreat with ICIs.

Keywords: Retreatment, non small cell lung cancer, immune checkpoint inhibitor

P3.07 NURSING AND ALLIED PROFESSIONALS
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.07-01 TELEPHONE PREASSESSMENT CLINIC INCORPORATING HOLISTIC NEEDS

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Background: Approximately 44,000 people are diagnosed with Lung Cancer in the United Kingdom (CRUK,2012). In Liverpool we serve a population of 330,00. As health care providers we constantly look to new models of care to aid earlier diagnosis . Introduction of a new referral system into the diagnostic service at our hospital including: pre planned investigations prior to first outpatient appointment, it was identified that some pre planned investigations were inappropriate for some patients due to unknown performance status and co-morbidities. There was an increase in patients failing to attend outpatient appointments. The Lung CNS team looked provide intervention to provide patients with early access to key worker support with the aim of enhancing and reducing the lung cancer pathway **Method:** In 2016 a pre assessment proforma was developed. CT scan reports and referrals are assessed by Lead Lung Physician and appropriate referrals fowarded to Lung CNS . Lung CNS team contact patients via telephone and a pre assessment proforma completed. Patients informed of date of outpatient appointment need for investigations and explanation provided of what to expect. Holistic needs assessment undertaken to enable any concerns to be raised and allow early intervention by the specialist team with an aim of improving symptoms and performance status prior to commencing a treatmnt pathway. **Result:** Initial audit results looking at case studies, failure to attend rates and patient satisfaction met our objectives. There has been a reduction in failure of patients attending investigations; reduction in cancellation of prebooked investigations; provides early rapport between lung CNS and patient/carer with earlier recognition of symptoms and earlier access to urgent treatments; allows health education prior to first outpatient appointment including: smoking cessation; exercise and nutrition. **Conclusion:** This work has been an opportunity to demonstrate a positive impact on the patient pathway by streamling complexities in the pre diagnostic phase. Whilst it had a marked impact on the Lung CNS job plan it accomodates a growing demand on a constrained service. A revised job plan has been put in place for Lung CNS, there is improved communication and coordination between departments, importantly patients view this service positively.

Keywords: assessment, telephone, holistic

P3.07 NURSING AND ALLIED PROFESSIONALS
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.07-02 EXPECTATIONS, STANDARDS AND PERFORMANCE FRAMEWORK TO SUPPORT THE LUNG CANCER SUPPORT NURSE IN LUNG FOUNDATION AUSTRALIA

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Background: A project initiated by Lung Foundation Australia (LFA) in 2015 entitled, Nurse-Led Lung Cancer Support Service commenced with four key objectives and limited other structure. A Lung Cancer Support Nurse (LCSN) was appointed to implement the project. To succeed, the LCSN required role definition. Given the novelty of the LCSN role in LFA and the scarcity of practice guidelines relative to similar roles in other organisations, an Expectations, Standards and Performance Framework (the framework) was developed. The framework supports the LCSN role with a theoretically sound, contextually relevant, empirically informed, "living" document where activity is captured, evaluated and used to inform practice and improve consumer outcomes. **Method:** Key questions directed an extensive literature search: 1) What structural features are required in a practice framework to meet LCSN, consumer and organisation needs? 2) How might a framework function to meet these needs in a real time and ongoing manner? Ritchie and Spencer's (1994) concept of Framework, which dictates the use of a tool such as Excel spreadsheet, inspired the "physical" construction of this framework. The approach offers practical, analytical and visual utilities to the data corpus. Three dominant pillars within the framework represent LCSN practice expectations, standards and performance. Data entered relevant to these areas of practice directly relate to the four key objectives of the project and an additional six objectives, defined as the role has evolved due to increasing consumer demand. As descriptive data are entered into the framework, they are evaluated against key lung cancer nursing literature for appropriateness of scope and purpose of the role. As activity data are entered, they are evaluated against organisation, practitioner and consumer driven indicators to ensure needs are met and improvements made. **Result:** The framework is contextualised to the role and setting and in doing so is intricately linked to the business of the organisation, LCSN practice and consumer outcomes. The framework offers the organisation an infrastructure, benchmarking and service development document. The framework provides the LCSN an ability to create a work environment that supports excellence in all aspects of practice, including scope of practice and decision-making, and capabilities development. In collaboration with consumers, the framework defines clear expectations about the engagement required by the LCSN to meet needs and improve outcomes. **Conclusion:** The framework is an empowering tool for the LCSN, LFA leadership team and consumers. Its potential applicability to other roles and settings furthermore makes the framework a valuable body of work.

Keywords: lung cancer nurse role definition, lung cancer nurse practice development, practice framework

P3.07 NURSING AND ALLIED PROFESSIONALS
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.07-03 LUNG CANCER CLINICAL NURSE SPECIALIST & PALLIATIVE CARE NURSE SPECIALIST – A DUAL ROLE

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Background: The majority of Lung cancer diagnoses are advanced at presentation. There have been advances in treatment over the last 5 years, with new therapies developed enabling improved prognosis for palliative patients. In the UK, just 20% of Stage 4 NSCLC will survive to one year. (CRUK2018). At East Cheshire in 2017, 66.1% of patients were non-curative on diagnosis, of these 42% were referred directly to specialist palliative care (SPC). Ferrel et al (2015) reported significant improvements in QOL, symptoms, and reduced distress for palliative NSCLC patients. While El et al (2014) suggested that palliative care providers need to become front-line team members, who provide a high-quality service in order to facilitate early integration of palliative care. At East Cheshire NHS Trust, England, the Lung Cancer CNS has a dual role as Community SPC nurse. This ensures patients are supported from pre-diagnosis through treatment, living with and beyond, then onto end of life care with the same keyworker. **Method:** The Lung CNS is present in clinic pre-diagnosis and at MDT when management plans are formulated. Patients who are referred directly for SPC due to frailty or co-morbidities that exclude them from anti-cancer treatment are allocated a key worker/ CNS. The CNS is present when bad news is broken to the patient and carers. They co-ordinate all services required for the patient and arrange follow up: either hospital inpatient review, a further nurse-led clinic appointment or a home visit. The CNS will discuss and organise advanced care planning ensuring patient wishes are met. **Result:** This model of working has been evaluated with excellent feedback. Carer response has been very positive: a patient's wife said *"thank you for being there when we heard the bad news and for being there at end of life. Having one person who knew the journey throughout has been very reassuring."* Another patient's daughter stated *"having the guidance of the CNS from diagnosis to death, for my father was invaluable in ensuring his wishes were fulfilled."* The Commissioners of Quality Care (CQC) in January 2018 rated care at the end of life in the community as outstanding. **Conclusion:** The service at East Cheshire offers a novel model of working for patients and carers. The same key worker being present throughout has a positive impact on their lives. Further research is required to fully understand the impact of the role on the quality of life and especially on prognosis.

Keywords: Palliative, lung cancer, Nurse Specialist

P3.07-04 MASSAGE CHAIR ENCOUNTERS FAVORABLY IMPACT OUTPATIENT ONCOLOGY RN'S PERCEIVED LEVEL OF STRESS, BP, HR

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Background: Oncology nurses are likely to experience compassion fatigue and secondary stress syndrome related to supporting patients through rigorous therapies, especially those dealing with pain or end of life care. Health care organizations are focusing on creating and ensuring healthy work environments. .Massage chairs provide basic massage strokes and have benefits which include increased circulation, release of endorphins, and relaxation. Therefore, the purpose of this initiative is to determine the impact of self-initiated mechanical massage chair on physiological (blood pressure (BP) and heart rate (HR)) and emotional distress (perceived stress). **Method:** This ongoing quality improvement initiative is being conducted in an outpatient oncology cancer center at Rush University Medical Center. A secured room with badge access has the massage chair, sound machine and a refrigerator stocked with refreshments. This room was repurposed specifically for this initiative and creates a relaxing environment. For the 100 registered nurses (RN) working in the cancer center, a massage can be prescheduled using Outlook calendar or used spontaneously in response to a difficult work situation. The massage chair is available for 20 minute cycles and RNs self-record BP and HR using an Omron wrist automated cuff device and perceived level of stress using the Numeric Stress Scale (visual analog rating 0 -10). Descriptive statistics were used to assess RN characteristics, BP, HR, and perceived level of stress. Percent change was calculated to determine whether self-initiated mechanical massage impacts RNs BP, HR, and perceived level of stress pre-post massage chair encounter. **Result:** Of the 134 massage chair encounters, RNs were aged 38 ± 12.7 and working in outpatient oncology 9.2 ± 9.9 years. With respect to physiologic outcomes, there was a 7.1% decrease in systolic BP (122.2 ± 14.6 vs 113.5 ±12.4 mmHg), a 5.5% decrease in diastolic BP (72.5 ±10.0 vs 68.5 ± 9.9 mmHg), and a 4.0% decrease in HR (71.8 ±11.9 vs 68.9 ± 10.3 bpm). Notably, there was a 43.5% decrease in RNs perceived level of stress (4.6 vs 2.6). Of the massage chair encounters, 51% were pre-scheduled. **Conclusion:** These preliminary data suggest that providing RNs with a secured respite room and offering massages and refreshments has a favorable impact on decreasing perceived levels of stress, BP and HR. Currently, the number of massage chair encounters is similar for prescheduled and spontaneous use.

Keywords: Outpatient Oncology Nurse, Massage Chair, Perceived Stress

P3.07-05 CAN IMPROVING WORKING PARTNERSHIPS WITH PRIMARY CARE PREVENT AVOIDABLE EMERGENCY ADMISSIONS FOR PATIENTS WITH LUNG CANCER?

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Background: A literature search was performed. Primary Care Professionals (PCP's) and National Lung Cancer Forum for Nurses (NLCFN) members were surveyed. Patients with a known diagnosis of lung cancer and their carers were interviewed following emergency care admissions. Lung Cancer Nurse Specialists (LCNS) from 15 NHS Trusts/Health Boards (HB) throughout the United Kingdom participated in data collection between May and August 2017. **Method:** A literature search (CINAHL, Embase, Proquest, PubMed, Medline) was performed. 120 PCP's from 7 CCG's/HB were surveyed to ask how and why they would contact a LCNS; any difficulties experienced contacting a LCNS and what support the LCNS could provide. 86 (72%) responded. 27 patients and their carers from 5 NHS/HB who were admitted as an emergency with a symptom related to their lung cancer were interviewed by a LCNS. A questionnaire was sent to all NLCFN members, asking "What do you do in your current practice to help prevent avoidable emergency hospital attendances?" **Result:** There was no published literature specific to the project aim. 46 (53%) PCP's knew how to contact the LCNS, 24 (28%) did not and 16 (19%) were unaware the service existed. PCP's reported that the LCNS could improve communication and provide education and specialist advice to help reduce avoidable emergency admissions. Following review by the LCNS, 25 (92%) of emergency admissions were deemed necessary. 2 (8%) patients contacted 999, with the rest seeking advice from the LCNS, Acute Oncology Service or GP prior to admission. 282 NLCFN members were surveyed with 59 respondents. Findings highlighted wide variations in practice, although a number of common themes were evident. Proactive communication with patients and HCP's and timely referrals and signposting were key to identifying and addressing potential problems as early as possible. **Conclusion:** This small data sample suggests that patients were admitted appropriately. The NLCFN survey highlighted the role of the LCNS in providing expert specialist knowledge and advice to patients and Health Care Professionals throughout the patients journey. PCP's expressed that they would like to know more about the role of the LCNS and would value better means of communication, advice and specialist support to improve patient care.

Keywords: Avoidable Emergency Admissions, Working Partnerships, lung cancer

P3.07-06 RECEIVING A DIAGNOSIS OF MESOTHELIOMA (RADIO MESO): RECOMMENDATIONS FOR PRACTICE TO IMPROVE THE PATIENT EXPERIENCE

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Background: Communicating a diagnosis of mesothelioma is complex and highly skilled[1, 2]. If done badly, 'it can cause long lasting distress, confusion and resentment'[1]. Receiving A DIagnosis Of MESOthelioma (RADIO Meso) is a qualitative research project designed to identify ways to improve patient and family carer experience of receiving a mesothelioma diagnosis by generating evidence based recommendations for practice. This abstract provides an overview of the findings and a summary of recommendations. **Method:** The study utilised a descriptive qualitative approach. Individual telephone interviews were conducted with people who had experience of giving or receiving a diagnosis of mesothelioma. This included patients, family carers (N=16) and health care professionals (N=16). Two separate focus groups were also carried out with patients and carers (N=27) and mesothelioma nurse specialists (N=15). A national web-based consultation with staff and patients/ family carers was then undertaken. Interview recruitment and the consultation were conducted via electronic mailshots and social media run by Mesothelioma UK, the National Lung Cancer Forum for Nurses and British Thoracic Oncology Group. Interview data was collected between January and December 2017. Consultation data was collected between January and March 2018. Framework analysis methods were used[3]. **Result:** The findings provide an in-depth understanding of patient, family carer and staff experiences of receiving a mesothelioma diagnosis. A number of patient centred requirements to improve this experience were identified. These requirements form the basis of the recommendations developed and refined through consultation. The recommendations highlight the importance of providing consistency and continuity in terms of who the patient sees and what is said on the diagnostic journey. The recommendations also emphasise the value in health professions having the following: specialist knowledge and skills of both mesothelioma and communication, a patient-centred approach, a quiet and private environment to facilitate communication, sufficient time to address patient and family concerns, access to good quality information resources, and effective partnerships for timely referrals to specialist services. Participants indicated that the involvement of the Clinical Nurse Specialist enhanced diagnostic experience. **Conclusion:** The study provides unique insight into the mesothelioma diagnostic experience. The recommendations will be launched by Mesothelioma UK on 1st May 2018. These recommendations will help to inform health professional's decisions and practice regarding the communication of a mesothelioma diagnosis and improve patient experience. The goal is to make the patient feel like the most important person in the room, and at the centre of the communication process.

Keywords: diagnosis, recommendations, qualitative

P3.07-07 MULTIDISCIPLINARY SUPPORTIVE CARE ASSESSMENT IN LUNG CANCER – A CASE STUDY EXAMPLE

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Background: Although many patients report positively on their experience of cancer care, their Supportive Care (SC) needs may not be met for several reasons, including services not being universally available, poor recognition of needs and poor inter-professional communication (NICE, 2004). Guys and St Thomas' NHS Foundation Trust has a dedicated SC service for lung cancer patients consisting of specialist Dietetics, Occupational Therapy (OT), Physiotherapy (PT) and Speech and Language Therapy (SLT). Here we describe a complex case study requiring extensive multimodal SC interventions. **Method:** Patient X was a 46 year old female with adenocarcinoma of the left lung T4N3M1b diagnosed August 2017. She presented with shortness of breath, chest wall pain, dysphagia, dysphonia, anorexia and weight loss. She received 3 cycles of first line chemotherapy, 3 cycles of 2nd line Pembrolizumab and a single fraction of stereotactic radiotherapy for brain metastases. She died in January 2018. **Result:** On initial dietetic assessment the patient had lost 16.5% of her body weight over the previous 4 months. Dysphagia and anorexia resulted in her only managing puree textures and liquids resulting in a significant nutritional deficit. She received dietary counselling and oral nutritional supplements to optimise her intake and minimise further weight loss. She received PT and OT intervention for fatigue, reduced mobility, deconditioning and reduced occupational performance within the clinic, including education regarding strengthening exercises, fatigue and breathlessness management. She was referred on to community services to progress her rehabilitation and assess equipment needs within the home setting. SLT provided assessment and management of oropharyngeal dysphagia and dysphonia. She was supported to use a left head turn swallow strategy to reduce the risk of aspiration. In addition vocal hygiene advice and education was provided, aiming to prevent vocal strain. **Conclusion:** Patient X benefited from assessment and intervention by a range of SC therapists which may have prevented aspiration pneumonia, minimised her weight loss and increased her functional independence thus having a significant impact on her quality of life. In many centres access to SC services may result in a high appointment burden and non-specialist intervention. Providing these services as part of a one stop MDT clinic prevented additional appointments and ensured effective communication between the MDT, so that medical and supportive goals were aligned. It can be argued this should be gold standard care for all lung cancer patients. To support this argument more robust clinical outcomes and patient experience data needs to be collected.

Keywords: Multidisiplinary, hollistic, supportive

P3.07-08 PAIN MANAGEMENT IN LUNG CANCER

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Background: Lung cancer is one of the most prevalent cancers worldwide and pain is its most common symptom. Pain can be brought about by several causes including local invasion of chest structures, metastatic disease or can also be a consequence of treatment. An active multidisciplinary approach is required to manage pain in patients with lung cancer **Method:** It is a cross-sectional study of 166 patients with lung cancer. We used the BPI ``Brief pain inventory`` to assess pain prevalence, intensity and impact on quality of life. Adequacy of pain management was evaluated by the Pain Management Index (PMI) **Result:** We interwiewed 166 patients with bronchogenic carcinoma, 163 men and 3 women. 116 with adenocarcinoma and 50 with epidermoid carcinoma. 80 (42.2%) of our patients have pain. Among them, 7 report low pain and 73 moderate to severe pain (91%). 149 (89,7%) patients have metastasis. The association between the intensity of pain and metastasis was statisticly significant (p<0,001). 21 patients (26.2%) are treated with antalgic. 18 with the second level and 3 with the third level. The Pain Management Index (PMI) is negative in 63 patients (81.2%). There is also a stastically significant correlation between the intensity of pain and the degradation of each quality of life parameter. **Conclusion:** Pain management still remains a challenge. This deficiency is due to the inadequate medical training and the unavailability of most third level of analgesics in ambulatory prescription.

P3.07-09 CHARACTERIZATION OF THE NUTRITIONAL STATUS IN LUNG CANCER PATIENTS: A RETROSPECTIVE STUDY

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Background: Lung cancer is one of the most common cancers in the world in terms of both incidence and mortality. In patients with advanced lung cancer, the progressive decline in nutritional and functional status - particularly unintended weight loss - has been strongly associated with reduced physical functioning, poor tolerance to anticancer therapy, decreased quality of life, and poor prognosis and survival. The aim of the present study was to assess and characterize the nutritional status of patients with lung cancer at the moment of diagnosis. **Method:** A retrospective study was conducted on 2655 patients with lung cancer at São João University Hospital, in Porto, between 1976 and 2016. From the total number of patients, 68,8% (n=1827) had the nutritional assessment for the nutritional characterization, therefore the sample of the present study was 1827 patients. The characterization of the nutritional status was based on the WHO classification of Body Mass Index (BMI) by Quetelet. The cut-off points of weight loss used were: <5%, 5-10%, ≥10%. The lung cancer histology was grouped by non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The sample was split by gender (female, male) and age groups (≤45, 46-69 and ≥70 years old). The statistical analysis was calculated using the SPSS® programme. **Result:** From the total sample (n=1827), 85,1% were male and 14,9% female. The median age was 63 years (min= 19 years old, max= 92 years old). According to the WHO BMI classification, 8,8% of the eligible patients were underweight, 55,4% had normal BMI, 23,1% were overweight and 5% were obese. 67,9% of the patients had NSCLC and 19% had SCLC. From the total sample with NSCLC, 3,1% presented <5% of weight loss, 15% had 5-10%, and 31,3% had ≥10% of weight loss. Furthermore, patients with NSCLC presented more underweight (9,8%) than those with SCLC. A high percentage of underweight (92,5%) was found in older patients (≥46 years old) and, simultaneously, a significantly percentage of weight loss (>10% of weight loss = 82,1%) was also shown. **Conclusion:** The high prevalence of weight loss supports the current literature. The progressive decline in nutritional status in the patient with advanced lung cancer demonstrates that a precocious assessment of the nutritional status and follow-up can be an effective tool.

Keywords: lung cancer, Weight Loss, nutritional status

P3.07-10 WHAT DO PEOPLE LIVING WITH LUNG CANCER WANT AND NEED FROM THE RECOVERY PACKAGE

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Background: The National Cancer Survivorship Initiative (NCSI 2013) supported by Macmillan and NHS England identified the Recovery Package as a key outcome for people living with and beyond cancer, yet little is known about whether it meets the needs of people with lung cancer. The aim of the research was to examine the experience, treatment and the recovery of people living with and surviving lung cancer.

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Method: The research was a single site, mixed methods study, incuding a survey and interviews of patients . ▶ a survey to identify and understand what people have experienced in terms of on-going support to enhance their recovery. ▶ interviews to improve understanding of the patient and family experience ▶ to generate initial recommendations through analysis of survey and interview data. 100 invites were sent out to those who met the eligibility criteria; 34 completed the questionairre and 17 agreed to be interviewed. **Result:** ▶ Understanding of the recovery package was lacking ▶ There was a mixed response of positive and negative comments related to the various health professionals involved in The Recovery Package ▶ Health and wellbeing programmes were welcomed ▶ An individualised exercise and rehabiliation programme would be preferable ▶ 70% surveyed wanted to know more about The Recovery Package **Conclusion:** For The Recovery Package to be effective it needs to be managed and maintained by all health care professionals involved in the patient pathway. Patients and carers need to be made aware of what is available locally and nationally to enhance their recovery and quality of life. Implementing a dedicated rehabilitation programme to promote the enhanced physical recovery and to address psycho-social needs of people living with and beyond lung cancer is required.

Keywords: survivorship, recovery package, quality of life

P3.07 NURSING AND ALLIED PROFESSIONALS
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P3.07-11 SURVIVORSHIP AFTER LUNG CANCER SURGERY – SOLACE – A MACMILLAN FUNDED PROJECT

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Background: Lung cancer remains the leading cause of cancer related death worldwide. Surgery is the mainstay of curative therapy for lung cancer. However, 75% of patients present over the age of 65yrs, many with co-morbidities which impact on the resection rate. Post treatment many cancer survivors experience fatigue, reduced physical capacity and quality of life. We have established a Macmillan funded service at our institution. Our aim is to optimise the patient pre-operatively, encourage self-management post operatively and extend the role of recovery beyond the immediate post-operative period and establish survivorship as the goal. **Method:** Each referred patient is offered a key worker and a tailored pre and post operative programme based on individual needs, which may incorporate some or all of the following; opportunity to discuss concerns, education regarding their condition, smoking cessation, healthy eating, pre and post-operative exercises. Baseline and follow up data is collected regarding the patient's current health status, respiratory parameters and qualitative data about patient experiences. **Result:** 249 patients (as of March 2018) have been referred since the service was established in September 2016. The level of contact these patients have received is summarised below:

Level of Intervention	Numbers of patients
Level 1 – No direct involvement with patient, advice via telephone or email provided	37
Level 2 – Single face to face consultation, to assess requirements and receive information, advice and referral to another health profession	93
Level 3 – More than one intervention involving advice on specific issues, for example provided with home exercise DVDs	90
Level 4 – Multiple contacts with the patient and/or carer over a long term period. Of these patients 16 attended pre- operative exercise classes	29

212 (85%) of patients met with either the ANP or ATP, 56% of those engaged in further support. Early evaluation of the project indicates that there are challenges in gaining patient engagement with the exercise classes. The reasons are multi factorial and include patients perceiving their current level of activity is sufficient and the need for multiple attendances (time, cost and difficulty parking) acting as deterrents. A home based exercise programme and exercise DVD is offered to address this challenge. **Conclusion:** The project has had a positive start; changes have been made based on our early experiences. Work continues to develop the service; ensuring patients receive a tailored programme to meet their needs.

Keywords: Service Development, survivorship, Surgery

P3.07 NURSING AND ALLIED PROFESSIONALS
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.07-12 IMPROVING CARDIAC TAMPONADE OUTCOMES THROUGH LESS INVASIVE INTERVENTIONS AND EARLIER RECOGNITION

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Background: Oncology patients are at increased risk for developing pericaridal effusions due to disease processes or treatment regimens. Approximately 20% of cancer patients have pericardial involvement. At one large NCI-Designated Cancer Center, emergent pericardial drainages and windows are increasing; some leading to poor outcomes. Seventy-three percent of the emergent cases were pericardial windows compared to 28% being less invasive pericardial drainages. A workgroup including Critical Care, Cardiology, Thoracic Surgery and Nursing was formed to improve workflows and earlier recognition of pericardial effusions and cardiac tamponade. **Method:** The team reviewed current workflows and barriers that hindered early recognition and intervention for patients with pericardial effusions. Guidelines were developed to aid in early recognition and treatment. An exhaustive literature search was completed and an education program was developed for nurses encompassing information on malignant and non-malignant pericardial effusions and cardiac tamponade using an interactive case study format. Highly impacted areas such as the Operating Room, recovery areas, emergency department and thoracic surgery/step-down unit were targeted. The program included information on risk factors, signs and symptoms, interventions and the new workflow. In addition to nurse training, implementation included training more LIP/PAs to complete bedside echocardiograms and establishing a new escalation workflow. **Result:** In July 2017, the education program for nursing was initiated and the revised workflows were enacted. Over the first 6 months, 173 nurses were trained. Since implementation, the total number of emergent pericardial windows reduced by 55%, with a shift to less invasive measures for emergent drainage to be utilized. This improved workflow has led to providing patients with less invasive procedures, as well as cost avoidance of more than $15,000 in direct hospital costs to date. Final presentation will include the training program curriculum and workflow algorithms, as well as pre- and post-metrics. **Conclusion:** Not only is early identification of pericardial effusions and cardiac tamponade critical to patient outcomes, but there is a significant cost difference to third payers and hospitals for these procedures. On average, pericardial windows cost 5-7 times the cost of a pericardiocentesis. Nurses have an important role in patient assessment and identification which can not only improve patient outcomes but aid in financial sustainability for organizations. Other organizations can implement similar collaborative response teams and educational programs for high risk, low volume patient situations where response time is penultimate to patient outcomes.

Keywords: outcomes, nursing, cost

P3.07-13 NON-ONCOLOGY PROVIDER IMMUNOTHERAPY NEEDS ASSESSMENT

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Background: It is critical for non-oncology providers such as the emergency department, internal medicine, and critical care, to have accurate, up-to-date information on new cancer treatments such as immunotherapy (IO), and have means to properly identify immunotherapy-related adverse effects (IrAEs). IOs have a distinct side effect (SE) profile from standard cancer treatments such as surgery, chemotherapy and radiation therapy. With a subclass of IO are checkpoint inhibitors (CIs). Common CI SE are dermatologic toxicities such as pruritus and rash, experienced by half of patients receiving CIs (Davies, 2016). Gastrointestinal toxicities such as abdominal pain, nausea/diarrhea, can develop into colitis. The risk of intestinal perforation is high in patients with colitis from immunotherapy due to tissue damage from autoimmunity (Kroschinsky et al., 2017). Also, a cough and shortness of breath can advance into immune-mediated pneumonitis, which is most common in patients previously treated with surgery and radiation to the lungs (Doyle, 2016). In October 2017 IASLC released the first published guidelines, followed in February 2018 by the National Comprehensive Cancer Network guidelines. Through this project we are actively raising awareness and education of these guidelines at our community hospital. **Method:** A needs assessment survey was given to St. Joseph Hospital Emergency Care providers and Sepsis work group at their department staff meeting in 2017. In April 2018, this same survey was given to Hospitalists. A one page pre in-service survey was administered, followed a brief in-service, and a post in-service survey immediately followed. The Pre and post survey was used to evaluate effectiveness of teaching. Sample size: 30 non-oncology providers Data from 2017 and 2018 surveys will be collated to evaluate knowledge deficits, effectiveness of teaching, and implementation of IO patient identification card. Knowledge of IO SE management was measured with an identical pre and post in-service survey. The survey contained 5 items measuring the individual's current knowledge/comfort with managing immunotherapy side effects for oncology patients receiving immunotherapy who are evaluated in St. Joseph Hospital. **Result:** Data analysis ongoing using SPSS- Preliminary results identified a gap. **Conclusion:** The field of oncology and treatment of advance malignancies is growing at a fast pace, the oncology team will need to coordinate and educate other organ-specific specialties through educational programs and algorithms for the management of these AEs. Consequently, we need to assess the most constructive framework that can aid in the understanding and adoption of these newly published guidelines for the broader immune-oncology multidisciplinary team.

Keywords: non-oncology provider, Immunotherapy, IrAE management

P3.07-14 COLLABORATIONS OF PHARMACISTS WITH LUNG CANCER TREATMENT BY PREPARED PATIENTS CONTROLLED ANALGESIA (PCA) FOR PERIOPERATIVE PAIN CONTROL

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Background: Pain control in perioperative is important because sufficient postoperative pain control make patients to be early raised and left hospital. In almost patients, PCA is used and played the large role for pain control and is especially effective for operation expected to cause large invasion and strong pain such as in lung cancer. In our hospital, pharmacists are stationed in operative department and also prepare PCA throughout the day. If PCA is occasionally ordered, it could be prepared by pharmacists in his/her stationed time. We investigated the postoperative PCA preparation and also evaluated the contribution of pharmacists to pain control for lung cancer treatment. **Method:** We selected the data between October 2014 and September 2017. Number of general and local operations, preparations of PCA (fentanyl contained) and epidural anesthesia (morphine and local anesthesia contained) were counted, respectively. Then the ratio of number of prepared PCA by pharmacists to that all prepared one and number of surgical procedure of respiratory surgery were investigated. **Result:** Number of operation was maintained about 5,700 through the year. Number of operated under general anesthesia and respiratory surgery were 3,300 and 200, respectively. All PCA preparation number was as mean of 993, and that for respiratory surgery operation was 170 similarly. PCA was prepared for 76.6% of respiratory surgery patients to control postoperative pain. Almost of our patients ware those of lung cancer, PCA prepared by pharmacists was found to be usually used. It was also revealed that number of PCA preparation was gradually increasing from 2015. Epidural anesthesia were prepared for 20 patients through the study period. **Conclusion:** Until now, in the operation part, the anesthesiologist and the chest surgery doctor had been prepared PCA. It is thought that the safe pain control is promoted by the stationed pharmacist while such business of a doctor was reduced. From the above findings, PCA was frequently prepared for almost the respiratory surgery, stationed pharmacists have contributed to reduce patients' pain and doctors' medical care and thus worked in closer cooperation as a team stuff in lung cancer treatment.

Keywords: Pain, patients controlled analgesia (PCA), perioperative pain control

P3.08-01 TREATMENT OUTCOMES IN OLIGOMETASTATIC DISEASE OF NON SMALL CELL LUNG CANCER: A SINGLE CENTER EXPERIENCE

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Background: Even if oligometastatic disease is staged as 4, survival rates are higher when curative approaches are performed for both primary tumour and metastasis. We analysed our institution data of oligometastatic disease. **Method:** 52 NSCLC patients with limited metastasis were retrospectively analysed. All treatment modalities (surgery, CRT, supportive-care, palliative chemotherapy) were compared in terms of survival. Curative treatment was defined as surgery or CRT (concurrent or sequential). **Result:** Median overall survival (OS) was 35.2±4.1 months. Surgery was superior to CRT in terms of OS (36.7 months vs. 27.4 months, p>0.05). Progression free survival (PFS) was 29.4±3.9, survival after first progression (SAFP) was 15.6±2.8 months. Patients performed metastasectomy had higher SAFP rates than others with significance (20.07±3.8 months vs. 7.9±1.7 months p=0.046). Adenocarcinoma was related better SFAP than non-adenocarcinoma group (23±4.1 vs 6.4±1.5, p=0.002). The 1- and 2-year OS were, 67% and 50.4%, respectively. Among curative treatment group, while patients under age 65 (n=25) had 31 months OS, patients above 65 (n=13) had 22 months (p=0.88).

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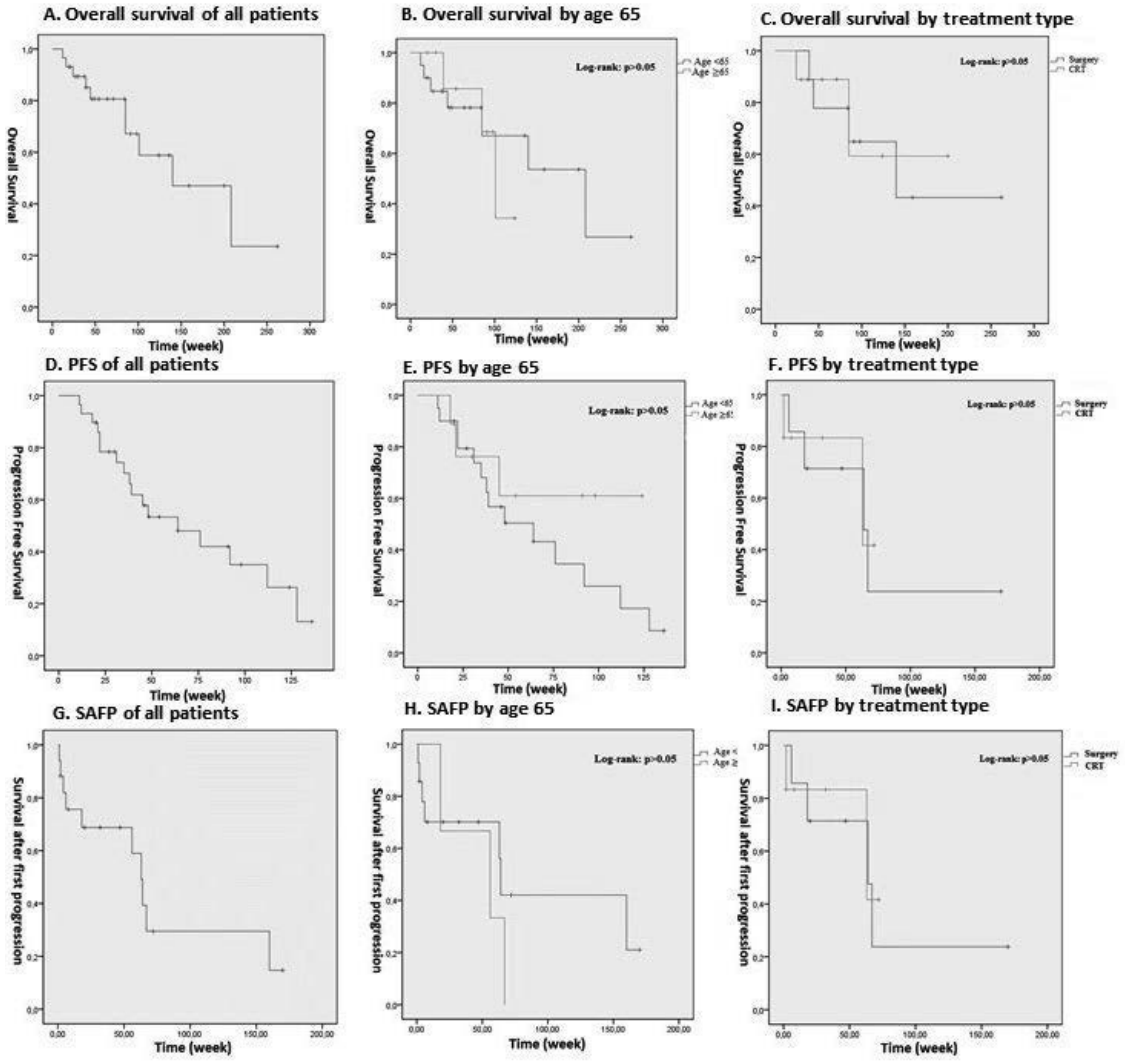

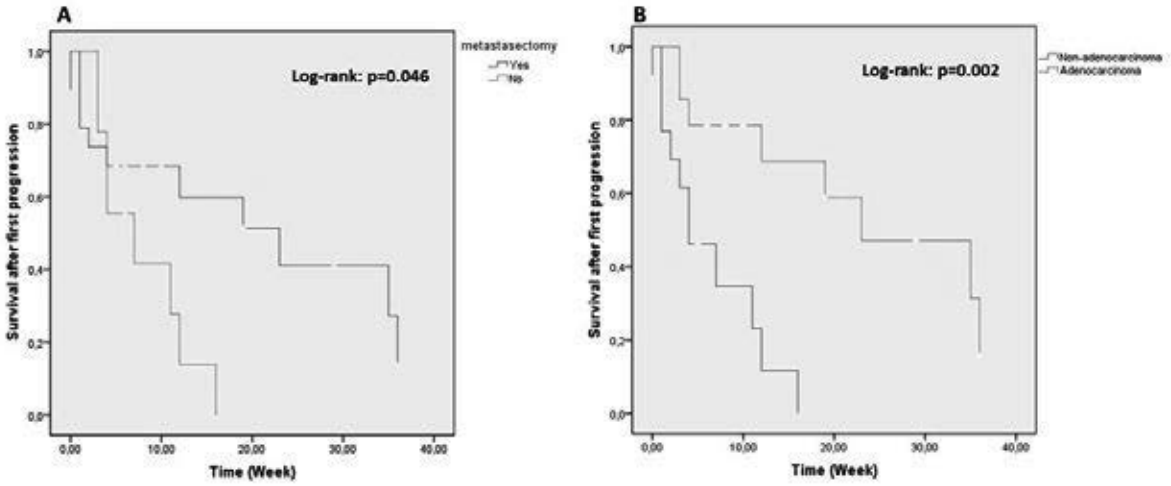

Conclusion: Our study revealed that in well-selected NSCLC patients with limited metastasis survival rates can reach up to 3 years even in geriatric population. And clinical N staging and co-morbidity are well known prognostic factors.

Keywords: Chemoradiotherapy, non-small cell lung cancer, Oligometastasis

P3.08-02 OLIGOMETASTATIC NON SMALL CELL LUNG CANCER PATIENTS TREATED WITH STEREOTACTIC BODY RADIOTHERAPY (SBRT), A SINGLE INSTITUTION EXPERIENCE

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Background: Oligometastatic disease is an intermediate state between localized and widespread diffuse disease. By definition, this state is amenable to local ablative approaches, like Stereotactic Body Radiation Therapy (SBRT), with curative intent. **Method:** Patients treated with SBRT for oligometastatic NSCLC (max 5 active lesions in max 3 different organs) between January 2014 and December 2015 in the Radiotherapy and Radiosurgery department of the Humanitas Clinical and Research Hospital were retrospectively analyzed. Primary endpoint of the study was local contro (LC)l; overall survival (OS), disease metastases free survival (DMFS) and progression free survival (PFS) were analyzed as well. LC and survival times were calculated from the first day of SBRT. Best local response (BLR) was defined according to RECIST criteria. **Result:** 83 patients were included in the study. Patients received different RT schedules according to number, site and size of the metastases. Treatment was generally well tolerated, no acute or late G3-4 toxicity was recorded. Complete response, partial response or stable disease were recorded in 30 (35%), 40 (47%) and 14 (16%) patients respectively. One patient had a local progression at first evaluation, while other 16 (19%) patients experienced local relapse during follow up. Actuarial local control time at 6, 12 and 24 months was 91.73%, 84.95% and 77.82% respectively. Distant progression was recorded in 64 patients (75%), in most cases (54 patients, 84%) patients progressed again in a oligometastatic way. Actuarial DMFS at 6, 12 and 24 months was 60.97%, 36.9% and 23.36% respectively. Actuarial PFS at 6, 12 and 24 months was 60.1%, 37% and 22.% respectively. With a median follow up time of 20 months (range 4.9-49.9), 33 patients (39%) were still alive, in 8 cases with no evidence of disease. Actuarial median overall survival (OS) was 24.5 months, OS at 6, 12 and 24 months was 97.6%, 81.6% and 50.2%. At univariable analysis type of oligometastases (p=0.015) and BLR (p=0.000) were found to be correlated with LC. Previous local ablative treatments (p=0.04, p=0.033), site of the irradiated lesion(s) (p=0.0016, p=0.0026), "adjuvant" medical therapies (p=0.0278, p=0.023) and BLR (p=0.011, p=0.018) correlated with DMFS and PFS. Site of irradiated lesion (p=0.000), RT BED (p=0.0019) and BLR (p=0.000) were statistically correlated with OS. **Conclusion:** SBRT for oligometastatic NSCLC is safe and effective. Local response is strongly correlated with patients' prognosis, underlying the relevance of local control also in a metastatic setting.

Keywords: Oligometastases, Stereotactic body radiation therapy, non small cell lung cancer

P3.08-03 STEREOTACTIC RADIOTHERAPY OF LUNG CANCER WITH SYNCHRONOUS BILATERAL NODULI OR OLIGOMETASTATIC DISEASE

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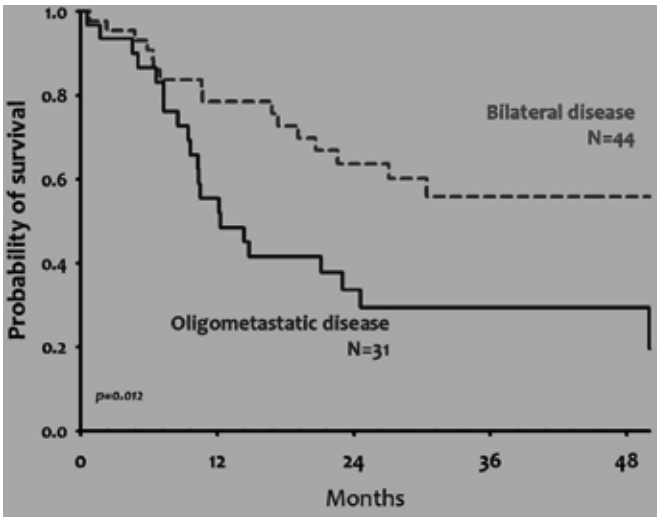
Background: Stereotactic radiotherapy (SBRT) is an efficient treatment for early stages of inoperable NSCLC. This retrospective study compares the outcome of patients diagnosed with either bilateral disease (BilatD) or oligometastatic disease (OligoD) prior to SBRT of the lung lesions **Method:** All cases of lung cancer treated with SBRT are prospectively recorded at our institution. We treated 75 patients with histological or cytological verified lung cancer 2009-2017 with IMRT or VMAT to a central dose 45-66 Gy in 3 fractions (F) for peripheral located tumors and 45 Gy-80 Gy/5-10F for centrally located tumors. BilatD was seen at the time of SBRT in 44 patients. In 35 patients, SBRT was used to treat simultaneous lesions in the two lungs, and in 9 patients SBRT was combined with surgical resection of a lesion in the other lung. OligoD was seen in 31 patients.

Result: The median, 1, 2, 3, and 4 year overall survival was 65 mo., 79%, 64%, 56%, and 56% in BilatD and 12.3 mo., 55%, 34%, 29%, and 29 % in OligoD (p=.01).

Patient characteristics			
	Bilateral (N=44)	Oligometastatic (N=31)	p-value
Age (yr.)	71.2 (47.3; 81.6)	67.8 (46.3; 86.3)	0.26
Female /Male	13 /18	25 / 19	0.30
PS 0-1	16 (52%)	13 (42%)	
PS 2	9 (21%)	34 (77%)	0.07
PS 3	1 (2%)	2 (6%)	
FEV1% of normal	63% (29-139%)	71% (28-123%)	0.51
Dose			
45 Gy /3F	13 (30%)	5 (16%)	
45 Gy/10F	1 (2%)	2 (7%)	
50 Gy /5F	3 (7%)	1 (3%)	
66 Gy /3F	23 (52%)	16 (52%)	
80 Gy /8F	4 (9%)	7 (23%)	
Metastatic site			
Lung		1 (3%)	
Brain		19 (61%)	
Adrenal gland		4 (13%)	
Bone		3 (10%)	
Pancreas/liver		2 (7%)	
Distant nodes		2 (7%)	

Conclusion: SBRT used in BilatD was associated with significant better overall survival compared with patients with OligoD.



Keywords: SBRT, Oligometastatic disease, Bilateral disease

P3.08-04 OMEGA, A RANDOMIZED TRIAL OF LOCAL ABLATIVE THERAPY VS. CONVENTIONAL TREATMENT IN OLIGOMETASTATIC NSCLC – TRIAL IN PROGRESS

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Background: A recent randomized phase 2 study has shown that local ablative therapy in addition to systemic treatment was superior to maintenance therapy in prolonging disease-free survival in NSCLC patients harboring up to three metastatic sites. Oligometastatic lung cancer (OM-NSCLC) seems thus to be associated with a better prognosis than usual Stage IV non-small cell lung cancer when radical local therapy of all metastatic sites is administered but the impact of such an approach on overall survival and quality of life remains unclear **Method:** A consortium of tertiary referral centres involved in Lung Cancer management at the national level was established with the aim of setting up a randomized trial addressing this issue **Result:** A randomized trial of local ablative therapy in OM-NSCLC patients with potentially resectable or locally controlled primary tumors has been designed and 7 tertiary referral centers agreed to participate Patients with synchronous or metachronous oligometastatic lung cancer (1-3 metastatic lesions) will be randomized to local ablative therapy + standard treatment Vs. standard treatment. Balancing between study arms will be performed according to synchronous vs. metachronous presentation, Number of oligometastases, Nodal status and Oncogene-addiction or PDL-1 expression. Primary outcome will be Overall Survival (OS) from randomization. The sample size is set to 195 patients. Inclusion criteria include adequate performance status, primary tumor controlled or controllable staging with whole-body FDG PET scan and brain MRI, fit to receive at least 3 cycles of platinum-based doublet chemotherapy, or immunotherapy or targeted agents according to molecular profile. Exclusion criteria include cerebral oligometastasis alone (will receive local therapy in any case), metastasis in sites where normal radiotherapy constraints cannot be met, multiple subsolid nodules in the absence of extrapulmonary metastasis, prior malignant tumor with some exceptions, relevant co-morbidities that would significantly reduce life expectancy on their own, Disease state and life status assessed on a 2-monthly basis by physical examination, whole-body CT scan plus repeat PET-scan if needed and Brain MRI if brain metastasis at enrolment. Toxicity and adverse events will be assessed according to NCI-Common Terminology Criteria. Quality of life will be assessed at randomization and after six months by the SF36/LCSS. **Conclusion:** There is a clear need for randomized controlled trials with overall survival as their main endpoint to confirm whether local ablative therapy indeed has a role in the management of oligometastatic lung cancer. The Omega trial will try to respond to such a need.

Keywords: Surgery, stereotactic radiotherapy, Oligometastatic

P3.08 OLIGOMETASTATIC NSCLC
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P3.08-05 STEREOTACTIC BODY RADIATION THERAPY (SBRT) OUTCOMES IN ELDERLY PATIENTS WITH LUNG OLIGOMETASTASES

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Background: Many non-randomized studies have shown that SBRT for lung oligometastases is safe and effective, with local control rates around 80%. In elderly patients SBRT represents an alternative and competitive option since many of them might have age-associated comorbidities that make them unsuitable for surgery The aim of this study is to assess the clinical results in terms of local control, toxicity and failure pattern of lung SBRT in patients 75 years old or more with lung oligometases of any origin treated at our institution. **Method:** Retrospective review of the medical records of 43 lung metastases in 28 consecutive elderly patients treated with SBRT between 2003 and 2017. One to four of inoperable (sinchronous or metachronic) metastatic lesions were treated per patient. SBRT was performed in case of controlled primary tumor, long-term of progression disease, exclusion of surgery, and number of metastatic sites≤5. Toxicity and radiologic response were assessed in follow-up visits, using standardized criteria and analyzed retrospectively. SBRT involved: computed tomography (CT) simulation with immobilization devices, contouring the target volume in 3 sets of CTs, superimposing the volumes in the planning system to represent the internal target volume and dose calculation using heterogeneity correction. Radiation delivery with multiple static non-coplanar beams and arc therapy assured conformal dose distribution and steep fall-off of the radiation. The prescribed dose was 3 fractions of 14-16 Gy each or a single 30-Gy fraction. Dosimetric constraints were set for surrounding organs at risk. **Result:** The median age was 79 years (75-87). Primary tumor was lung cancer in 44% of patients, colorectal cancer in 23% and a variety of other origins in 33%. After a median follow-up time of 15.3 months, the 1 and 2 year actuarial local control rates for all treated lesions were 95 and 91 %, respectively. Overall survival at 1 and 2 years was 86.7 and 60.4 %. Cancer-specific survival was 95.3 and 75.2 %, respectively. Treatment-related grade 1-2 toxicity was observed in 8 %. There were no grade 3-4 toxicity. **Conclusion:** In our experience, elderly patients with pulmonary metastases treated with SBRT achieved excellent local control and promising overall survival. SBRT is a safe local treatment option even in fragile patients with multiple comorbidities/low functional reserve, given its very low morbidity and excellent tolerability. Since main failure pattern is distant progression, there is room for improved clinical selection of most adequate candidates and optimization of systemic treatment.

Keywords: SBRT, Metastases, elderly

P3.08 OLIGOMETASTATIC NSCLC
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P3.08-06 LONG-TERM SURVIVAL FOR BRAIN-ONLY OLIGOMETASTATIC NSCLC PATIENTS TREATED WITH ABLATIVE THERAPY (AT): PROGNOSTIC FACTORS

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Background: Although brain metastasis (BM) have been associated with poor prognosis,brain-only oligometastatic(BOO)-NSCLC patients represent a special population for whom CAT may represent a reasonable therapeutic approach **Method:** Retrospective cohort with BOO-NSCLC (defined as 1-5 metastases in brain as only metastatic site) treated between 2010-2018 at Hospital La-Fe.Recursive Partitioning Analysis (RPA) group-score was calculated **Result:** 67 patients were identified (Table-1). Median-overall survival (mOS) was 20.2 months (95CI%:11.5-28.9). RPA-group score was associated with OS (HR:5.7;p<0.001); mOS was not reached in RPA-I, 16.2 m (95%CI:8.3-24.1) in RPA-II and 4.5 m ((IC95%:2.2-6.8) in RPA-III. Other factors associated with OS in univariable analysis were: radical treatment of the primary tumor (HR:2.6,p<0.005); radical treatment of the BM (HR:5.6,p<0,001); lymph node involvement (HR:2.17,p=0.031).Radical treatment in both primary and BM was associated with an increased mOS (HR:2.62;p<0,001). In the multivariable model, only RPA-group (HR:1.8 CI95%:2.8-12.7;p<0.0001), radical treatment of BM (HR:1.7;CI95%:2.4-13.1;p<0.0001) and lymph node involvement (HR:0.82;CI95%:1.1-4.9;p=0.03) were associated with an improved survival(table-2). **Table-1.Patients´ characteristics**

VARIABLES	ALL PATIENTS	
	NUMBER	%
Patients enrolled	67	100
Gender Male Female	48 19	71.6 28.4
Age Median (range)	59 (40-85)	---
Pathology Adenocarcinoma Squamous NSCLC NOS	49 8 10	73.1 11.9 14.9
RPA groups RPA-I RPA-II RPA-III	19 39 9	28.4 58.2 9
Brain metastases Synchronous to diagnosis Metachronous to diagnosis	47 20	70.1 29.9
Number of brain metastases 1 2 3 4-5	46 11 4 6	68.7 16.4 6 9

(See next page)

Table-2.Univariate and multivariate analysis.

Variable	Survival (months)	Univariate			Multivariate		
		HR	IC95%	p-value	HR	IC95%	p-value
RPA-I	Not reach		Not reach				
RPA-II	16.2	5.7	8.3-24.1	<0.001	1.8	2.8-12.7	<0.0001
RPA-III	4.5		2.2-6.8				
Radical treatment of the primary tumor	31.4		13.7-49.1				
No radical treatment of the primary tumor	8.4	2.6	3.0-14.4	<0.005	0.4	0.8-3.4	0.2
One BM	24.5		8.7-40.4	>0.5	----	-------	---------
More than one BM	11.4		1-22				
radical treatment of the BM	36.2	5.6	15.2-57.2	< 0,001	1.7	2.4-13.1	<0.0001
No radical treatment of the BM	6.5		5.8-7.3				
N0-N1	36.7	2.7	Not reach	p=0.031	0.82	1.1-4.9	0.03
N2-N3	16.2		5.2-27.3				
Radical treatment in both primary and BM	36.2	2.62	28.1-44.4	<0,001	0.8	0.55-10.69	0.25
No radical treatment in both primary and BM	7.2		3.9-10.5				

Conclusion: A radical approach in patients with stage-IV NSCLC with a limited number of BM may achieve long-term disease control in a subgroup of patients. Patients with RPA-I and II, one-BM, radical treatment, and N0-N1 have improved OS and may be suitable for this approach

Keywords: BRAIN-ONLY OLIGOMETASTATIC, Oligometastatic, Recursive Partitioning Analysis (RPA) group

P3.08 OLIGOMETASTATIC NSCLC
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P3.08-07 AN INSTITUTION REVIEW OF OUTCOMES OF LUNG STEREOTACTIC BODY RADIOTHERAPY IN VARIOUS OLIGOMETASTATIC DISEASE STATES

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Background: There is growing interest to use ablative techniques in patients with limited metastases to improve on local control (LC) and possibly survival outcomes. We review the outcomes of metastatic patients treated with pulmonary stereotactic body radiotherapy (SBRT) at our centre and analyse variables that might have affected outcomes. **Method:** Institutional review board approval was obtained before a retrospective review of patients treated at our centre from Jan 2010 to Dec 2016 was conducted. The data of patients treated with lung SBRT in the oligometastatic (≤3 lesions) setting was obtained from electronic medical records. The data was analysed using SPSS ver23. Survival was calculated from start of SBRT. **Result:** A total of 46 patients with 53 lung lesions were treated with SBRT. All patients had ECOG of 0-2. Primary cancers were varied with majority from lung (n=18, 39.1%) and colorectal cancers (n=13, 28.3%). There were 33 oligorecurrent, 10 oligoprogressive and 3 oligometastatic cases. Median age at SBRT was 66.8 years. Median lesion diameter was 18mm (range 7-57mm). Median SBRT biological effective dose (BED) was 105.6Gy (range 78.6 – 132.0Gy). The median follow-up was 26.9 months (range 4.5 – 59.6 months). There were 12 (22.6%) local failures at last follow-up. Median progression free survival (PFS) was 13.7 months (95% CI: 3.9 -23.5 months). Median overall survival (OS) was 42.2 months (95% CI: 30.8 - 53.5 months). The 2 year PFS and OS was 32.6% and 81.9% respectively. There were 3 (6.5%) likely radiotherapy related grade 3-4 pulmonary toxicities. On univariate analysis, a higher BED and squamous cell histology predicted for better LC. Oligorecurrent cases, higher BED, radical treatment to primary, single active/enlarging lesion and single metastatic involved organ, previous lung interventions, biopsy of lung lesion and radical treatment to all metastatic lesions predicted for better PFS. Local failure and progression predicted for worst OS. On multivariate analysis no variable had a significant impact on survival outcomes. **Conclusion:** The patients in this study are heterogeneous. Target lesion control after lung SBRT for metastatic disease is comparable to that of primary lung cancer. The excellent survival outcomes in this group of metastatic patients may be due to selection of patients with indolent disease biology. Better disease control outcomes were seen in oligorecurrent cases and when radical treatment to all lesions and higher BEDs were used. Further studies are needed to select for patients that are most likely to benefit from local ablative therapies.

Keywords: Lung SBRT, Oligometastatic, Pulmonary SBRT

P3.08 OLIGOMETASTATIC NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.08-08 OUTCOMES OF PULMONARY METASTASECTOMY IN BREAST CANCER: PROGNOSIS BASED ON THE METASTATIC LUNG TUMOR STUDY GROUP OF JAPAN

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Background: Although pulmonary metastasectomy is a common treatment in other primary cancers, its role in patients with primary breast cancer is still controversial. The purpose of this study was to analyze a Japanese multi-center database to assess the prognostic factors and indications of metastasectomy in breast cancer. **Method:** Data of 387 patients with histologically proven pulmonary metastases from breast cancer have been prospectively enrolled in the Metastatic Lung Tumor Study Group of Japan between December 1982 and March 2017. Those with inadequate information about perioperative data, surgery for biopsy, male or non–epithelial malignancies were excluded. A total of 253 female with invasive breast carcinoma between 1982 and 2017 constituted the study population, and their clinical and prognostic data were retrospectively analyzed. **Result:** The median follow-up period was 5.4 (range, 0–24) years. The mean age of patients was 56 (range, 32–82) years, the median disease-free interval was 4.8 (range, 0–31)

years, pulmonary metastasis (215 solitary, 38 multiple) was treated with surgeries, namely, wedge resection (n = 113, 45%), segmentectomy (n = 22, 9%), lobectomy (n = 116, 45%), and pneumonectomy (n = 2, 1%). Nodal metastases were found in 56 (22%) patients. There were 24 (9%) patients with incomplete resection. Additional treatments after metastasectomy were performed in 141 patients (56%). Recurrence after pulmonary metastasectomy developed in 98 of 229 (43%) patients without incomplete resection, namely, intrathoracic lesion (n = 21, 23%), distant metastasis (n = 47, 51%), and unknown (n = 25, 27%). The 5-year and 10-year survival rates after pulmonary metastasectomy were 66% and 52%, respectively, and the median survival period was 10 years. In the univariate analysis, early treatment period (<2001; p = 0.02), short disease-free interval (<3 years; p < 0.01), large tumor size (>2 cm; p < 0.01), surgical procedure (lobectomy and pneumonectomy; p = 0.01), intrathoracic nodal metastasis (p < 0.01), and incomplete resection (p = 0.05) were shown to be associated with poor survival. Multivariate analysis revealed that only short disease-free interval (<3 years; p < 0.01) was significantly worse prognostic factor in 253 patients. **Conclusion:** The main poor prognostic factor was disease-free interval (<3 years). However, complete resection of metastases was not a significant prognostic factor. The efficacy of pulmonary metastasectomy in breast cancer is still controversy. For pulmonary metastais from breast cancer, pulmonary metastasectomy is considered to be optional treatment.

Keywords: Breast cancer, metastatic lung tumor, pulmonary metastasectomy

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P3.08-09 SURGICAL RESECTION OF PULMONARY OLIGO-RECURRENCE OF NON-SMALL CELL LUNG CANCER

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Background: The concept of oligo-recurrence, which is theoretically curable by definitive local therapy, has been proposed in several cancers. But the efficacy of surgical resection for pulmonary oligo-recurrence of lung cancer is unclear. The aim of this study was to investigate the efficacy of surgical resection of pulmonary oligo-recurrence of non-small cell lung cancer (NSCLC). **Method:** We retrospectively analyzed the data on 21 patients who underwent lung resection for pulmonary oligo-recurrence in our institution, between 2000 and 2016. We evaluated independent risk factors for progression-free survival after pulmonary resection. **Result:** There were 14 men and 7 women with median age of 71 years [interquartile range (IQR), 65-72]. The median follow-up time was 48.8 months [IQR, 17.2-69.2]. Previous therapies for NSCLC were pulmonary resections in 16 (76.2%) patients, stereotactic radiosurgery for brain metastasis in 2 (9.5%), chemoradiotherapy in 2 (9.5%) and chemotherapy (ALK-TKI) in 1 (4.8%). Median progression-free interval between previous therapy and pulmonary resection of oligo-recurrence was 28.0 months [IQR, 16.0-40.0]. Histopathology was adenocarcinoma in 18 (85.9%) patients, squamous cell carcinoma, adenosquamous carcinoma and large cell neuroendocrine carcinoma in 1 (4.7 %). Surgical procedures were wedge resection in 11 patients, segmentectomy in 3, lobectomy in 5 and pneumonectomy in 2. There were no perioperative deaths. Three-year overall survival and progression-free survival were 68.6% and 59.3%. Postoperative recurrence occurred in 8 (38.1%) patients (local; 4, distant; 2, local and distant; 4). Univariate analyses identified progression-free interval between previous therapy and pulmonary resection of oligo-recurrence as independent risk factor for progression-free survival after pulmonary resection. **Conclusion:** Surgical resections of pulmonary oligo-recurrence of NSCLC are feasible and the postoperative survival is acceptable. But there are highly selective patients in our study, further study is needed for curative intent treatment.

Keywords: lung cancer, Surgical resection, Oligometastasis

P3.08 OLIGOMETASTATIC NSCLC
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P3.08-10 A RETROSPECTIVE STUDY OF OLIGO-RECURRENCE IN PATIENTS WITH RESECTED NON-SMALL CELL LUNG CANCER

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Background: In recent years, local therapy has been shown to be a first-line treatment for patients with postoperative oligo-recurrence of non-small-cell lung cancer (NSCLC). The aim of this study was to clarify the clinical features and outcomes of patients with postoperative oligo-recurrence of NSCLC. **Method:** Of 230 patients with resected pathological stage IA–IIIA NSCLC between 2008 and 2016, 56 who developed recurrence were included in this study. Oligo-recurrence was defined as 1 to 3 loco-regional or distant recurrent lesions restricted to a single organ. Other recurrences were classified as poly-recurrence. Second primary lung cancers and suspected lesions were excluded. Definitive local therapy (DLT) included surgery, stereotactic radiotherapy, and radiotherapy performed with curative intent. **Result:** Oligo-recurrence was identified in 26 (44%) patients, mainly as a solitary recurrence (n = 19, 73%) in regional lymph nodes, lung, brain, bone, or adrenal gland. The pathological stage was IA in 7 patients, IB in 7, IIA in 4, IIB in 1, and IIIA in 7. Histology was adenocarcinoma in 18, squamous cell carcinoma in 6, adenosquamous carcinoma in 1, and large cell neuroendocrine carcinoma (LCNEC) in 1. Epidermal growth factor receptor (EGFR) mutation was positive in 13, anaplastic lymphoma kinase (ALK) mutation was positive in 3, and 10 were unknown. Sixteen (62%) of the 26 patients first received DLT, and 9 (35%) received systemic chemotherapy including EGFR and ALK-tyrosine kinase inhibitors (TKIs). Four patients (lung in 3, adrenal gland in 1) underwent surgical resection, and the remaining 12 patients received stereotactic radiotherapy and radiotherapy. The three-year post-recurrence survival (PRS) after DLT and after systemic chemotherapy was 79.0% and 75.0%, respectively. Neither recurrence location nor initial treatment by DLT or systemic chemotherapy affected PRS in oligo-recurrence patients. There was no significant difference in the time to recurrence of oligo-recurrence patients compared with poly-recurrence (median time to recurrence: 1.49 years vs. 1.32 years, p=0.91). The entire population of oligo-recurrence patients had better PRS than those with poly-recurrence (5-year PRS: 67.9% vs. 9.0%, p<0.01). **Conclusion:** Oligo-recurrence of NSCLC is not uncommon. For oligo-recurrence, DLT or systemic chemotherapy should be given because it improves prognosis.

Keywords: oligo-recurrence, tyrosine kinase inhibitors (TKIs), NSCLC

P3.08 OLIGOMETASTATIC NSCLC
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P3.08-11 DIFFERENCES IN EVALUATIONS OF EARLY THORAX CT'S POST LUNG STEREOTACTIC BODY RADIOTHERAPY (SBRT)

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Background: Radiological changes after lung SBRT reflect variety and diversity compared to the changes after irradiation with other radiotherapy techniques. This leads to confusion in evaluating treatment response and changes in lungs,especially for the physicians who are not aware of the radiological changes after SBRT.Our study has aimed to compare evaluations of clinicians with various expertise on post SBRT early Thorax CT images in patients with early stage lung cancer or pulmonary metastasis. **Method:** Posttreatment CT scans from 19 patients and 20 lesions treated with lung SBRT during 2015-2017 were reviewed retrospectively.Thorax CT within 3 months after SBRT were evaluated individually by 8 physicians from radiology,radiation oncology,nuclear medicine and chest disease.Two physicians were chosen from each departments.One senior and one junior 2 physicians were assessed the CT images.The physicians were blinded to the original CT reports and they assesed CT scans independently.These evaluations were compared with evaluation of the radiation oncologist who was experienced in thoracic radiology and applied SBRT.Four choices were provided to physicians who were asked to choose one(0:Stable,1: Regression,2:Progression,3:Reactive changes due to SBRT).CT images were reviewed through ExtremePacs® Pacs Software version 4.3 programme.Coherence coefficients of the evaluations were calculated by the Cohen-kappa test. **Result:** SBRT was applied to 6 patients with stage 1 lung cancer,10 with stage 4 lung cancer and 3 pulmonary metastasis. One patient received SBRT for 2 nodules in different lobes in the ipsilateral lung.The median SBRT dose was 55 Gy(32-60)/3-10 fractions and biological effective dose (BED_{10}) was 115,5Gy(48 -180).When we took into account all CT scans during the whole follow-up period,all lesions had complete or partial response.When the evaluations of the physicians were compared with the reference radiation oncologist,the strongest coherence coefficient was found with the senior radiation oncologist(κ: 0,72).The Kappa coefficients between the junior radiation oncologist,junior nuclear medicine physicians and the reference physician were 0.61, 0.55 respectively.The compliances were lower for the other physicians(κ:0,48,κ:0,48,κ:0,45,κ:0,37). It was observed that such non-conformity was caused by misinterpretation of RT changes and mostly confused with progression. **Conclusion:** Early radiological changes after lung SBRT can be observed in different forms and misinterpreted by physicians from different specializations and the acute changes are confused with progression,mostly.Although our study was conducted with a small number of patients,findings support this argument.

Therefore,radiation oncologists who apply SBRT have to be aware of these radiological changes and evaluate accurately by themselves.

Keywords: SBRT, Thorax CT, Evaluations

P3.08 OLIGOMETASTATIC NSCLC
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P3.08-12 LONG-TERM OUTCOME AFTER ADRENALECTOMY FOR ISOLATED ADRENAL METASTASIS IN OTHERWISE OPERABLE PATIENTS WITH NSCLC - TWO INSTITUTIONS STUDY

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Background: Isolated adrenal metastasis (IAM) from non-small cell lung cancer (NSCLC) is a rare event and the management in such patients remains controversial. Our objective is to evaluate the long-term outcome after resection of IAM in operable NSCLC patients as a part of multimodality treatment. **Method:** Twelve patients (mean age 58.4 years) underwent adrenalectomy for NSCLC IAM. IAMs were synchronous (7) and metachronous (5), 4 of them were contralateral and 8 ipsilateral. Locoregional pStages I-II were found in 11 patients and pStage IIIA - in 1 patient. One-stage left lower lobectomy and left adrenalectomy through phrenotomy was performed in 1 patient. In 10 cases the curative lung resection was carried out first, followed by adrenalectomy via laparotomy (3), transperitoneal laparoscopy (1) and retroperitoneal endoscopic adrenalectomy (REA) (5). Two years after left lower lobectomy, the metachronous ipsilateral adrenal and contralateral lung metastases were eradicated by REA (first stage) and right polysegmentectomy S7-S10 in 1 patient from this subset. In the last case REA was performed at a first stage, followed by right lower lobectomy. The mean interval between the lung resection and the adrenalectomy was 6 months. All patients were followed up for the mean period of 42 months. The survival was studied by Kaplan-Meier method. Log-Rank test for comparisons was applied. **Result:** There was no perioperative mortality. The mean overall survival (OS) time is 42.0 months (95% CI 33.8-50.3). One-year and 3-years OS rate is 90.9% and 64.6%, respectively. Six patients are still alive until the last follow-up, four of them are with progression. One of the patients underwent radio- and immunotherapy with good response for local recurrence 20 months after left upper lobectomy. Brain metastases were found in one patient 2 years after initial surgery, which were treated by stereotactic radiosurgery and metastasectomy. Preaortic intraabdominal metastatic lymph node was extirpated in one patient 19 months after left pneumonectomy. One patient underwent irradiation for local recurrence on the bronchial stump 27 months after left pneumonectomy. Mean progression free survival (PFS) time is 25.1 months (95% CI 19.9-30.4). One-year and 2-years PFS rate is 80.0% and 40%. There is no significant difference in mean OS and PSF time between synchronous vs metachronous IAM (p=0.208; p=0.364), ipsilateral vs contralateral IAM (p=0.366; p=0.156) and laparoscopic vs conventional adrenalectomy (p=0.163; p=0.754). **Conclusion:** Long term survival is possible after resection of IAM in carefully selected NSCLC patients with early locoregional stages without involvement of mediastinal lymph nodes.

Keywords: NSCLC, oligometastasis

P3.08 OLIGOMETASTATIC NSCLC
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P3.08-13 STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OLIGOMETASTATIC LUNG NODULES: A SINGLE INSTITUTION SERIES

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Background: Lung metastases from a primary extrapulmonary malignancy often represent widespread metastatic disease. There are circumstances, however, where disease may truly be limited. For patients that cannot undergo surgical metastatectomy, SBRT represents a non-invasive option. Herein, we report the results of using lung SBRT to treat limited lung lesions from extrapulmonary malignancies. **Method:** We retrospectively reviewed outcomes in 44 patients with 50 lung nodules treated with SBRT. Fifty percent of the patients were male and median age was 64 (38-86). The median number of nodules was 1 (1-3) and almost all patients had oligometastatic disease (90%). Thirty-four percent of patients had extrathoracic disease. Primary malignancies included bladder (2%), breast (14%), endometrial (7%), Ewings sarcoma (2%), cholangiocarcinoma (2%), colon cancer (30%), rectal cancer (20%), small bowel (2%), head and neck (14%), renal cell (5%), and thyroid (2%). Seventy-five percent of patients had systemic therapy prior to any lung SBRT. **Result:** As above, 50 lung nodules were treated with SBRT in 44 patients. Median dose was 48 Gy (36-54 Gy) in 5 fractions (3-8). This dosing scheme yielded a median BED_{10} of 100 Gy (60-105.6 Gy). Follow up imaging was available for review in 96% of nodules. Median follow up from SBRT was 17.5 months (1-68). One year local control was 82%. BED_{10}>72Gy predicted improved local control (90% vs 57% at 1 year). Local control was inversely related to SUV on pre treatment PET/CT using a cut off of 4. If lesions had SUV>4.0 local control was 67% compared to 92% at one year. One year overall survival from SBRT was 66%. There was no difference in OS if patients had extrathoracic disease. Forty-six percent of patients had distant failure at 6 months. There was no acute or late grade 3 or higher toxicity. **Conclusion:** Lung SBRT is an effective and safe tool for treatment of limited lung metastases. Dose selection remains important for local control, and lesions with increased SUV show higher predilection for local failure.

Keywords: SBRT, lung metastases, oligometastatic

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P3.08-14 LONG-TERM SURVIVAL FOLLOWING SURGICAL RESECTION OF ISOLATED BRAIN METASTASIS IN NON-SMALL CELL LUNG CANCER.

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Background: Lung cancer is one of the leading causes of death all over the world and the prevalence is still growing. About half of the patients are diagnosed with stage IV disease at presentation with the most common sites of distal metastasis including the brain, liver, adrenal glands, and bones. Brain metastases remain a significant problem in patients with lung cancer. Surgical resection of metastasis limited to brain had been recommended by guidelines. However, few patients received metastasectomy of brain metastasis and the benefit of such intervention is unclear. So, we reviewed such patients of a medical center to see if those patients achieved long term survival after operation. **Method:** All patients of non-small cell lung cancer with brain metastasis diagnosed in 2011/1/1 to 2017/12/31 from a medical center were reviewed. The characteristics of the patients, local control rate, survival time after diagnosis of brain metastasis, EGFR status and surgical complications were recorded. The survival rate was calculated using Kaplan-Meier model. **Result:** We identified 276 patients diagnosed with non-small cell lung cancer with brain metastasis. Of these, 24 patients received metastasectomy of brain lesions. 22 of the 24 patients had distal metastasis limited to brain. 2 patients were excluded due to loss of follow up within one month after surgery. 20 patients were included in the analysis, of which 19 were adenocarcinoma, 1 was sarcomatoid carcinoma.16 of them had solitary brain metastasis, 2 with 2 lesions and 2 with 4 lesions. The average size of brain mass was 3.67cm (range 0.5cm to 7.4cm, standard deviation 1.78cm). To the date of our data collection (2018/4/30), 8 of them were dead, 4 were censored and 8 were still alive with regular follow up. The median survival after diagnosis of brain metastasis was 40.3 months. The 3 year and 5 year survival rate were 72% and 24% respectively. Recurrence of brain metastasis was documented in 2 patients only. One patient died 26 days after operation due to intracranial hemorrhage. No cognitive function impairment or wound infection leading to prolonged hospitalization was recorded after operation **Conclusion:** For non-small cell lung cancer patient with isolated brain metastasis, surgical resection of brain metastasis is likely to lead to long term survival with acceptable risk. Randomized case control study is needed to determine the best treatment strategy for this group of patients.

Keywords: Brain metastasis, non-small cell lung cancer, metastasectomy

P3.08-15 LUNG SQUAMOUS CELL CARCINOMA WITH SOLITARY OCULAR METASTASIS,SUCCESSFUL TREATMENT: AN INTERESTING AND RARE CASE REPORT

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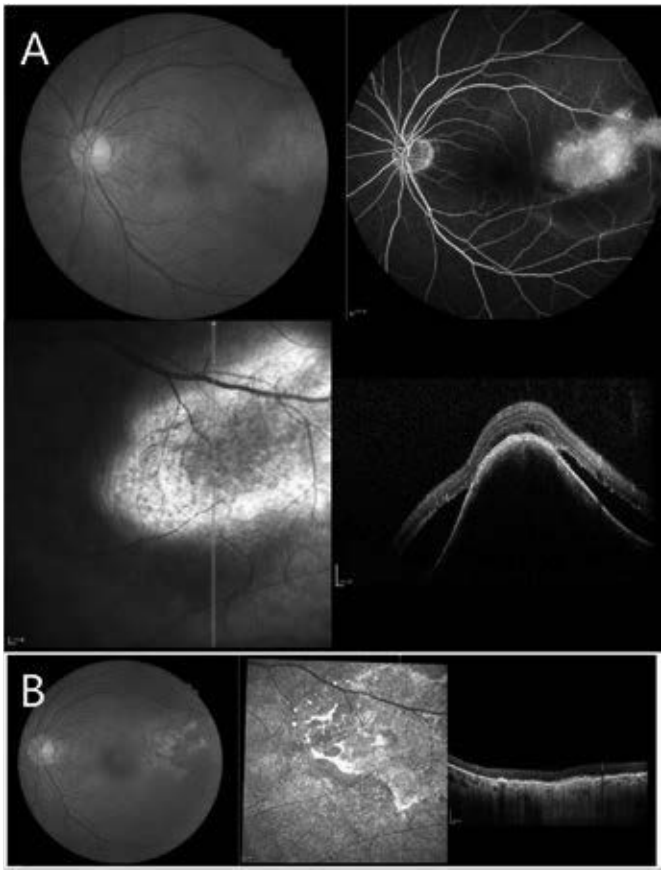
Background: The incidence of ocular metastases from lung cancer is reported to be 0.1%-7% according to the international literature. Adenocarcinoma and small-cell lung cancer occupied the most proportion. Lung squamous cell carcinoma with solitary symptomatic ocular metastasis as the initial manifestation who accepted the multidisciplinary team (MDT)treatment has never been reported. **Method:** In the diagnosis of intracranial disease, ophthalmofundoscopy can be used for follow-up observation and evaluation of therapeutic effects. Whole body PET -CT imaging can be used to identify the primary cancer and determine the disease staging. **Result:** A 62-year-old woman presented to ophthalmology of hospital with a 1-week history of left eye pain, blurred vision. The ophthalmologist performed ophthalmofundoscopy and optical coherence tomography on the patient(Fig.1A). The ophthalmologist initial diagnosis is metastatic carcinoma to the eye. The diagnostic work was completed with PET-CT which confirmed the central lung cancer in the lower lobe of the right lung with ocular metastasis.After multiple disciplinary team consultations, including surgery, internal medicine, ophthalmology, radiotherapy and imaging department, the patient underwent the right lower lobe resection and lymph node dissection in December 2016. Postoperative pathology diagnose the right lung-squamous-cell carcinoma staged T2aN1. In February 2017, the patient reviewed the eye examination and indicated that the ocular lesions were enlarged. The patient received 4 courses of gemcitabine plus cisplatin regimen chemotherapy. The eye symptoms disappeared completely after 4 courses(Fig.2B). The progression-free time was 11.9 months. There're 16.5 months for the patients has been followed up(March,2018) from surgery, and the lesion of ocular was still controlled very well without any specific ocular treatment.



Conclusion: It's the first report of a rare case with solitary ocular metastasis as the initial manifestation of lung squamous cell carcinoma. The successful treatment of this case was reported to provide a new therapeutic reference for clinicians to encounter similar cases in the future.

Keywords: Lung Squamous cell carcinoma, rare case, solitary ocular metastasis

P3.08-16 PROGNOSTIC VALUE OF PDL-1 EXPRESSION AND CORRELATION BETWEEN PRIMARY TISSUE AND BRAIN METASTASES IN OLIGOMETASTATIC NSCLC

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Background: Immunotherapy with anti-PD-1/PDL-1 agents in first-line metastatic non-small cell lung cancer (NSCLC) is chosen based on tumor cell PDL-1 expression. However, the incidence and prognostic value of PDL-1 expression in NSCLC patients with oligometastatic brain disease has never been characterized. **Method:** We retrospectively analyzed in our SARDO clinical database NSCLC patients with only 1-3 brain metastases (oligometastastic) treated in our University Health Care Center CHUM from 2007-2014. Samples were stained with SP263 (Ventana) antibody against PDL-1. A membranous staining of >25% was considered positive, and scoring was performed by an experienced pathologist. Kaplan-Meier survival curves of all clinical data were performed in SPSS 25. **Result:** In our cohort of 39 oligometastatic NSCLC patients treated before 2014, none received immunotherapy. A total of 49 specimens (biopsy or surgical) from either the primary or metastatic site were adequate and included in the study. In 10 cases, both primary and metastatic tissue were available for correlation. Overall PDL-1 positivity was 40.8% (20/49), with a positivity of 54.5% (12/22) in primary site samples and 29.6% (8/27) in metastatic brain tissue. Correlation of PDL-1 status between primary and metastatic site in a sub-group of 10 patients was 80% (8/10). Median overall survival (mOS) was significantly shorter for PDL-1 positive patients (8 mos) compared to PDL-1 negative patients (20 mos, p=0.05). 59% (23/39) of patients were aggressively treated for the primary tumor, and 86% (31/39) were aggressively treated for metastatic brain disease. When we controlled for treatment aggressivity of the primary tumor, mOS of PDL-1 positive patients treated aggressively was significantly shorter than mOS of PDL-1 negative patients treated aggressively (15 vs 22 mos, p=0.046). When the primary lung tumor was not addressed aggressively, mOS was the same regardless of the PDL-1 status (4 vs 4 mos). Median progression free survival (mPFS) tended to be longer in PDL-1 positive patients (6.0 vs 9.8 mos, p=0.254). **Conclusion:** PDL-1 status is concordant between primary and metastatic tissue in 80% of cases. PDL-1 expression is an adverse prognostic factor in NSCLC patients with oligometastatic brain disease, despite treating the patients aggressively for their primary lung cancer and their brain metastasis. In the future, giving early PD1/PDL-1 to oligometastatic PDL-1 positive NSCLC patients could significantly improve their outcome.

Keywords: oligometastatic, PDL-1, brain

P3.08-17 PAEDIATRIC MOTION MANAGEMENT SOLUTIONS FOR PARTICLE THERAPY BASED THORACIC STEREOTACTIC ABLATIVE BODY RADIOTHERAPY (SABR)

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Background: We have recently developed a paediatric protocol for the treatment of pulmonary metastases using Stereotactic Ablative Body Radiotherapy (SABR). In thoracic SABR the treatment is commonly planned to the internal target volume, which encompasses the gross tumour and excursion of the tumour in space.Particle therapy has been shown to be beneficial in paediatric patients, but unfortunately, most systems do not have respiratory motion management thereby limiting their utility in thoracic patients. We model the implementation of strategies such as ventilation using CPAP or deep inspiration breath hold (DIBH).The purpose of this study was to establish the benefit seen in a prospectively evaluated paediatric cohort to inform clinical trials. **Method:** *Patients* Two patients with a single lesion, and one patient with 3 lesions were volumed. Average age was 12 years (range 6 to 16), prescription dose was 24Gy in one fraction. Clinical volumes were

based on the Maximum Intenstiy Projection (MIP) and this ITV covered all motion seen on 10 phases of respiratory binning. The test dataset was contoured on the maximum exhale dataset (ME), as this was felt to be the most stable respiratory phase. 5 mm was added to create the PTV. Dynamic conformal arc (DCAT) was used for planning using 6MV photons with 3 to 5 arcs. **Result:** *Reduction in radiotherapy target volumes*:Exhale scans resulted in a reduction in the radiotherapy target volumes for all lesions with the average± standard deviation of the PTV being 3.85± 2.52 cc and 2.51± 1.35cc for MIP vs. ME scans respectively. *Reduction in dose to lung and heart*: V5Gy (%) was also reduced from a mean of 6.0±4.10 vs. 4.63 ±2.73 % for MIP vs. ME scans respectively. For the 2 patients with lesions near the heart the mean heart dose was also reduced from 2.35±0.78 Gy vs. 1.8± 0.28 Gy for the MIP vs. ME scans respectively. The maximum reduction was seen for patient 3, PTV was reduced from 8.2 to 4.9 cc, the V5Gy(%) was reduced from 10 to 4.9% and the mean heart dose dropped from 2.9 to 2.0 Gy. **Conclusion:** Respiratory motion management strategies such as DIBH and CPAP may be suitable for paediatric patients who are old enough to comply with these strategies, and who do not require general anaesthesia. As in adult patients, the implementation of these strategies reduces the radiotherapy target volume, and results in lower doses to critical normal organs such as the lung and heart.

Keywords: Pulmonary stereotactic ablative body radiotherapy, Paediatric, Respiratory motion management

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P3.08-18 CHANGING RESISTANCE MECHANISMS IN REBIOPSIES OF ALK-POSITIVE NSCLC DURING MULTIPLE LINES OF THERAPY: ALK/BRAF-MUTATIONS FOLLOWED BY EMT

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Background: 4-7% of NSCLC patients harbor the oncogenic ALK-rearrangements and may obtain clinical benefit from different ALK-inhibitors. Despite long remissions, resistance inevitably appears in alternative dominating forms. We present a case of a 38-year old male with metastatic ALK-positive NSCLC. The patient received four consecutive ALK-TKIs and two lines of chemotherapy in-between. Significant clinical benefit was observed during different ALK-TKIs, as well as resistant ALK- and BRAF-mutations, and rapid progression shortly before death associated with phenotypical changes related to epithelial-mesenchymal transition (EMT). **Method:** The diagnostic biopsy from cervical lymph nodes showed ALK-positive adenocarcinoma-metastasis with fusion variant 2 of EML4-ALK rearrangement. To identify TKI-resistance mechanisms during treatment, 4 rebiopsies from new metastatic lesions were analyzed histologically and by IHC, FISH and NGS. Additionally, two liquid biopsies were performed. **Result:** The treatment was initiated by Crizotinib. After 10 months, the 1st rebiopsy from new hepatic metastases showed a new p.C1156Y-mutation.The patient then received Cisplatin/Vinorelbine, progressed after two cycles and received 3rd line Ceritinib. The 2nd rebiopsy from new metastasis appearing 8 months later displayed persistence of ALK-fusion and p.C1156Y, but also new p.D1203N ALK- and p.V600E BRAF–mutations. Therapy was changed to 4th line Alectinib. A 3rd rebiopsy taken 4 months later from progressing sites revealed persisting ALK-fusion without p.C1156Y and p.D1203N mutations, and still p.V600E BRAF-mutation. No mutations were detected in plasma cfDNA 3 months later. Due to mixed response Pemetrexed was added and the patient had regression for a year. At subsequent progression a 4th rebiopsy from new lesions revealed maintained ALK-fusion without any ALK- or BRAF-mutations. Histology (appearance of spindle cells) and IHC (strong positivity for the mesenchymal marker Vimentin, loss of the epithelial marker E-cadherin) revealed phenotypical changes related to EMT. A liquid biopsy did not show any DNA-mutations either. Meanwhile, 6th line Lorlatinib was initiated without response. The patient died 34 months after initial diagnosis. **Conclusion:** Following the treatment course of this case we observed heterogeneous and transitional mechanisms of resistance to different ALK-TKIs, such as secondary ALK-mutations, BRAF-mutation, and phenotypical changes consistent with EMT. This resistance heterogeneity suggests a continuously changing state of the disease. Sequential use of different ALK-TKIs and combination therapies may allow long responses with satisfactory quality of life, however phenotypical EMT-related changes remain a significant hurdle for TKI-based therapy that may explain lack of response to 3rd generation's ALK-TKI, despite preserved ALK-positive status of the tumor.

Keywords: ALK-positive NSCLC, resistance mechanisms, EMT

P3.09 PATHOLOGY
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P3.09-01 PDL1 PROFILE OF FILIPINO LUNG ADENOCARCINOMA PATIENTS SHOW MODERATE POSITIVITY AND LOW EGFR CORRELATION

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Background: The recent approval of anti-PD1 or PDL1 immunotherapy based on promising clinical trial results ushers in the accelerated adoption of pertinent companion diagnostics to make available the relevant therapy to cancer patients. The Lung Center of the Philippines established a routine immunohistochemistry-based diagnostic for PDL1 in collaboration with pharmaceutical companies to address the existing gap in diagnostic information that may have therapeutic implications in terms of who and to what extent, this subset of population may benefit from this new targeted therapy. This study aims to report the PDL1 profile of Filipino lung adenocarcinoma patients and evaluate its possible correlation with EGFR mutation. **Method:** Tumor block samples from 345 Filipino lung adenocarcinoma patients were processed for PDL1 testing using the Ventana PDL1 Assay. Samples with positive results were subjected to Cobas EGFR mutation testing. **Result:** One hundred forty-two samples (i.e., 41.2%) were positive for the PDL1 markers. Majority of samples tested were males (i.e., 62-65% males vs. 35-38% females) with ages ranging from 64-66 years for both males and females. From a subset of eleven PDL1 positive samples, only three showed positive EGFR mutations (i.e., 27.3%) with two, showing L858R mutation and one T790M mutation. **Conclusion:** Moderate presence of the PDL1 markers were shown by Filipino lung adenocarcinoma patients suggesting that a moderate population could potentially benefit from anti-PD1 or PDL1 immunotherapy. Meanwhile, the low presence of EGFR mutation detected from the subset of PDL1 positive samples suggest a possibly mutually exclusive pattern for these biomarkers consistent with those reported in other studies. Albeit preliminary, co-EGFR testing could provide rationalization of clinical response and an alternative therapeutic targeting for this subset of patients.

Keywords: PDL1 profile, Filipino lung adenocarcinoma, co-EGFR testing

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P3.09-02 UTILIZATION OF LABORATORY DEVELOPED TESTS FOR PD-L1 EVALUATION IS DEPENDENT ON TUMOR TYPE

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Background: PD-L1 expression level evaluated by immunohistochemistry plays an important role in immunotherapy for many malignancies including non-small cell carcinoma of the lung (NSCLC), adenocarcinoma of the gastroesophageal junction/stomach (GEJ-G), melanoma and etc. With the growing number of indications for the use of PD-L1 immunotherapy, it has become impracticable for laboratories to adopt and maintain the various FDA approved assays for different tumor types. Harmonization to a standard assay would alleviate the current challenges and allow testing to be uniform among laboratories. The primary objective of this study was to determine if laboratory developed tests (LDTs) utilizing available antibodies are concordant with the FDA approved assays in NSCLC, melanoma and GEJ-G, and can therefore serve as alternatives for FDA approved assays. **Method:** Multiple tissue microarray slides containing NSCLC (714 cases), melanoma (87 cases) and GEJ-G (194 cases) were stained for PD-L1 with the 22C3 pharmDx Kit, the 28-8 pharmDx Kit, and/or three LDTs (clones 22C3, 28-8 and E1L3N). PD-L1 expression on tumor cells was scored for NSCLC and malignant melanoma, whereas expression on tumor cells and immune cells was scored for GEJ-G. All TMA slides were digitally scanned and independently evaluated by three board certified pathologists (JQ, AC, and BB) who were blinded to staining conditions. Raw scores were converted to a composite score based on the range of raw scores. Composite scores were compared for level of agreement utilizing a Kappa score and interclass correlation coefficients displayed on Bland-Altman plots. **Result:** For NSCLC, the two FDA approved assays have a high level of concordance (Kappa 0.88, 95% CI 0.85-0.90) and the two LDTs (22C3 and E1L3N) also have high level of concordance (Kappa 0.82, 95% CI 0.78-0.85); however, concordance between two FDA approved

assays and the two LDTs was low. For gastric adenocarcinoma, the 22C3 FDA approved assay and 22C3 LDT has a high level of concordance (Kappa 0.90, 95% CI 0.86-0.94), but the E1L3N LDT has a low level of concordance with both the 22C3 FDA approved assay and the 22C3 LDT. For malignant melanoma, there was low concordance among two FDA approved assays and two LDTs (28-8 and E1L3N). **Conclusion:** These results suggest that although LDTs can be used for evaluating PD-L1 in tumor, the utilization of LDT is tumor type dependent. One single LDT may not be sufficient to serve as appropriate alternative for the FDA approved assays on different types of tumor.

Keywords: PD-L1, laboratory developed tests

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P3.09-03 ALTERATION OF GUT MICROBIOME IN LUNG CANCER PATIENTS

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Background: Lung cancer is the leading cause of cancer death. Better understanding of factors and pathways involved in lung cancer is needed to improve diagnose and treatment strategies. Recent studies have provided insights into the possible correlation between intestinal dysbiosis and cancer development. Although the immunological relationship between gut and lung had been suggested by many researches, however, to date, no study had investigated the characterization of gut microbiome in treatment naïve lung cancer patients, whether it is distinct from that of health individuals and contribute to the onset and development of lung cancer remain unclear. **Method:** In this study, we investigated whether gut microbiome of lung cancer patients (LC, n=28) is altered compare with that of matched healthy individuals (HC, n=19) by high throughout sequencing of the V3-V4 regions of 16S rDNA in their fecal samples. We also identified microbiota signatures specific for different histological types of lung cancer, including SSC, ADC, and SCLC. **Result:** The gut microbiome of lung cancer patients is characterized by decreased relative abundance of Prevotella, and increased bacteria groups such as Actinomyces, and Streptococcus, etc. We also detected an mild structural shift in gut microbiome between ADC and SCLC patients. **Conclusion:** Our results showed that the gut microbiome of lung cancer patients altered significantly compared with healthy individuals. However, the association between microbial dysbiosis and lung cancer is not clearly understood, future studies involving larger cohorts and metagenomics, or metabolomics, may elucidate the correlations between gut microbiota and lung cancer development.

Keywords: gut microbiome, dysbiosis, lung cancer

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P3.09-04 ASSESSMENT OF PD-L1 EXPRESSION IN CYTOLOGY SAMPLES: AN ANLAYSIS OF 263 CONSECUTIVE NSCLC BIOPSIES.

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Background: FDA approved anti-PD1 therapy can be considered for first-line use in advanced NSCLC with high (≥50%) PD-L1 expression. FDA approval was based on resection and core biopsy specimens, thus excluding most cytology samples. Since the majority of lung cancer patients are diagnosed with advanced stage disease and therefore are not candidates for surgical resection, bronchoscopic biopsies targeting N1 or N2 lymph nodes and/or the primary tumor are often the first biopsies these patients are subjected to. There is a great clinical need to determine the suitability of cytology specimen in the assessment of PD-L1 expression of NSCLC since often these are the only tissue samples available in advanced stage lung cancer. **Method:** PD-L1 immunohistochemistry was performed using the 22C3 antibody (Dako) on a Ventana automated platform on 263 consecutive clinical cytology samples in a 14 month period. The assay was cross validated with the FDA approved companion diagnostic test. The samples included 216 cell blocks of fine needle aspirates of various sites, as well as cell blocks of body cavity effusions, and 42 core biopsies of various organs (20 gauge cores). Tissue clots (majority) or cell blocks were made from the aspirates followed by fixation in 10% buffered formalin. After fixation the tissue clots, cell blocks, core biopsies and lung biopsies were subjected to routine tissue processing. **Result:** There were 246 (93.5%) samples with adequate tumor cellularity and 17 (6.5%) samples with no or less than 100 viable tumor cells (all cell blocks). The majority of samples (n216) were tissue clots/cell blocks, followed by core biopsies (n42) and other biopsy types (n5). No (<1%) PD-L1 expression was seen in 93 (35%), low (1-49%) expression in 57 (22%) and high (≥50%) expression in 96 (36.5%) cases. High PD-L1 expression was detected in 42 of 94 (44.7%) N2, 9 of 21 (42.8%) N1 lymph nodes and in 15 of 37 (40.5%) pleural/pericardial fluids. The cohort included 37 biopsies of distant metastases with high expression detected in 12 (32.4%) samples. Interestingly, all 12 liver metastases showed no (n6) or only low (≤10%, n6) PD-L1 expression. The rest of the specimens included lung mass aspirates, as well as core biopsies and FNA of N3 lymph nodes. **Conclusion:** Tissue blocks of cytology specimens appear to be an adequate source of non-small cell carcinoma tissue for PD-L1 testing. Additional analysis is pending to determine response rates to immunotherapy in order to confirm the validity of testing results of cytology samples.

Keywords: Immunohistochemistry, PD-L1, cytology

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P3.09-05 SIGNIFICANCE OF THE EXPRESSION OF PD-L1/PD-1 BY TUMORAL AND IMMUNE CELLS IN NON-SMALL CELL LUNG CANCER.

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Background: Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer, including adenocarcinoma, squamous cell carcinoma and large cell carcinoma. There is solid evidence that demonstrates the existence of anti-tumor adaptive T-cell mediated immunity activation in lung tumors, indicating that lung cancers are immunogenic. PD-L1and PD-1 expression level in lung cancer may be a predictive biomarker for the use of PD1/PD-L1 inhibitors. However, the reproducibility of PD-L1 staining using different antibodies and platforms is still a matter of debate. We assessed whether PD-L1 expression in non-small cell lung cancer is associated with specific clinical features or survival using four different antibodies and if the expression of PD-1 in TILs correlates with the expression of PD-L1 in same group of cells. **Method:** PD-L1 and PD-1 status was assessed with IHC (AB clone SP142 and SP263 - Ventana, 22C3, 28-8 – Dako and PD-1) on archival FFPE surgical tumor specimens, arrayed on tissue microarrays (TMAs) with duplicate 1 mm cores, from Karolinska University Hospital. All patients (n = 598) underwent curative surgery between 1987 and 2015. The following cases were excluded from survival analysis (n = 89): R1 resection, early post-operative mortality, adjuvant chemo- or radiotherapy. PD-L1 staining was scored as positive if present in > 1% of tumor cells, independently of staining intensity. **Result:** Patient and tumor characteristics were as follows. Median age (IQR): 68 years (27-89); gender: male/female 54%/46%; histology: squamous-cell carcinoma (SCC)/Non-squamous (N-Sq)-NSCLC/carcinoid 219 (32%)/394 (58%)/45(7%); p-stage: IA/IB/IIA/IIB/IIIA/IIIB 50%/26%/10%/10%/2%/0.2%. PD-L1 28-8 was positive in 11% of cases, Pearson Chi-square p<0.0001). PD-L1 positivity 22C3/SP263/SP142 was 10%/13%/3%. All carcinoids were negative for PD-L1. In NSCLC, PD-L1 positivity for each antibody was associated with tumor size (T1/T2-4; Fisher's exact test, p<0.001) and grade of differentiation (G1, G2 and G3; p<0.0002). Statistically significant association between PD-L1 expression and OS was only observed using the clone SP263 (log-rank p=0.013). PD-1 expression in TILs correlates with those of PD-L1 (clone 28-8). **Conclusion:** In this surgical series, the clone SP142 showed less PD-L1 expression in the tumor cells. PD-L1 status was associated with tumor size, grading and only the clone SP263 showed association between its expression and survival ratio. PD-1 expression in TILs correlates with those of PD-L1.

Keywords: NSCLC, Immunocheckpoints, PD-L1/PD-1

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P3.09-06 THE LINK BETWEEN TUMOR PROMOTING FIBROUS MICROENVIRONMENT AND IMMUNOSUPPRESSIVE MICROENVIRONMENT IN STAGE I LUNG ADENOCARCINOMA

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Background: Podoplanin-positive cancer-associated fibroblasts (PDPN (+)CAFs) play an important role in cancer progression in non-small-cell lung cancer (NSCLC). The aim of this study is to clarify the correlation between fibrous microenvironment containing PDPN (+) CAFs and immune microenvironment. **Method:** 174 cases with stage I primary lung adenocarcinoma were analyzed in this study. We evaluated PDPN (+) CAFs and immune-related cells; CD 204-positive tumor-associated macrophages (CD204 (+) TAMs); CD8-positive T cells; and FOXP3-positive T cells in cancer stroma by immunohistochemical staining method. By analyzing the gene expression profiles of lung adenocarcinoma (n=442), we compared the expression level of immune-regulatory cytokines between PDPN expression-high group and PDPN expression-low group. **Result:** Presence of PDPN (+) CAFs was a risk factor for recurrence (P = 0.012). The number of CD204 (+) TAMs was significantly higher in PDPN (+) CAFs cases than in PDPN (+) CAFs cases (P < 0.001). Furthermore, CD8 (+)/FOXP3 (+) T cell ratio was significantly lower in PDPN (+) CAFs cases (P = 0.027). Within the same tumor, the number of CD 204 (+) TAMs was significantly higher in PDPN (+) CAFs area than in PDPN (-) CAFs area (P < 0.001). Moreover, CD8 (+)/FOXP3 (+) T cell ratio tend to be lower in PDPN (+) CAFs area than in PDPN (+) CAFs area (P = 0.062). Microarray analysis revealed PDPN expression-high group had significant higher levels of M-CSF; a cytokine inducing M2 macrophage polarization, and TGFβ1, IDO, VEGFA and galectin 1; immunosuppressive cytokines. **Conclusion:** The current results revealed that lung adenocarcinoma with PDPN (+) CAFs is typified by an immunosuppressive microenvironment, suggesting the close link between tumor promoting fibrous microenvironment and immune microenvironment.

Keywords: cancer associated fibroblasts, immune microenvironment, podoplanin

P3.09 PATHOLOGY
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P3.09-07 IMMUNOHISTOCHEMICAL EXPRESSION OF PROGRAMMED DEATH-LIGAND 1 IN DIABETIC PATIENTS VS NON-DIABETICS WITH NON-SMALL CELL LUNG CANCER

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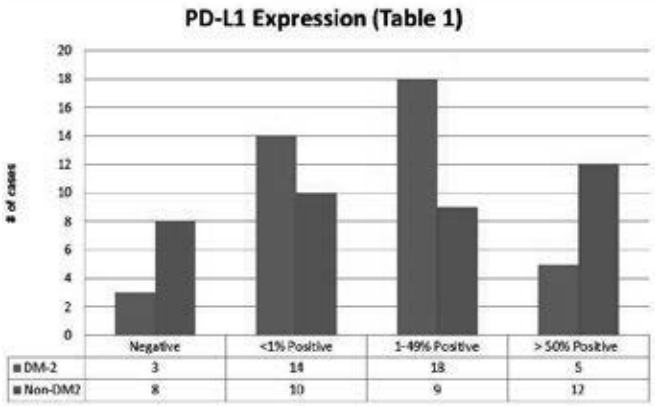
Background: Immunohistochemical (IHC) expression of programmed death-ligand 1 (PD-L1) serves as a predictive biomarker to select a subgroup of patients who may benefit from immunotherapy. Diabetes mellitus type 2 (DM2) has been shown to be present in approximately 20-25% of lung cancer patients and adversely affects lung cancer outcome. Yet, there are no established studies which investigate potential differences in PD-L1 expression in this group of patients. **Method:** To investigate expression of PD-L1 in DM2 patients compared to non-DM2 patients, we assembled a retrospective cohort of 79 surgically-resected NSCLC cases (39-adenocarcinoma, 40-squamous cell carcinoma) without previous malignancies or pre-operative radiation. Clinical data were obtained by chart review. Patients with DM2 had Hb1Ac levels of 7.5-7.7. Histologic slides were methodically reviewed. PD-L1 (DAKO 22C3) immunohistochemistry was performed on slides with the maximum amount of viable tumor. Tumor positive score (TPS) was evaluated based on IASLC guidelines as follows: 0: no staining; 1: <1%; 2: 1-49%; and 3: >50%. Immunoreactivity was compared using Chi-square and Fisher's exact tests. **Result:** Of the 79 cases of NSCLC, 40 (50.6%) were patients with DM2, and consisted of 20 (50%) adenocarcinoma, and 20 (50%) squamous cell carcinoma. Non-DM2 patients showed a relatively equal TPS distribution from 0 to more than 50%; however, DM2 group largely showed TPS of less than 50% (P=0.0319 Chi-square test); (P=0.0347 Fisher's Exact test); (Table 1). No significant difference was observed between the two groups in terms of overall survival, local recurrence, metastasis, peritumoral inflammation, and necrosis.



Conclusion: DM2 patients were less likely to have PD-L1 >50%, and therefore they may be less likely to respond to PD-L1 inhibition alone in the adjuvant setting. These findings are in accordance with the literature that supports a worse prognosis, tendency for co-morbidities, and known immunologic defects for DM2 patients with NSCLC.

Keywords: PD-L1, non-small cell lung cancer, Diabetes mellitus type 2

P3.09 PATHOLOGY
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P3.09-08 TUMOR HETEROGENEITY AND MOLECULAR PROFILE OF NSCLC IN THAI POPULATION

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Background: Oncogenic driven mutation is the key to develop targeted therapy in lung cancer. Different ethnicity and tumor heterogeneity affect the prevalence of molecular alteration. This study aimed to explore the unique molecular profile of lung adenocarcinoma in Thai population. **Method:** We studied 166 lung adenocarcinoma patients' molecular profile using Next Generation Sequencing (NGS) on 45 genes lung cancer panel (Ion Torrent system). Variants from NGS with coverage of higher than 1000X and cut off at 2% alternate variant frequency were considered positive. We validated the positive mutation of *EGFR*, *BRAF,* and *KRAS* by Real- Time PCR using the Amoy DX kit. **Result:** This study found 68%(113/166) of *EGFR* mutation, 9.6%(16/166) of *BRAF V600E*, 32.5% (54/166) of *KRAS* mutation, 9%(15/166) of *MET* exon14 splice site, 4.8% (8/166) *AKT* mutation (E17K), 2.4% (4/166) of *ROS1* mutation, 0.6% (1/166) of *PIK3CA* mutation (H1047R), and 0.6% (1/166) of *PTEN* mutation. Furthermore, we also found 40 patients (24.1%) who had more than one mutation in each person. We further validated the positive results by Real-Time PCR. Thirteen patients were obtained tissue from different organs and some with different period of time. T790M usually develop later in EGFR-positive patients who failed 1st or 2nd generation EGFR-TKI. Two patients (patient 5&9) who had lung surgery different lobe in same operation, had different mutation in tissues and one patient (patient 13) who obtained tissue from lung and pleural effusion cell block in different period of time had totally different mutation (Table1).

(See next page)

Table 1 Tumor heterogeneity profile in lung cancer patients

case	Hetrogenety in different organ	date obtained tissue	Gene mutation						
			EGFR	KRAS	ROS	PTEN	AKT	MET	BRAF
1	RLL lobectomy	12-Jun-2012	Exon 19 Deletion	negative	negative	negative	negative	negative	negative
	Right lung	4-May-2016	Exon 19 Deletion T790M	negative	negative	negative	negative	negative	negative
2	lymph node	16-Mar-2017	negative	negative	negative	negative	negative	negative	negative
	Bone	9-Apr-2017	negative	negative	negative	negative	negative	negative	negative
3	Right upper lung biopsy	20-Jan-2016	Exon 19 Deletion	negative	negative	negative	negative	negative	negative
	Lung biopsy	31-Mar-2017	T790M	negative	negative	negative	E17K	negative	negative
4	lymph node	13-Jan-2016	negative	G12A	negative	negative	negative	negative	negative
	skin	17-Jan-2016	negative	G12V G12D	negative	negative	negative	negative	negative
	left humerous	30-Jun-2016	negative	G12V	negative	negative	negative	negative	negative
5	RML lobectomy	13-Nov-2013	Exon 19 Deletion	G13D	negative	negative	negative	negative	negative
	LUL lobectomy	14-May-2014	negative	G12D G13D	negative	R233*	negative	negative	negative
	LUL lobectomy	14-May-2014	negative	G12V G12D	D2033N	negative	negative	negative	negative
6	Right pleura biopsy	11-Jan-2016	Exon 19 Deletion	negative	negative	negative	negative	negative	negative
	RUL biopsy	1-Mar-2017	Exon 19 Deletion	negative	negative	negative	negative	negative	negative
7	RUL biopsy	28-Sep-2015	L858R	negative	negative	negative	negative	negative	negative
	Left pleural fluid cell block	27-Jun-2016	negative	negative	negative	negative	negative	negative	negative
8	Right pleural fluid cell block	25-Mar-2016	Exon 19 Deletion	negative	negative	negative	negative	negative	negative
	Left pleural fluid cell block	9-Dec-2016	T790M	negative	negative	negative	negative	negative	negative
9	RML lobectomy	14-Mar-2013	negative	G13S	negative	negative	E17K	negative	negative
	RLL wedge resection-RLL lo	30-Mar-2017	G719A L861Q	negative	negative	negative	negative	negative	negative
10	RLL lobectomy	26-Aug-2013	negative	G12C G12D	negative	negative	negative	negative	negative
	Left lingular lobe segmental resection	9-Oct-2014	negative	G12D	negative	negative	negative	negative	negative
	LUL wedge resection	11-Feb-2016	negative	G12D	negative	negative	negative	negative	negative
	LUL lobectomy	4-Jun-2017	negative	G12D	negative	negative	negative	negative	negative
	LLL resection	9-Oct-2014	negative	G12D	negative	negative	negative	negative	negative
11	Right pleural cell block	21-Jul-2014	L858R	negative	negative	negative	negative	c.3028G>A exon 14 splicing	negative
	Ascites	9-Jun-2017	T790M L858R	negative	negative	negative	negative	negative	negative
12	LUL biopsy	24-Feb-2015	L858R	negative	negative	negative	negative	negative	V600E
	Lt lung biopsy	8-Jul-2016	L858R	negative	negative	negative	negative	negative	negative
13	RLL biopsy	14-Oct-2015	negative	negative	negative	negative	negative	c.3028+1G>T exon 14 splicing	negative
	pleural fluid cell block	15-Nov-2016	Exon 19 Deletion T790M	negative	negative	negative	negative	negative	negative

Conclusion: Thai populations have unique molecular alteration compared to the other ethnicities, especially, higher of BRAF V600E and MET exon14 splice site. Our population also has high co-mutation prevalence. Tumor heterogeneity is needed to explore in the larger cohort.

Keywords: molecular alteration in lung cancer

P3.09-09 "PREVALENCE OF EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION IN NON-SMALL CELL CARCINOMA LUNGS AT A CANCER CENTER IN NEPAL"

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Background: Mutations in the epidermal growth factor receptor (EGFR) gene are commonly observed in non-small-cell lung cancer (NSCLC), particularly in adenocarcinoma (AC). The prevalence of EGFR mutations in different parts of the world is well documented but there is lack of information for patients in Nepal. This study aims at exploring the proportion of EGFR mutation among Nepalese patients with NSCLC/AC. **Method:** A retrospective study was conducted in patients with all lung primary lesions diagnosed as NSCLC/AC and treated at Nepal Cancer Hospital and Research Center from March, 2015 till Feb, 2018. The related information on age, gender, histomorphological diagnosis, geographic distribution, ethnicity and EGFR mutational analysis were collected from the Department of Pathology and Laboratory Medicine at Nepal Cancer Hospital and Research Center, Nepal and were analyzed. **Result:** Total 106 cases of primary malignant lung lesions diagnosed as NSCLC/AC were evaluated for EGFR mutational analysis. 3%, 12% and 86% were well, moderately and poorly differentiated NSCLC/AC respectively. 21% metastasized to lymphnodes, bone, liver and others and 8% had local invasion into pleura. EGFR mutation were seen in 36%(n38 out of 106) of NSCLC/AC, most common in exon 19(55%) followed by exon 21(37%), exon 20(5%) and both exon 19&20(3%). There was no mutation found in exon 18. Malignancies were predominant in males (M: F=1.3:1) with median age 66years. However, EGFR mutation were predominant in female (M:F=0.6:1). Most of the patients were from Brahman/Chetri community(42%) followed by Newar(30%), Tarai Madhesi(11%), Janajati(10%), Dalit(6%) and Tamang(1%). Despite of being second in population for NSCLC/AC Newars had the most number of EGFR mutation of 16% followed by 10%, 5%, 3% and 2% in Brahman/Chetri, Janajati, Tarai Madhesi and Dalit respectively. Most of the patients were from central Nepal(Kathmandu, Lalitpur, Bhaktapur)(52%) followed by East Nepal(32%) and West Nepal(19%). **Conclusion:** EGFR mutation in lung cancer in our center was more than one third(36%) which is relatively high when compared to other parts of the world. Most of them were female from Newar community from central part of Nepal. Though rare, mutation in both the exons 19 and 20 were also observed. To our knowledge this is the first report in Nepalese population about EGFR mutation. A detail population base and multicentric studies are recommended to know about the actual prevalence of EGFR mutation and it's types in the Nepalese lung cancer patients.

Keywords: Adenocarcinoma, EGFR, Non small cell lung carcinoma

P3.09-10 CIRCULATING CELL-FREE DNA (CFDNA) MOLECULAR PROFILE OF THAI NSCLC PATIENTS USING DIFFERENCE VARIANT FREQUENCY OF NGS

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Background: Detecting cfDNA in the liquid biopsy has become a promising method to explore the genetic landscape of tumor heterogeneity. We developed a pilot-study to find the suitable cutoff of variant frequencies detected from liquid biopsy by NGS to track tumor-associated mutations in NSCLC patients. **Method:** Ninety-four samples (24 early-stage NSCLC, 70 late-stage NSCLC) were collected from Ramathibodi Hospital, Thailand. Profiling cfDNA using Ion Proton NGS platform. Overall average base coverage depth from NGS was 10,000x, all variants selected have read depths >10x in order to reach 0.1% sensitivity. Each of selected variants has threshold variant quality (QUAL) >20. Droplet digital PCR (ddPCR) was performed for *EGFR*-mutation testing to determine the appropriated cutoff variant frequency from NGS. **Result:** In early-stage NSCLC, a minimum-threshold variant frequencies at 0.1% could detect *EGFR* exon19 deletion in all samples (24,100%), with *BRAF* (12,50%), *KRAS* (21,87.5%) and other mutations in *AKT1, MET, PIK3CA, PTEN, ROS1* (14,58%). None of these mutations identified when using conventional level cutoff at 3% (Table1). ddPCR observed *EGFR*-mutations in 2 early-stage cases only (8.3%). In late-stage NSCLC, 64 (91.4%) cases were observed multiple mutations, suggesting tumor heterogeneity. At 0.1% cutoff in NGS, Thirty-six (52.9%) cases of *EGFR*-mutations in NGS and ddPCR were identical. Thirteen (18.6%) samples shown partial discrepancies in the mutations. Interestingly, NGS found *EGFR*-mutations in 20 (28.6%) samples which ddPCR failed to detect, 12 of them contained *T790M*. Only one sample (1.4%) using 0.1% cutoff was unable to detect EGFR-mutation. Higher variant allele frequencies were found in EGFR-positive detected by ddPCR compared to not-detected by ddPCR.

(See next page)

Table1

Mutations detected		variant allele frequencies detected from liquid biopsy by NGS at minimum threshold cut-off 0.1%	variant allele frequencies detected from liquid biopsy by NGS at minimum threshold cut-off 0.1%	variant allele frequencies detected from liquid biopsy by NGS at con-ventional level detection of somatic variants cut-off 3%	variant allele frequencies detected from liquid biopsy by NGS at con-ventional level detection of somatic variants cut-off 3%	variant allele frequencies detected from liquid biopsy by ddPCR (EGFR only)	variant allele frequencies detected from liquid biopsy by ddPCR (EGFR only)
		N (%)	median (range)	N (%)	median (range)	N (%)	median (range)
BRAF (V600E)	early stage total N=24	12 (50%)	0.8 (0.3-2.5)	0 (0%)	0	NA	NA
BRAF (V600E)	late stage total N=70	11 (15.7%)	0.6 (0.1-1.1)	0 (0%)	0	NA	NA
KRAS	early stage	21 (87.5%)	0.1 (0.1-0.5)	0 (0%)	0	NA	NA
KRAS	late stage	50 (71.4%)	0.2 (0.1-13.6)	3 (4.3%)	11.1 (5.8-14.3)	NA	NA
AKT1 (E17K)	early stage	7 (29.2%)	0.1 (0.1-0.7)	0 (0%)	0	NA	NA
AKT1 (E17K)	late stage	12 (17.1%)	0.1 (0.1-0.7)	0 (0%)	0	NA	NA
MET exon 14 splicing	early stage	4 (16.7%)	0.1 (0.1-0.1)	0 (0%)	0	NA	NA
MET exon 14 splicing	late stage	3 (4.3%)	0.2 (0.2-0.2)	0 (0%)	0	NA	NA
PIK3CA	early stage	9 (37.5%)	0.2 (0.1-0.8)	0 (0%)	0	NA	NA
PIK3CA	late stage	19 (27.1%)	0.3 (0.1-0.7)	0 (0%)	0	NA	NA
PTEN (R233*)	early stage	6 (25.0%)	0.1 (0.1-0.4)	0 (0%)	0	NA	NA
PTEN (R233*)	late stage	11 (15.7%)	0.1 (0.1-0.2)	0 (0%)	0	NA	NA
ROS1	early stage	0 (0%)	0	0 (0%)	0	NA	NA
ROS1	late stage	4 (5.7%)	0.55 (0.1-0.7)	0 (0%)	0	NA	NA
EGFR Exon 19 Deletion	early stage	24 (100%)	0.35 (0.1-2.1)	0 (0%)	0	1 (4.2%)	0.5 (0.5-0.5)
EGFR Exon 19 Deletion	late stage	25 (35.7%)	0.6 (0.1-49.0)	6 (8.6%)	9.4 (4.5-49.5)	20 (28.6%)	0.65 (0-49.0)
EGFR L858R	early stage	5 (20.8%)	0.2 (0.1-0.5)	0 (0%)	0	0 (0%)	0
EGFR L858R	late stage	21 (30%)	1.4 (0.1-9.7)	4 (5.7%)	4.6 (4.4-6.4)	14 (20%)	1.8 (0.3-9.7)
EGFR T790M	early stage	8 (33.3%)	0.1 (0.1-0.2)	0 (0%)	0	0 (0%)	0
EGFR T790M	late stage	30 (42.9%)	0.1 (0.1-4.6)	2 (2.9%)	7.5 (5.3-9.7)	16 (22.9%)	0.15 (0-4.1)
EGFR Exon18 (G719X)	early stage	6 (25%)	0.2 (0.1-0.4)	0 (0%)	0	1 (4.2%)	0.4 (0.4-0.4)
EGFR Exon18 (G719X)	late stage	4 (5.7%)	4.5 (0.1-49.2)	2 (2.9%)	27.9 (6.7-49.2)	2 (2.9%)	25.6 (2-49.2)
EGFR Exon 20 Insertion	early stage	0 (0%)	0	0 (0%)	0	0 (0%)	0
EGFR Exon 20 Insertion	late stage	1 (1.4%)	73.8 (73.8-73.8)	1 (1.4%)	91.7 (91.7-91.7)	0 (0%)	0

Conclusion: Detecting variant frequencies at 0.1% could reveal more hidden tumor-associated mutations compared to variant frequency cutoff at 3%. With a careful validation, profiling cfDNA using NGS can be a crucial method to accurately select treatment for NSCLC patients in the future.

Keywords: liquid biopsy, cfDNA, NGS

P3.09-11 GENOMIC ORGANIZATION AT LARGE SCALES (GOALS) WITHIN NUCLEI AND CELL SOCIOLOGY FOR PREDICTING LUNG CANCER OUTCOMES

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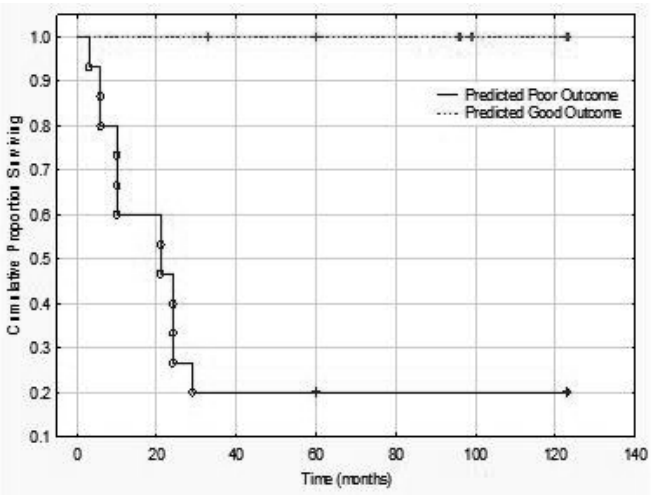
Background: Accurate prediction of the biological aggressiveness of lung cancers in patients from limited material could have utility with respect to patient treatment planning. We examined the hypothesis that the quantification of large scale DNA organization or GOALS within the nucleus combined with tumour microenvironment as quantified by cell sociology (which cells types are adjacent which cell types) could predict patient outcomes. **Method:** Tissue (TMA cores) from patients with poor outcomes (lung cancer mortality within 24 months) and good outcomes (5+ year survivors) was stained using a stochiometric DNA stain (Feulgen-Thionin). High resolution brightfield imaging of 29 cores was performed using multiple wavelengths and spectral unmixing used to retrieve the DNA concentration at every pixel. In house software was used to automatically segment all the nuclei within each core, calculate 100+ features for each nucleus and classify each nucleus as epithelial, stromal or immune in origin. Further each nucleus was scored as coming from a patient with poor or good outcome. For each TMA core the percentage of these cell categories was tabulated as well as cell-cell association frequencies (for example the frequently an epithelial cell predicted to have come from a patient with good outcome was found next to a stromal cell predicted to come from a patient with poor outcome). Cell percentages and cell-cell interaction frequencies were used to predict patient outcome. **Result:** Many of the individually calculated features had a statistically significant association with patient outcome. Four+ features could predict outcome with an 79% accuracy, 15+ different pairs of features could predict patient outcome with greater than 85% accuracy. Epithelial- stromal cell interactions and stromal cell – immune cell interactions were particularly predictive of outcome suggesting that microenvironment cell - tumour cell interactions predict future biological activity.



Conclusion: This pilot study suggests that GOALS and cell sociology could predict patient outcomes.

Keywords: quantitative pathology, cell sociology, tumour microenvironment

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P3.09-12 MOLECULAR AND IMMUNOHISTOCHEMICAL CORRELATES OF RB1 INACTIVATION IN SMALL CELL LUNG CARCINOMA

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Background: Retinoblastoma (RB1) is a critical negative regulator of cell cycle progression, and serves as a tumor suppressor gene that is inactivated in many tumor types, including small cell lung carcinoma (SCLC). Because biallelic inactivation of RB1 has been observed in virtually all SCLC, loss of RB1 expression in the correct context is considered highly suggestive of SCLC or SCLC-like neuroendocrine carcinomas. However, the relationship between the genomic inactivation of RB1 and expression in SCLC has yet to be fully defined. Here, we characterize the genetic and immunohistochemical correlates of RB1 inactivation in SCLC. **Method:** SCLC (n=57), and combined SCLC cases with a non-neuroendocrine component (CSCLC; n=5), that had undergone targeted next generation sequencing (NGS) (Oncopanel, 309-447 genes) were retrospectively identified. Designation of the molecular mechanism of RB1 inactivation was pursued by integrative analysis of RB1 variant type, variant allele fraction, and heterozygosity of the RB1 locus. RB1 protein status was interrogated in a subset of SCLC (n=25, 19 with biallelic inactivation) and CSCLC (n=2) by immunohistochemistry (IHC). **Result:** 77% (44/57) of SCLC showed biallelic inactivation of RB1 by NGS, most commonly through a loss-of-function (LOF) variant and associated loss of heterozygosity (LOH, 65%). The most common mechanisms of RB1 genetic inactivation in these cases were nonsense (32%), frameshift (25%), and splice site (23%) variants, respectively. RB1 protein expression was lost in 89% (17/19) of SCLC with biallelic RB1 inactivation; the two remaining cases harbored RB1 splice site variants and displayed weak, patchy RB1 expression. Additionally, 80% (5/6) of SCLC without molecular evidence of RB1 biallelic inactivation showed loss of RB1 expression. Overall, 60% (3/5) of SCLC harboring splice site variants retained weak RB1 expression. 60% (3/5) of CSCLC showed molecular RB1 inactivation in all tumor cells. While one CSCLC showed loss of RB1 expression in both histologic components, the other tumor, which harbored a RB1 splice site variant, retained strong RB1 expression. **Conclusion:** Genetic inactivation of RB1 in SCLC may not be identified in ~20% of cases via targeted NGS . While most SCLC with biallelic RB1 inactivation show loss of RB1 expression, retention of weak RB1 expression in SCLC does occur and may be associated with RB1 splice site variants. While additional investigation is needed to interrogate the functional and clinical significance of retained RB1 expression in SCLC, these data suggest that genetic RB1 inactivation does not always result in loss of protein expression, which may have implications for disease classification.

Keywords: small cell lung carcinoma, next generation sequencing, retinoblastoma (RB1)

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P3.09-13 MOLECULAR PROFILING SUGGESTS THE DIFFERENT MECHANISMS AMONG LOCAL INVASIVENESS IN RESECTED HUMAN LUNG ADENOCARCINOMA

T. Menju, T. Sowa, N. Imamura, S. Nishikawa, K. Takahashi, R. Miyata, H. Ishikawa, M. Noguchi, M. Hamaji, D. Nakajima, A. Ohsumi, T. Sato, T. Chen-Yoshikawa, M. Sonobe, H. Date

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Background: Local invasive factors are pathologically defined as pleural or lymphovascular invasion in lung cancer. Accumulating evidences have shown that these factors are associated with metastatic activity finally leading to poor survival of the patients. Here we examined the correlations of cancer-progressive molecular markers with local invasiveness in resected human adenocarcinoma. **Method:** Clinical samples were obtained from the 256 cases of lung adenocarcinoma which were consecutively operated to treat from January 2001 to December 2007 in our institution. Pathological stage distribution of the cases by TNM classification was below: 1A: 118, 1B: 71, 2A: 22, 2B: 4, 3A: 23, 3B: 1, 4:17. Tissue microarrays were immunohistochemically (IHC) stained. The previously published IHC data of molecular markers and DNA mutation data of EGFR and K-ras using our same cohorts were integrated. These markers included TP53, E-cadherin, vimentin, TWIST, CD133, CD44, Aldehyde dehydrogenase (ALDH), Carbonic anhydrase (CA)-9, Lactate dehydrogenase (LDH)-A, Glucose transporter (GLUT)-1, Hypoxia inducible factor (HIF) 1α, Ubiquitin C-terminal hydrolase (UCH)-L 1, Grb2, GEP100, Arf6, AMAP1, EPB41L5, phosphorylated receptor tyrosine kinases (EGFR, HER2, cMet, VEGFR2). Statistical analyses were performed by chi-square test or log-rank test. For survival data analyses,

stage4 cases were excluded. **Result:** Positive rates for these markers were from 9.6~63.4% as shown in the table. The most significant correlations with pleural, lymphatic, and vascular invasion were found in EPB41L5 (p=0.0005), LDH-A (p<0.0001), and, p53 (p<0.0001) and GLUT-1 (p<0.0001), respectively. The probable markers predicting both the nodal metastases and the occurrence of events were associated with EMT, glycolytic, hypoxia, and Arf6-related pathways.

	TP53	E-cadherin	vimentin	TWIST	CD133	CD44	ALDH	CA-9	LDH-A	GLUT-1	HIF1a	UCHL1
positive rate (%)	33.0	50.2	20.9	15.9	10.9	20.1	37.3	9.6	36.4	23.0	59.8	14.2
<p-value>												
pleural	0.0063	NS	0.0483	NS	0.0163	NS	NS	NS	0.0016	0.0006	NS	NS
lymphatic	0.0329	NS	0.0063	NS	NS	NS	NS	NS	<0.0001	NS	NS	NS
vascular	<0.0001	0.0301	0.0007	NS	0.0421	NS	NS	NS	0.0001	<0.0001	0.02	0.0084
LVI	<0.0001	NS	0.0005	NS	0.03	NS	NS	NS	<0.0001	<0.0001	0.0272	0.0055
node mets	0.0348	<0.0001	0.001	NS	NS	NS	NS	NS	0.0026	0.0001	0.0051	<0.0001
DFS (n=239)	NS	0.0029	0.0354	NS	0.0006	NS	NS	NS	0.0006	<0.0001	NS	0.0407
OS (n=239)	0.0036	0.0034	0.0048	NS	<0.0001	NS	NS	NS	0.0009	<0.0001	0.0119	0.001

	pEGFR	pHER2	pMet	pVEGFR2	Grb2	GEP100	Arf6	AMAP1	EPB41L5	mut EGFR	mut Kras
positive rate (%)	26.8	25.2	37.4	21.8	13.8	27.3	56.3	58.4	63.4	48.0	12.3
<p-value>											
pleural	NS	NS	NS	NS	NS	NS	NS	0.0043	0.0005	NS	0.0079
lymphatic	NS	0.0008	NS	0.0316	NS	NS	NS	NS	0.0033	NS	NS
vascular	NS	0.0246	NS	NS	NS	NS	NS	NS	NS	0.0295	NS
LVI	NS	0.0004	NS	0.0467	NS	NS	0.0242	0.048	0.0036	NS	NS
node mets	0.0348	0.0016	NS	0.0022	NS	NS	0.0006	NS	0.0001	NS	NS
DFS (n=239)	NS	NS	NS	NS	0.0211	0.0014	0.0055	0.0007	0.0012	NS	NS
OS (n=239)	NS	NS	NS	NS	0.0049	NS	0.0174	0.0006	0.0018	0.0058	NS

LVI: lymphovascular invasion

DFS: disease-free survival

OS: overall survival

NS: not significant

Conclusion: The pivotal markers were different among the types of local invasiveness. Pathways commonly used in local invasiveness, nodal and distant metastases were suggested to be EMT, glycolysis, hypoxia-related.

Keywords: lung adenocarcinoma, molecular marker, local invasiveness

P3.09 PATHOLOGY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.09-14 PATHOBIOLOGY OF NOTCH2 IN LUNG CANCER

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Background: Notch signaling is known to be involved in the initiation, progression, and suppression of various types of cancers. The pathological significance of Notch1 has been well studied in lung cancer, but that of Notch2 is still unclear. **Method:** Immunohistochemical study was performed to measure the expression of NOTCH2 in non-neoplastic lung tissues and lung cancers in comparison with the Clara (Club) cell 10 kD protein (CC10), and Western blotting analysis was performed to detect NOTCH2 in human cancer cell lines. Notch2 gene knockdown experiment and transient transfection of the intracellular domain of the Notch2 (N2ICD) gene were conducted to reveal the function of Notch2. In addition, we studied the relationships between the expressions of Notch1, 2, and 3. **Result:** Immunohistochemical study of lung tissues revealed that NOTCH2 was detected in bronchiolar epithelial cells and was often colocalized with CC10, and that adenocarcinoma tissues were more positively stained than those of squamous cell carcinoma and small cell carcinoma tissues. In human lung cancer cell lines the expression of NOTCH2 was similar to that of NOTCH1 and preferentially detected in non-small cell lung carcinoma (NSCLC) cell lines. Knockdown experiments of the Notch2 gene in NSCLC cell lines showed no significant changes in the expression of molecules associated with cell differentiation, proliferation, apoptosis, and motility. The effects of Notch2 gene knockdown could have be masked by concomitant Notch1 activation, as indicated by an increase in the intracellular domain of NOTCH1. Additionally, the transient transfection of the N2ICD gene induced CC10 expression in an adenocarcinoma cell line. **Conclusion:** The present study revealed that Notch2 is important in Club cell differentiation in normal lungs and in adenocarcinoma. We also determined that Notch1 and Notch2 are covariant, and the balance of the expression of Notch receptors could determine the biological behaviors of lung cancer cells.

Keywords: Notch2, lung cancer, Club cell differentiation

P3.09-15 GENETIC PROFILING OF IDIOPATHIC PULMONARY FIBROSIS ASSOCIATED NON-SMALL CELL LUNG CANCER BY TARGETED NEXT-GENERATION SEQUENCING

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Background: Little is known about the pathogenesis or genetic profiles of idiopathic pulmonary fibrosis (IPF) associated non-small cell lung cancer (NSCLC). This study was performed to investigate the genetic profiles of IPF associated NSCLC and to explore the possibility of defining potential therapeutic targets by using next-generation sequencing (NGS). **Method:** The Oncomine Comprehensive Assay v3 (OCAv3) from Thermo Fisher was used to detect clinically relevant single nucleotide variants (SNVs), insertions/deletions (INDELs), copy number variations (CNVs), and gene fusions from 161 unique cancer-related genes. **Result:** Surgically resected tumor specimens from 18 patients with IPF associated NSCLC (adenocarcinoma, n=9; squamous cell carcinoma, n=9) were collected. A total of 61 gene mutations was identified by targeted NGS and a median number of mutated genes per patient was 5 (range, 2–26). No sensitizing *EGFR* mutation (exon 19 del, L858R, G719X, L861Q) and fusions genes (*ALK*, *ROS1*, *RET*) were identified. Fourteen samples had one or more mutations in oncogenes including *PIK3CA* (n=7, 39%), *BRAF* (n=5, 28%), *PTEN* (n=4, 22%), *EGFR* (n=4, 22%), *MET* (n=3, 17%), *KRAS* (n=2, 11%), *HRAS* (n=2, 11%), *NRAS* (n=1, 6%), *ERBB2* (n=1, 6%) and *DDR2* (n=1, 6%). In addition to these potentially druggable oncogenes, loss-of-function mutations in *ARID1A* (n=10, 56%) and *TP53* (n=7, 39%), tumor suppressor genes regulating DNA damage checkpoint were frequently identified. Furthermore, loss-of-function deletions (P2415del) in *NOTCH1* which plays a role in cell fate determination, growth, and survival was observed in six (33%) patients. **Conclusion:** This study demonstrated novel genetic profiles of IPF associated NSCLC using NGS.

Keywords: idiopathic pulmonary fibrosis (IPF), non-small cell lung cancer (NSCLC), next-generation sequencing (NGS)

P3.09-16 TRANSCRIPTOME PROFILING FOR SUBTYPING NSCLC: OFF THE BEATEN PATH(OLOGIST)

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Background: Histopathological distinction between non-small cell lung cancer subtypes is still relevant in the age of targeted therapy due to the relatively low number of patients with actionable molecular alterations such as EGFR mutations or ALK rearrangements in squamous cell carcinomas. In addition, for patients without these alterations, the choice of most effective chemotherapy regimens is often based upon non-squamous vs squamous cell histology. However, histopathology scoring typically requires resected or biopsied tissue to be fixed, sliced, stained, and subjectively scored by a pathologist. Here we endeavor to demonstrate that subtle variances in gene expression within NSCLC patient samples can be used to classify the cancer subtype with a high degree of accuracy to pathology classification. **Method:** RNA extracted from 46 resected NSCLC cases (34 stage IIA/B, 12 stage IIIA/B; primarily adenocarcinomas and squamous cell carcinomas) were profiled using a transcriptome microarray platform (Illumina) and analyzed and compared to normal tissue using several Bioconductor R package pathway analysis tools and DAVID Bioinformatics Resources 6.8. Expression profiles were grouped by principle component score in a blinded manner. **Result:** Clustering samples based on the top 10% most variable genes resulted in a highly accurate separation of adenocarcinoma samples and squamous cell carcinoma samples, with only one case of squamous cell carcinoma being misclassified as adenocarcinoma. The altered pathways that differentiated these samples included p53 signalling and PI3K-Akt signaling pathways, Cell adhesion molecules (CAM), ECM-receptor interactions, Wnt signalling and several other key pathways. **Conclusion:** Due to the successes of targeted therapeutic approaches, evaluating patient biopsies or other samples for EFGR mutations and ALK rearrangements are currently the standard of care for advanced-stage NSCLC. Immunohistochemical staining for the purposes of subtyping NSCLC can aid in developing treatment strategies for patients without these molecular alterations, but this can significantly reduce the quantity of tissue available for subsequent molecular tests. Based on our data, we believe that expression variances in a relatively small pool of genes and pathway analysis is sufficient to accurately predict the subtype of NSCLC, or at least narrow the number of cases requiring input from a pathologist to a small number of more difficult cases.

Keywords: transcriptome, Pathology, NSCLC subtypes

P3.09-17 MOLECULAR PROFILE IN LUNG ADENOCARCINOMA. A MUTICENTER STUDY IN CORDOBA, ARGENTINA.

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Background: Substantial advances have been made in the understanding of the biology of NSCLC in relation to the characterization of molecular abnormalities such as activations of oncogenes by mutations, translocations and amplifications, which are being used as molecular targets and predictive biomarkers. Molecular analysis of NSCLC, adeno carcinoma (AC) is now the standard of care for therapy selection **Method:** We determined the frequency of molecular alterations in EGFR and gene fusion ALK in our Caucasian and Hispanic populations to decide the adequate treatment . 206 small biopsies and resection specimens of patients with NSCLC (AC) in different institutions of Cordoba were studiesduring a period (2014 - 2018). In addition to Histopathology Type, we analyzed immunohistochemistry (IHC) characteristics and molecular profiles and Several clinical variables were studied. Different tests were used to detect alterations of EGFR and fusion gene EML4-ALK expression, with the aim to identify our own profile and decide the adequate therapeutical option. EGFR mutation was studied by therascreen kit, PCR, in order to detect genetic alterations in exons 18, 19, 20 and 21. ALK translocations were analyzed by FISH (Vysis- Break Apart, Abbott) and IHC (clon D5F3, ventana, Roche). We correlated the molecular profile with different clinical variables (age, gender, and tobacco habits). The statistical method used was the multiple regression logistic model. **Result:** 146 men and 60 women out of 206 samples were tested for EGFR expression. Twenty nine men and sixteen women expressed EGFR positive. Activating kinase-domain mutations in EGFR were identified in 45 pts (21, 95 %): exon 19 deletion = 23, L858R = 7, exon 20 insertion = 11, other = 4. EGFR alterations were associated with gender (p=0.044), women showed more alterations of the genes. Age and smoking habit of patients did not show significant association (p=0.757 and p=0.547, respectively). We used the multiple regression logistic model to correlate EGFR expression to age, gender, tobacco habits. We identified 10 pts (5%) with fusion gene EML4-ALK. ALK alterations were not related to gender (p=0.449), age (p=0.837) and smoking habit (p=0.452). **Conclusion:** Our results showed a comparable frequency in EGFR mutations and gene fusion ALK in relation to the data published in western population. These results allow a proper diagnosis to provide pts with the most adequate therapy.

Keywords: Molecular , genetic expression

P3.09-18 IDENTIFICATION OF MET EXON 14 SKIPPING MUTATIONS BY FUSIONPLEX™ SOLID TUMOR PANEL

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Background: *MET* exon 14 skipping (*MET*ex14), or splice site, mutations result in the deletion of the juxtamembrane domain of MET, leading to increased MET receptor pathway signaling. Non-small cell lung cancer (NSCLC) patients with *MET*ex14 mutations are eligible for therapy with MET inhibitors like crizotinib. *MET*ex14 mutations are diverse and complex and can be challenging to detect by targeted DNA NGS assays alone. The Archer FusionPlex™ Solid Tumor panel use anchored multiplex PCR chemistry to detect fusions and other mutations including oncogenic isoforms in 53 genes associated with solid tumors. **Method:** In July 2016, we implemented the FusionPlex panel in our clinical laboratory for routine testing of NSCLC. RNA is extracted from FFPE tissue using the AllPrep DNA/RNA FFPE Kit and RNA quantity is assessed using the Qubit HS RNA Assay, and RNA quality is assessed using the PreSeq RNA QC Kit. cDNA synthesis and library preparation are performed according to the manufacturer's recommendations. Libraries are quantified using the KAPA Library Quantification Kit, diluted to 4 nM, pooled and sequenced on

the Illumina MiSeq System. Data analysis is performed using the Archer Analysis platform (v4.0.11). *MET* exon 14 isoforms were confirmed by an orthogonal method (DNA NGS assay and/or melt curve analysis). **Result:** Since July 2016, samples from 275 NSCLC patients were successfully sequenced. Six (2.2%) *MET* oncogenic isoforms, consistent with *MET* exon 14 skipping mutations, were identified and subsequently confirmed. All six patients were female with an age range of 61-82 years. Two presented with stage I disease, two stage II, one stage III and one stage IV. To date, none of the patients have been treated with MET inhibitor therapy.

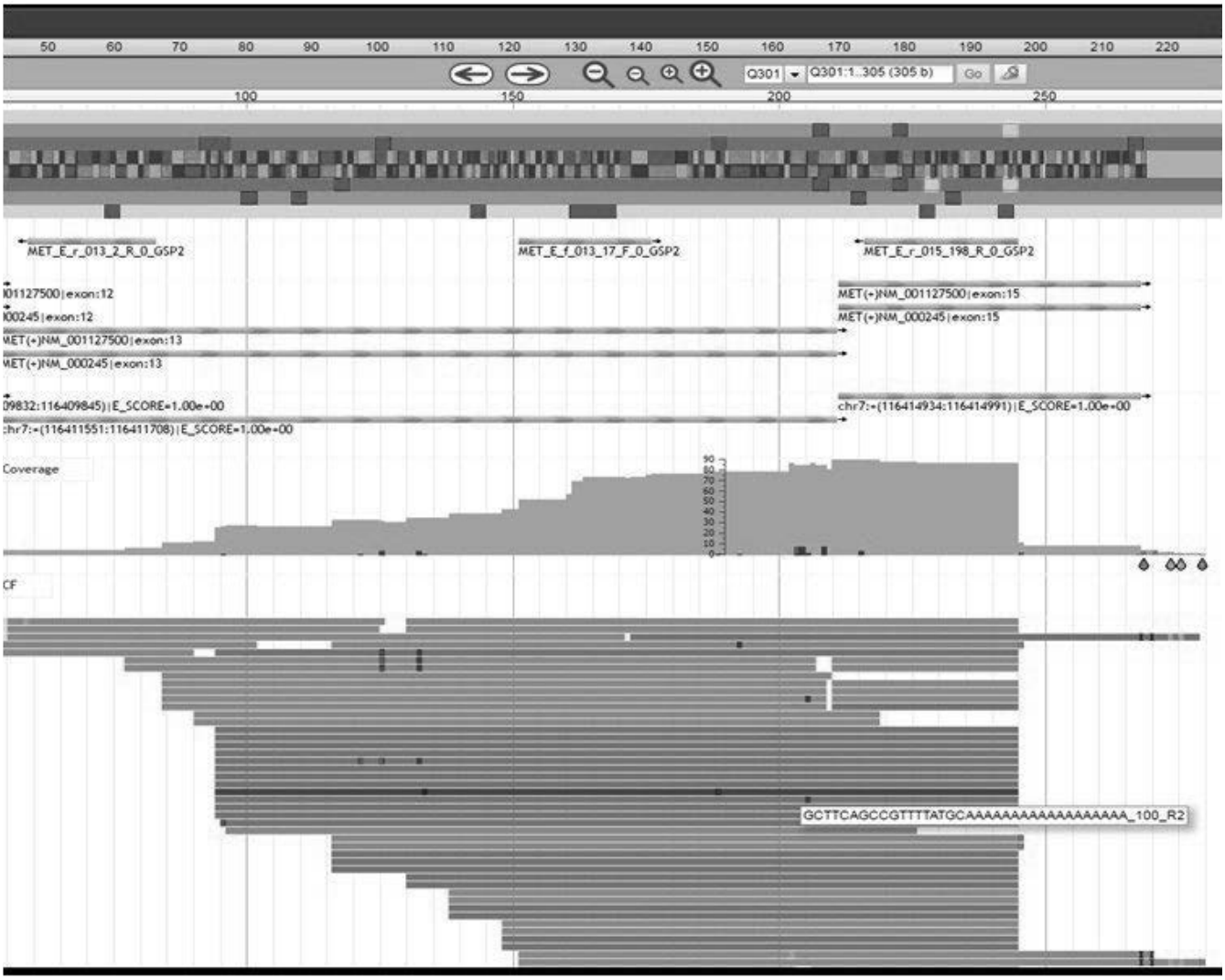

Figure 1. Sequencing data reads detecting a MET exon 14 skipping mutation.

Conclusion: The FusionPlex™ Solid Tumor NGS panel can be routinely performed in the clinical laboratory to optimize detection of *MET* exon 14 mutations as well as other clinically actionable gene fusions.

Keywords: MET exon 14 skipping mutations; FusionPlex Assay; Next Generation Sequencing

P3.09-19 MATCHED THAI LUNG CANCER PATIENTS TISSUE AND CFDNA MOLECULAR PROFILE BY NGS

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Background: Liquid biopsy is the new non-invasive technology to explore the molecular profile. We evaluate molecular alteration from matched tissue and liquid specimen in NSCLC patients using NGS. **Method:** A total 61 matched tumors and cfDNA in NSCLC patients were retrieved for DNA extraction. All qualified samples were analyzed by using Next Generation Sequencing (NGS) with Gene read Qiagen Lung Cancer Panel sequencing 45 Genes on Ion Torrent system.Variants from NGS with coverage of higher than 1000X of tissues and 10000X of liquid biopsy, cutoff at 3% variant frequency were considered positive. Each detected mutation was validated by the different method. *EGFR*-mutation detected at this cutoff was validated by Real-time PCR technique using the ARMS-PCR (Amoy DX Kit) for tissue samples and droplet-digital PCR (ddPCR) for blood samples in all samples. **Result:** This study found 59.0% and 19.7% of *EGFR* mutation, 14.75% and 8.20% of *KRAS* mutation in tissues and cfDNA, respectively. Moreover, we found 3.29% of *BRAF V600E*, 1.64% of *MET* exon14 splice site, and 1.64% of *ROS1* mutation in tissue NGS and also confirmed by the other techniques, but there was none of these mutations in the blood sample. Looking at *EGFR*-mutation detected by different techniques, higher sensitivity, specificity, positive-predictive value, negative-predictive values, and concordant rate were found in tissue NGS and liquid ddPCR compared with liquid NGS at cutoff 3% of variant frequency detection, when the gold standard for validation was ARMS-PCR in tissue testing (Table 1).

Table 1. Performance of NGS, ARMS and ddPCR for EGFR mutation detection in matched tissue and cfDNA in lung cancer patients.

	Tissue by ARMS PCR			Result
Tissues by NGS	negative	positive	total	Sensitivity= 87.7%
negative	14	11	25	Specificity= 100%
positive	0	36	36	Positive predictive value= 100%
Total	14	47	61	Negative predictive value= 75.6%
				Concordance = 82%
	Tissue by ARMS PCR			
cfDNA by NGS	negative	positive	total	Sensitivity= 35.7%
negative	12	37	49	Specificity= 98.2%
positive	2	10	12	Positive predictive value= 97.9%
Total	14	47	61	Negative predictive value= 38.9%
				Concordance = 42.6%
	Tissue by ARMS PCR			
cfDNA by ddPCR	negative	positive	total	Sensitivity= 82.7%
negative	14	14	28	Specificity= 100%
positive	0	33	33	Positive predictive value= 100%
Total	14	47	61	Negative predictive value= 69.4%
				Concordance = 77.05%
	Tissue by NGS			
cfDNA by NGS	negative	positive	total	Sensitivity= 36%
negative	20	29	49	Specificity= 93.2%
positive	5	7	12	Positive predictive value= 84.8%
Total	25	36	61	Negative predictive value= 55.8%
				Concordance = 60.66%
	cfDNA by ddPCR			
cfDNA by NGS	negative	positive	total	Sensitivity= 45.5%
negative	25	24	49	Specificity= 97.7%
positive	3	9	12	Positive predictive value= 94.5%
Total	28	33	61	Negative predictive value= 65.6%
				Concordance = 65.58%

Conclusion: Using tissue for molecular profile testing is still being the gold standard testing. Liquid biopsy is less invasive, but in our study, liquid NGS performed less sensitivity, specificity, PPV, NPV, and concordance rate compared with tissue NGS. We need to explore more for proper cutoff of variant allele frequency to develop more sensitivity and specificity of liquid NGS.

Keywords: lung cancer, liquid biopsy, NGS

P3.09-20 A SIMPLE AND VERSATILE NEXT-GENERATION SEQUENCING TECHNOLOGY FOR CO-DETECTION OF RNA STRUCTURAL VARIANTS AND DNA MUTATIONS IN LUNG CANCER

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Background: Variants associated with non-small cell lung cancer (NSCLC) initiation and progression include DNA mutations, copy number variants, RNA fusions and splicing isoforms. Co-detection of DNA and RNA variants has become increasingly important to shorten time from samples to results and optimize personalized medicine for NSCLC. Here we describe the unification of next-generation sequencing (NGS) workflows using library pooling to reliably and sensitively quantify both DNA and RNA variants from tumor FFPE nucleic acids. **Method:** Total nucleic acid (TNA) and DNA were isolated from residual FFPE NSCLC biopsies and cancer cell lines. The QuantideX® NGS RNA Lung Cancer Kit (RUO, Asuragen) and QuantideX® NGS DNA Hotspot 21 Kit (Prototype, Asuragen) were evaluated on the MiSeq® System. DNA and RNA libraries were sequenced on a single MiSeq flow cell. Multiple library pooling strategies were assessed to provide workflow flexibility. All data was analyzed using QuantideX® NGS Reporter 3.0 software. **Result:** The average time from sample QC to MiSeq loading was 10 hours. Including 40-hour instrument run time and data processing and analysis, the sample-to-answer time was less than three days. Library pooling experiments evaluated sample run capacity, coverage uniformity, and variant call accuracy from FFPE TNA and DNA. For example, a single pool of 8 RNA and 16 DNA libraries yielded >500,000 reads for each library, with RNA fusions called with 189 to 11,274 reads and DNA mutations detected down to 5% variant allele frequency. Variant calls were 100% concordant with independent results and included mutations in *EGFR*, *RAS*, *PIK3CA*, and *BRAF*, along with fusions in *ALK*, *RET*, and *NRG1* and skipped *MET*ex14. **Conclusion:** The co-detection strategy generated reliable quantitative information from low-input tumor FFPE DNA and TNA within three days. The simplicity and speed of the approach, coupled with a standardized workflow, has the potential to increase the accessibility of NGS analysis and accelerate the return of results for NSCLC patients.

Keywords: Next-generation sequencing, DNA mutation, RNA fusion

P3.09-21 MIXED MUCOEPIDERMOID CARCINOMA AND ADENOCARCINOMA OF THE LUNG: A CASE REPORT AND A LITERATURE REVIEW

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Background: Primary mucoepidermoid carcinoma of the lung is a rarely reported neoplasm. Synchronous primary malignancies of the lung comprising mucoepidermoid carcinoma and conventional adenocarcinoma are highly unusual neoplasm. **Method:** Case Report: A 75-year-old woman presented with lung mass. Chest computed tomography showed a single 3.5 cm mass over the right lower lobe. **Result:** Microscopic examination revealed the tumor comprised two different histologic components of adenocarcinoma and mucoepidermoid carcinoma. This unique combination of lung malignancies showed characteristic morphologic and immunohistochemical features. Molecular differentiation and genetic mutation analysis would be a valuable tool for the diagnosis of primary lung malignancy with two different histologic types. **Conclusion:** Herein, we present a rare case of mixed mucoepidermoid carcinoma and adenocarcinoma of the lung. In this work, we discuss the clinicopathological features of previously reported mixed mucoepidermoid carcinoma and adenocarcinoma of the lung with its mutation by molecular and genetic analysis.

Keywords: Mucoepidermoid, Adenocarcinoma, lung

P3.09-22 CORRELATION BETWEEN MAXIMUM TUMOUR DIAMETER MEASUREMENT ON CT-SCAN AND HISTOPATHOLOGICAL SPECIMEN: AN INDIAN EXPERIENCE

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Background: Lung cancer is staged according to TNM classification, which encodes the anatomic extent of the disease. This is the most important prognostic factor in patients diagnosed with lung cancer. CT scan is a basic imaging modality used for pre-treatment tumour staging (T staging). Each centimetre increase in size leads to worsening of prognosis. Adjuvant treatment decisions are based upon the final histopathological tumour size. Accurate clinical and pathologic correlation has been an important focus of research in many cancers. The objective of our study is to see for any discordance with respect to tumour size calculated by CT scan and final histopathological specimen in patients of carcinoma lung undergoing upfront surgery. **Method:** All patients of lung cancer operated upfront between 2012 to 2017 were included in the study. Any patient with chest wall involvement, significant pleural effusion and tumours of main bronchus were excluded. CT scans were acquired from the supraclavicular region through the adrenal glands using a 1.25 mm slice thickness with 1.25 mm spacing following deep inspiration. Based on tumour perimeter maximum tumour size was calculated. The largest diameter of resected lung tumour was recorded using a standard ruler by the pathologist. A mean, median and range for both the CT diameter and pathology diameter were obtained. A paired t-test was used to examine the measurement difference between CT and pathology. **Result:** A total of 109 patients were included in the study. Most common histology was Squamous cell carcinoma (n=40,36%), followed by Adenocarcinoma (n=32,29.3%), Neuroendocrine tumour(n=27,24.77%) and other histologies(n=10,9.17%). Among these patients, 22 tumours were located in right upper lobe (20.18%), 10: right middle lobe(9.17%), 25:right lower lobe(22.93%), 31: left upper lobe(28.44%) and 21: left lower lobe(19.26%). The mean size of tumour on CT scan is 4.92cm (SD=1.852cm, range:1-10 cm) and mean size on grossing is 4.5cm(SD=1.774cm,range:0.5-9.5cm)($p<0.05$). The difference between the CT diameter and histopathological size is statistically significant. Tumour location and histology did not add any difference to tumour shrinkage. **Conclusion:** Our study demonstrates that there is a statistically significant difference between tumour diameter as measured by CT and its pathologic size. These differences could have implications in the treatment and prognosis of patients with lung cancer.

Keywords: Pathology, lung cancer, imaging

P3.09-23 ACCURACY AND REPRODUCIBILITY OF TOUCH IMPRINT CYTOLOGY IN RESECTED LUNG CANCER

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Background: With the development of high-resolution computed tomography (CT), small-sized tumors showing ground-glass opacity (GGO) on chest CT images has been more frequently encountered. However, methods such as the transbronchial biopsy and the computed tomography-guided fine-needle aspiration cytology are limited in their ability to diagnose such small lung tumors. We evaluated about the association of the cytological features with the histological examination using the surgically resected specimen. **Method:** 169 patients, age between 31–87 years old, who showed radiological signs of peripheral lung tumors less than 3.0cm in diameter on CT images, underwent surgical resection at our institution between 2015 and 2016. The histological examination was performed on surgical specimen, fixed with 10% formalin and stain with Hematoxylin–Eosin. The cytological examination was performed on stamps from surgical material by Papanicolaou staining. The morphological features were compared both histopathogical diagnosis and cytological diagnosis of imprint cyotology derived from the resected specimen. Interobserver reproducibility was assessed by Kappa coefficient providing a measure for agreement beyond chance. **Result:** By histological examination (in the 169 cases), the diagnostic of lung cancer was given with the establishing of the histological type. In 139 cases (82.2%) of the cases diagnosed as adenocarcinoma, in 25 cases (14.8%) squamous cell carcinoma, in 3cases (1.7%) was neuroendocrine tumors, and one case each of adenosquamous carcinoma and pleomorphic carcinoma. There was 86.3% (146 of 169 cases) agreement with a k statisticvalue of 0.65. Obtained kappa values from imprint cytology showed good (from 0.60 to 0.8) for detection of epithelial cell abnormalities indicating high observer diagnostic reproducibility. **Conclusion:** This kappa statistic method allows assessment of the diagnostic quality of a respiratory cytology. Imprint cytology for small peripheral lung cancer is a useful method for evaluating tumors. Our data indicate the fact that the cytological examination on stamps from surgical material offers a very high percentage of positive results, close to the histological one. But in the tumor size less than 1.0cm, the establishing of the histological type of lung cancer is more difficult by cytological examination. Despite this, the cytology may be extremely useful in diagnose of the small peripheral tumors. The cytological characteristics of small peripheral adenocarcinoma were little reference to the differentiation at the cellular level. Our findings indicated that the presence of several nucleoli and granular chromatin densely are the factors of adenocarcinoma.

Keywords: ground-glass opacity cytology reproducibility

P3.09-24 THE CONCORDANCE OF HISTOLOGICAL DIAGNOSIS FROM TRANSBRONCHIAL BIOPSY AND RESECTED SPECIMEN OF LUNG CANCERS

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Background: Advances in radiological and diagnostic technics have improved the evaluation of pulmonary nodules, leading to an increase in preoperative histological diagnosis. For thoracic surgeons, it is important to know histological types of lung cancer preoperatively for the determination of surgical treatment strategy. The aim of this study is to evaluate the concordance of histological types between biopsy and resected specimens. **Method:** A total of 653 patients with primary lung cancer were operated on in our hospital between January 2013 to March 2018. Among them there were 438 patients who underwent bronchofiberscopic examination, and 364 patients (83.1%) were diagnosed preoperatively as lung cancer. We retrospectively reviewed 316 patients who underwent both transbronchial biopsy (TBB) and

then surgical resection for primary lung cancer between January 2013 to March 2018. We compared diagnosed histological types, examined the accuracy of preoperative diagnosis by TBB, and evaluated the concordance between those two kinds of specimens. **Result:** In 302 of the 316 patients (95%), the histological types of lung cancer diagnosed from TBB matched those from resection specimens (κ=0.878). Concordance rate was the highest in adenocarcinoma (243/245; 99%), followed by squamous cell carcinoma (52/55; 95%). On the other hand, it was only 50% in neuroendocrine carcinoma (small cell carcinoma and LCNEC ± combined with adenocarcinoma / squamous cell carcinoma). Due to histological heterogeneity, 6 of 14 patients were diagnosed with different types of postoperative diagnosis, and four were due to the inconsistency of immunohistochemical (IHC) staining between biopsy and resected specimens. **Conclusion:** We considered that lung cancer has not only histological heterogeneity but also IHC heterogeneity. If larger samples are taken, the preoperative diagnosis of histological type could be more reliable.

Keywords: transbronochial biopsy, resected specimen, Concordance

P3.09 PATHOLOGY
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P3.09-25 SURVIVAL ANALYSIS IN YOUNG ADULTS WITH LUNG CARCINOMA

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Background: Lung cancer is uncommon in young adults and there is no consensus about its behavior in this age group. The aim of this study was to compare clinical and pathological characteristics and median overall survival in young adults (≤ 40 years) and older adults (intermediate: 41-65 years and elderly: > 65 years) with lung carcinoma. **Method:** A retrospective cohort study including information from 21,285 lung cancer cases (ICD – O: C34) diagnosed in the period 2000 – 2009 was performed. Cases were retrieved from the hospital based cancer registries in the state of Sao Paulo, Brazil. Study variables included sex, histological type, cancer staging based on the TNM System, status in the last follow-up, date of diagnosis and date of death. For 1,410 patients, who were initially considered lost to follow-up, a consultation was made through Brazilian databases, such as national registry of deceased, registry of living individuals and voting status in political elections (Brazilian compulsory voting system). After this search, 202 patients remained as loss of follow-up (1.02%). Survival analysis was performed by Kaplan-Meier curve and log-rank tests. **Result:** Among 21,285 patients, 19,900 were further analyzed, after exclusion of patients diagnosed with malignant neoplasms without specification, carcinoid and neuroendocrine tumors and in situ carcinomas. Most patients were diagnosed with adenocarcinoma (49.55%) or squamous cell carcinoma (27.67%) in advanced stage (clinical stages III and IV) (80.26%). Young adults were 542 patients (2.72%), intermediate adults were 10,661 (53.57%) and elderly people were 8,697 (43.70%). Adenocarcinoma was the most prevalent histological type in all age groups (63.09%, young adults vs 49.85%, intermediate adults vs 48.33%, elderly patients) and squamous cell carcinoma was the second most prevalent (14.02%, young adults vs 25.71%, intermediate adults vs 30.93%, elderly patients). In all age groups, most patients presented metastatic disease (stage IV: 58.85%, young vs 51.19%, intermediate vs 43.14%, elder adults). Median overall survival was significantly different among age groups: young adults, 9 months (CI 95%: 7.71-10.28); intermediate adults, 8 months (CI 95%: 7.74-8.25) and elder patients, 7 months (CI: 95%: 6.73-7.26)(p<0.001). **Conclusion:** Most young adults were diagnosed with adenocarcinoma in advanced stage. Although still very troublesome, our results indicated median overall survival was longer in young adults than in older adults.

Keywords: lung carcinoma, survival, young adult

P3.09 PATHOLOGY
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P3.09-26 CONCORDANCE OF SURGICAL RESECTIONS AND FINE NEEDLE BIOPSY-DERIVED CELL BLOCK SECTIONS FOR PD-L1 22C3 IMMUNOHISTOCHEMISTRY

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Background: A significant proportion of lung cancer patients presents at an advanced disease stage. Diagnosis and treatment in these patients is frequently based on small tissue samples such as fine needle biopsies. Eligibility for pembrolizumab immunotherapy requires assessment of the PD-L1 expression. Data on the concordance of PD-L1 assessment by immunohistochemistry between quantitatively limited samples, in particular cytology specimens, and resections are scant. We studied PD-L1 in formalin-fixed paraffin-embedded (FFPE) cell block sections of CT-guided transthoracic fine needle biopsies in comparison with the subsequent resection specimens of the primary lung tumors. **Method:** Paired specimens of fine needle biopsy-derived cell blocks and subsequent lung tumor resections of the same anatomic site were obtained from the archives of the Department of Pathology, University Health Network. Cell blocks were produced from normal saline needle rinse fluids fixed with a final concentration of 10% neutral-buffered formalin and processed using the Histogel method for paraffin-embedding. Cytology samples treated with alcohol-based fixatives were not included. Cell block sections were reviewed for a minimum of 100 tumor cells. Cases below the cellularity threshold were excluded. Staining was performed using the 22C3 pharmDx™ assay (Agilent). All cell block and representative tumor sections were assessed by three observers (1 expert pulmonary pathologist, 2 cytopathologists). Tumor proportion scores (TPS) were recorded and a final TPS was determined using the mean between expert and second closest observer. Cases close to the ≥50% cut-off underwent multiheader microscope review. Pearson, intraclass correlation coefficients and test parameters were calculated using standard statistical methods. **Result:** 43 paired cases were informative. Mean interval between biopsy and resection was 1.5 months (range 0-4). TPS of cell blocks and resections showed positive correlation (Pearson: 0.8; range 0.78 - 0.84 for individual observers). Intraclass correlation coefficients were 0.97 (cell blocks) and 0.92 (resections). 10/43 (23%) cell blocks and 9 (21%) resections were positive at TPS≥50%. 21/43 (49%) cell blocks and 19 (44%) resections were positive at TPS≥1%. Sensitivity, Specificity, PPV, NPP and accuracy were 78/74, 91/71, 70/67, 94/77 and 88/72% for the ≥50/≥1% cut-off, respectively. **Conclusion:** Cytology FFPE cell block sections showed strong positive correlation with resection specimens of the same anatomic site for PD-L1 assessment using the 22C3 pharmDx™ immunohistochemistry assay. Reliability between observers was excellent. Test parameters, in particular for the ≥50% cut-off value, were deemed acceptable for clinical use. Selected slide review of cases with discordant scores indicated tumor heterogeneity as cause.

Keywords: cytology, PD-L1, Immunotherapy

P3.09 PATHOLOGY
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P3.09-27 HISTOPATHOLOGIC PARAMETERS DEFINE FEATURES OF TREATMENT RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER

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Background: Previous studies indicate that neoadjuvant chemotherapy improves survival in patients with loco-regionally advanced non-small cell lung cancer (NSCLC). The amount of residual viable tumor has been associated with long-term overall survival. This histopathologic

measure has potential to become a standard method for evaluation of the effectiveness of neoadjuvant therapy regimens. However, adequate comparison of chemotherapy-treated and untreated lung cancers is lacking. We analyzed histopathologic characteristics of resected NSCLC with and without prior neoadjuvant chemotherapy. **Method:** Histopathologic assessment was performed of specimens obtained from patients enrolled on the immunogenomic lung cancer study (ICON), which integrates clinical, pathologic, immune, genomic and outcome data from surgically resected NSCLC. Cases included material from 10 patients who underwent neoadjuvant chemotherapy and 10 patients treated with primary surgery (adenocarcinoma, n=5; squamous cell carcinoma, n=5; for each cohort). Hematoxylin and eosin-stained tumor sections (mean, 6; range, 3-10) were evaluated and semiquantitatively scored for parameters commonly attributed to treatment response. The percentage of viable tumor was estimated by comparison to the proportion of fibrosis and necrosis on each slide. Additional parameters analyzed included the presence of inflammation, tertiary lymphoid structures (TLS), macrophages, lymphovascular invasion (LVI), cholesterol clefts, giant cells and neovascularization (score 0-3). For each patient, the results for all slides were averaged to determine a mean value. P values were calculated using the Mann-Whitney test. **Result:** All histopathologic parameters typically associated with treatment response could also be identified in untreated specimens, albeit in different proportions. Compared to the untreated cohort, samples after chemotherapy were characterized by lower proportion of viable tumor (42.4% vs 67.7%, p=0.04) and higher degrees of fibrosis (46.6% vs 26.6%, p=0.08), and necrosis (11.0 % vs 5.6%, p=0.35). Among the additional parameters, similar scores were seen for inflammation (1.54 vs 1.46, p=0.60), TLS (1.00 vs 0.80, p=0.47), LVI (0.16 vs 0.23, p=0.62), and neovascularization (both 0) while macrophages (0.94 vs 0.12, p=0.20), cholesterol clefts (0.92 vs 0.13, p= 0.03) and giant cells (0.80 vs 0.40, p=0.17) were more common among the neoadjuvant cohort. **Conclusion:** Histopathologic variables commonly associated with chemotherapy treatment response can also be identified in treatment naïve lung cancers. However, the amount of viable tumor, fibrosis and cholesterol clefts are parameters strongly associated with neoadjuvant therapy. These results highlight the importance of assessing the type and extent of treatment response. Analysis of larger patient cohorts will reveal potential prognostic value in primary tumors, chemotherapy-treated, and eventually immunotherapy-treated tumors.

Keywords: NSCLC; chemotherapy; pathology

P3.11 SCREENING AND EARLY DETECTION
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P3.11-01 METHYLATION MARKERS THAT CORRELATE WITH OCCULT LYMPH NODE METASTASES OF NSCLC AND A PRELIMINARY PREDICTION MODEL

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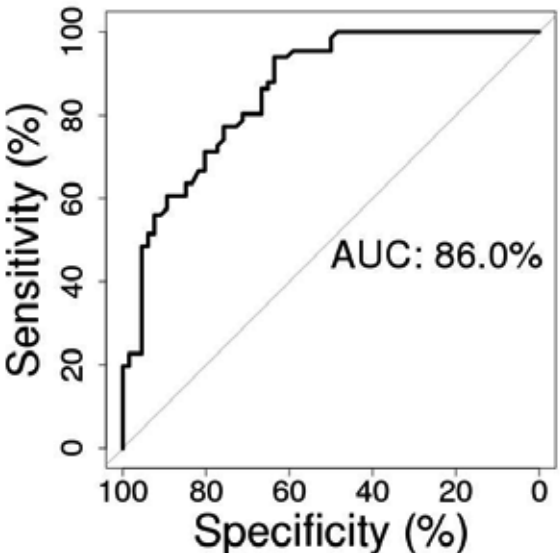
Background: Lymph node (LN) metastasis status is the most important prognostic factor and determines the treatment strategy. The current imaging approaches are not sufficiently precise to diagnose occult LN metastasis before surgery, while the invasive biopsy fails to be widely used. Therefore, more precise and non-invasive methods are warranted to determine the lymph node status preoperatively and lead to appropriate treatment strategy. Methylation alteration is an optimal candidate to trace the signal from early stage tumors due to its early existence, multiple loci and stability in blood. To build a diagnostic tool, we shall firstly screen and identify a set of plasma methylation markers. **Method:** High-throughput targeted methylation sequencing was performed on plasma and matched tissue samples from a cohort of 134 lung cancer patients with a primary lesion less than 3 cm in diameter. The methylation profiles were compared between patients with and without occult LN metastases. A preliminary prognostic model was built by random forest by integrating both top 5 hypermethylated genes and top 5 hypomethylated genes. **Result:** Within this cohort, 22 cases were found to have occult LN metastases found by pathological examination. Thus, we selected the other 22 cases without occult LN metastasis by matching gender, age, smoking history and tumor histology. Hypermethylation on 32 genes, such as TNFRSF1B, DMRTA2, VAV3-AS1, HIST3H2A, PALD1, NKX2-3, MAP3K12, MAPK10, were identified between the two groups. Hypomethylation on 20 genes, such as RAB42, KCNN3, UBE2L6, RARG, CRY1, MTUS2, TMEM179, MEGF11, were also detected. 25% (13 out of 52 genes) of these markers could be found in the matched tissue samples. The AUC of ten fold cross validation of the preliminary prediction model is 0.86.



Conclusion: We found some specific plasma methylation markers for occult LN metastasis of NSCLC. Further efforts should be made in establishing a non-invasive blood diagnostic tool.

Keywords: OCCULT LYMPH NODE METASTASES, NSCLC, methylation

P3.11 SCREENING AND EARLY DETECTION
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P3.11-02 LUNG CANCER SCREENING IN A HIGH INCIDENCE POPULATION: RESULTS OF LOW-DOSE CT SCREENINGS IN A NORTHERN KENTUCKY COMMUNITY HEALTHCARE SYSTEM

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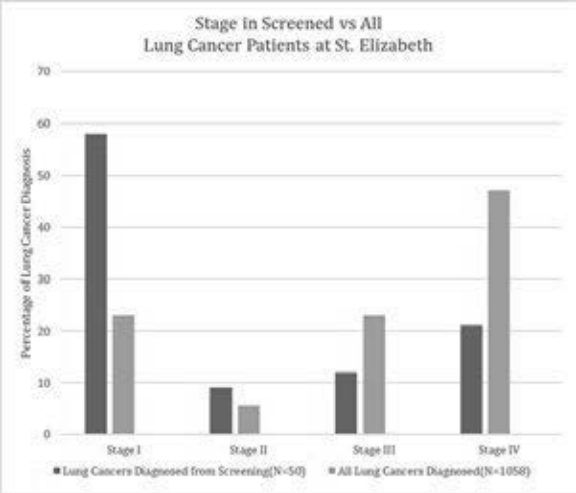
Background: The National Lung Screening Trial (NLST) demonstrated that low-dose CT screening increases lung cancer-related survival in at-risk patients. In the U.S., Kentucky has the highest rate of lung cancer, worst historical survival rates and could benefit greatly from a robust screening program. However, concerns have been raised that lung cancer screening performed broadly in the community may not replicate NLST results. Here we evaluate the initial 3 years of a Northern Kentucky community healthcare system lung cancer screening program. **Method:** Medical records related to screening low-dose CTs performed in the St. Elizabeth Healthcare System from January 1, 2015 through February 28, 2018 were retrospectively reviewed. Statistical significance was calculated using a two-sample t-test ($p < 0.05$). **Result:** Overall, 3,496 low-dose CTs were completed. Screenings increased annually, with 218 performed in 2015, 716 in 2016, 1933 in 2017 and 629 through February 2018. Incidences of interventions resulting from screening findings were tallied (Table 1). Screenings produced a shift to an earlier stage at diagnosis (Figure 1). Table I

	Number	Adverse Events	Death
Total Screens	3496	0	0
Additional Imaging	428	NM	NM
Diagnostic Procedures	70	4(6%)	0
Lung Cancers	50(1.4%)	NA	NA
Surgical Resections	30	9(30%)	1(3%)
Chemotherapy and/or Radiation	28	NM	NM

NA-Not Applicable NM-Not Measured Figure I



Conclusion: The NLST results can be replicated in a community healthcare system with a high incidence of lung cancer.

Keywords: community healthcare system, lung cancer stage shift, lung cancer screening

P3.11 SCREENING AND EARLY DETECTION
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P3.11-03 IMPLEMENTING LUNG CANCER SCREENING IN CANADA: EVIDENCE ON ADHERENCE AND BUDGET IMPACT FROM THE PAN-CANADIAN EARLY DETECTION STUDY

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Background: High-risk lung cancer screening has favourable cost-effectiveness ratios; making it an attractive intervention for lung cancer control. Relatively little is known, however, about the implementation of lung cancer screening in universal health care systems. To address this, we characterize screening adherence rates in the Pan-Canadian Early Detection of Lung Cancer Study (PanCan) and prepare a budget impact analysis for Canada. **Method:** We retrospectively characterized screening adherence to short-term (first-year) and long-term (year-four) annual screening rounds in the PanCan study and explored association with socio-demographic and screening characteristics with logistic regression models and Mann-Whitney rank sum and Chi square likelihood tests. We did a four-year budget impact analysis using published utilization rates for screening-related and incidental healthcare resources, smoking cessation, opportunistic screening and projected market dynamics for entrant treatments in Canada. **Result:** The PanCan study screened 2537 participants with a baseline LDCT exam; of these, 2254 (88.9%) adhered to the second annual screening exam and 1,762 (69.5%) adhered to the year four exam. After adjusting for lung cancer incidences and other-cause mortality, we found significant associations between self-reported "current smoker" status and lower, second annual scan adherence rates ($p<0.05$); while variables related to the delivery of the intervention—such as the use of screening autofluorescence bronchoscopy and finding a lung nodule on the baseline LDCT—were significantly associated with greater adherence ($p<0.05$). Adherence to year-four screening exams was positively associated with age, family history of lung cancer, baseline quality of life and prior screening exam adherence (all $p<0.05$). Non-adherence was significantly associated with participants who had greater than 100 pack-years of smoking history and a lower level of formal education ($p<0.05$). Compared to participants who adhered to their scheduled, year-four annual screening exams, non-adherent participants had a higher predicted risk of developing lung cancer at baseline ($p<0.05$). The budget impact analysis indicates that the incremental program costs for screening an estimated 257, 914 eligible, high-risk, Canadians would be highly favourable compared to selection based on age and smoking history alone. The budget impact was also sensitive to uncertainty around the cost to treat actionable incidental findings and the adoption of entrant systemic therapy drugs. **Conclusion:** Study participants who were at the highest risk of developing lung cancer, were the least likely to adhere to screening. Using risk selection would enable affordable programs; however, programs may be compromised by barriers to participation for individuals who are at the greatest risk of developing lung cancer.

Keywords: high-risk screening, Cost-effectiveness, Screening Implementation

P3.11 SCREENING AND EARLY DETECTION
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P3.11-04 TRENDS AND BARRIERS IN LUNG CANCER SCREENING IMPLEMENTATION ACROSS THE UNITED STATES.

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Background: In 2010, the National Lung Screening Trial was halted after showing a 20% reduction in mortality for high risk individuals when three years of annual lung cancer screening was performed by low dose computed tomography(NEJM, 2011). Many questions remained about whether screening could be properly implemented in non-academic, community settings. Lung Cancer Alliance developed a National Framework for Excellence in Lung Cancer Screening and Continuum of Care in 2012 and began a nationwide network dedicated to responsible lung cancer screening. The Screening Center of Excellence (SCOE) designation requires a center to ensure shared decision-making, comply with best practice standards, work with a multidisciplinary care team, deliver or refer for smoking cessation, provide results in a timely manner, and meet technical specifications set by the American College of Radiology. Our aim is to promote high-quality, responsible lung cancer screening throughout the United States, including in community settings where most lung cancer is diagnosed. **Method:** From 2012 through 2017, over 500 centers were designated as SCOEs. These centers represented 42 states and more than 60% were from community/non-academic centers. High-risk individuals who come to the Lung Cancer Alliance website or contact the organization by phone to find a screening center are directed to a SCOE. A data collection effort in 2017, being repeated in 2018, collected comprehensive information about the state of lung cancer screening and care at the SCOEs. Nearly 70% of SCOEs responded to the 2017 survey. **Result:** The SCOE program data shows that screening is being performed widely across the United States, including in non-academic centers. For centers who were able to provide numbers of screenings performed and diagnoses, we identified a clear trend in diagnosis of Stage 1 lung cancer, indicating these screenings are able to find lung cancer early. We also identified a number of implementation challenges around referral patterns, insurance and billing, and determining appropriate risk criteria. Rates of adherence to both annual scans and recommended follow-up varied widely across different institutions indicating a key area of focus for future implementation research. **Conclusion:** We have shown that a patient advocacy group working with medical professionals can help deliver high quality care to a broad population. Data collection from the SCOEs provides a snapshot of the state of lung cancer screening in the United States that underscores the success of screening and the importance of early detection but also identifies barriers in implementation that still need to be addressed.

Keywords: implementation, Screening, LDCT

P3.11 SCREENING AND EARLY DETECTION
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P3.11-05 USE OF ELECTRONIC MEDICAL RECORD (EMR)-EMBEDDED CLINICAL DECISION SUPPORT TOOLS IMPROVES LUNG CANCER SCREENING RATES

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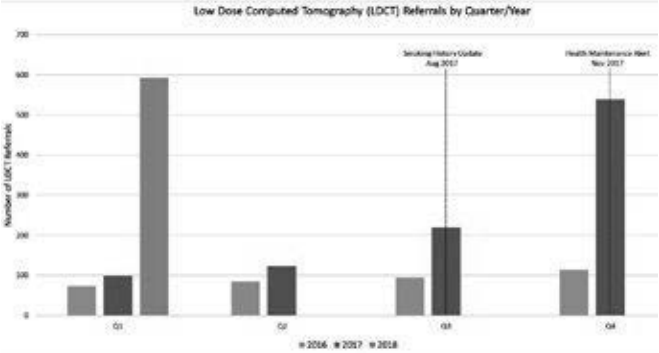
Background: Atrium Health (AH) is a large, community-based healthcare system serving approximately 1.1 million primary care patients in the southeastern United States. In this region lung cancer incidence, death rates and rate of advanced stage of disease at diagnosis are among the highest in the nation. Previous work demonstrated that primary care providers in our region were not aware of lung cancer screening eligibility requirements. AH aimed to improve lung cancer outcomes for our patients by integrating new clinical decision support tools within our electronic medical record (EMR) to increase referral rates to our lung cancer screening program. **Method:** We collaborated with the AH Information and Analytics Services team to embed new clinical decision support tools within the EMR simplifying identification of patients eligible

for lung cancer screening. We first revised the smoking history section of the EMR with data fields to record the number of years a patient smoked, the average packs consumed per day and the specific quit date for former smokers. A health maintenance alert (HMA) was then designed which would appear in a conspicuous location in the charts of patients aged 55 to 77 with a 30 pack/year smoking history who were active smokers or former smokers with quit dates within the last 15 years. **Result:** Since integration of the clinical decison support tools into the EMR, over 22,000 patients in our system who meet eligibility criteria have been identified. Lung cancer screening referrals in the first quarter of 2018 increased by almost 500% compared to quarter 1 2017.



Conclusion: Clinical decision support tools embedded into the EMR have increased lung cancer screening rates among AH patients.

Keywords: clinical decision support tool, lung cancer screening, health maintenance alert

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P3.11-06 IMPROVING LUNG CANCER SCREENING COMPLETION RATES IN A PRIMARY CARE PRACTICE IN LARGE URBAN ACADEMIC MEDICAL CENTER

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Background: Despite implementation of a physician-facing electronic health record (EHR) best practice alert (BPA) with robust medical decision making and documentation, only 7.3% of eligible patients (85 of 1170) throughout the institution completed a low-dose CT (LDCT) for lung cancer screening in 6 months (May 1st to November 1, 2017). The objective is to improve lung cancer screening by: 1. Describing primary care referral patterns and status among eligible patients 2. Identifying system, patient and provider-level barriers to referral and completion 3. Developing and testing targeted interventions Success will be measured by reducing number of eligible patients overdue for screening by 50% in the next 6 months. **Method:** An Epic EHR report identified patients with an overdue lung cancer screening BPA within one practice representing approximately 40% of primary care (16,000 visits in 6 months). Through chart review, we quantified number of patients at different points of the referral pathway. New interventions were developed for the most common categories of patients overdue for screening: Those with orders that had not scheduled the exam and those with no order and no documentation of why in the EHR. Lung Cancer Screening Coordinators contacted patients with current orders and began scheduling LDCT exams. (Intervention 1). Division leadership, medical directors, primary care providers (PCP), and the practice nurse manager were engaged to design an intervention to address patients with no LDCT order (Intervention 2) **Result:** The total number of LDCTs performed in the first 12 weeks after starting the intervention was almost equal to the performed in the 6 month baseline period. (12 vs 14). The percentage of patients overdue with orders increased from 28% to 37.5%. Only 7 of the original 18 with orders not scheduled remained in that category at 12 weeks. The percentage of patients overdue with no order and no documentation decreased from 65.9% of to 51.3%. Fifteen of 41 with no order and no reason documented (36.5%) were newly identified at 12 weeks, i.e. not identified by the baseline query. The most significant limitation to measuring 12-week outcomes is that patients have not yet completed their scheduled PCP appointments and LDCT appointments. **Conclusion:** Multiple challenges were identified at system, patient and provider levels: *The BPA lacks specificity. *This patient subpopulation has a high prevalence of comorbidities and chronic conditions. *PCPs expressed skepticism regarding evidence for lung cancer screening, perceived lack of benefit for some patients and competing demands.

Keywords: LDCT, lung cancer screening best practice alert (BPA), lung cancer screening

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P3.11-07 THE QUALITY OF SCREENING: COMPARING THE RUSH LUNG CANCER SCREENING PROGRAM TO THE NLST AND THE VA LUNG CANCER SCREENING DEMONSTRATION PROJECT

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Background: The National Lung Screening Trial (NLST) was conducted for the purpose of determining the efficacy of using a low dose computed tomography (LDCT) scan to screen for lung cancer screening versus chest x-ray. Findings demonstrated a reduction in mortality by 20.0%. In 2013, informed by the findings from the NLST, the United States Preventative Services Task Force (UPSTF) gave lung cancer screening a grade B recommendation. This recommendation eventually led to both private insurance coverage and in 2015, Centers for Medicare and Medicaid Services (CMS) coverage of low dose computed tomography (LDCT) scans to screen for lung cancer. In 2017, the US Department of Veterans Affairs (VA) published *the experience of implementing a lung cancer screening program* (LCSDP). This publication attracted the attention of the medical community and media, generating concern over the value of LDCT scans indicated to screen for lung cancer. The Rush University Medical Center Lung Cancer Screening Program (RLCSP) is in its third year of implementation and adheres to best practices for the evolving discipline of lung cancer screening. **Method:** To compare the structure and findings of the Rush Lung Cancer Screening Program (RLCSP) to two well-known published initiatives: the National Lung Screening Trial (NLST) and Implementation of Lung Cancer Screening in the Veterans Health Administration (LCSDP). **Result:** 1 in 29 people screened with the RLCSP has lung cancer, compared with 1 in 68 people screened with the LCSDP, and 1 in 320 screened with the NLST. The RLCSP has a more diverse demographic base, and fewer false positive scans than the NLST or LCSDP. **Conclusion:** The NLST is a research study that was conducted for the purpose of testing the efficacy of using a LDCT scan versus chest x-ray to screen for lung cancer. The purpose of the LCSDP is to address feasibility of implementing a lung cancer screening program within the VA system; The LCSDP is an implementation project and not a clinical research study. RLCSP is a screening program that was implemented in a university hospital setting, which closely adheres to best practices with strong results. Data from the RLCSP supports findings from the NLST that LDCT is an effective scan to screen for lung cancer.

Keywords: lung cancer screening, low dose computed tomography (LDCT), National Lung Screening Trial (NLST)

P3.11 SCREENING AND EARLY DETECTION
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.11-08 LUNG CANCER SCREENING AT AN ACADEMIC MEDICAL CENTER: EARLY PATTERNS OF PRACTICE

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Background: Lung cancer screening with low dose computed tomography (LDCT) is associated with a reduction in lung cancer mortality. The Center for Medicare and Medicaid Services (CMS) offers coverage for LDCT, indicated for lung cancer screening, if patients are between ages 55 and 77, are a current smoker or former smoker who has quit smoking in the past 15 years, have a greater than 30 pack year smoking history, and shows no signs or symptoms of lung cancer (hemoptysis and/or weightless). Rush University Medical Center has a Best Practice Alert (BPA) in Epic to notify physicians of patients who meet criteria to receive LDCT scans for lung cancer screening. The BPA fires based on patient's age and documented pack year smoking history. Successful utilization of the BPA relies heavily on accurate smoking documentation. As part of an ongoing project characterizing the population who ultimately undergoes screening, it became evident that a significant number of patients whom may be eligible for screening are missed due to incomplete smoking documentation. These initial findings highlight the need to develop an improved, accurate, and more convenient system to document smoking history. **Method:** A retrospective chart review was performed, utilizing electronic medical records, for data from October 2015-October 2017. Data was collected on age, gender, and smoking status. Based on this timeframe, data for 50,421 patients from Rush University Medical Center (RUMC) and Rush Oak Park Hospital (ROPH) was analyzed. Age was

restricted to 55-77 years to match CMS re-imbursement criteria. **Result:** Of the 50,421 patient charts analyzed, 2,720 (5%) met eligibility criteria for lung cancer screening based on their documented smoking history. The majority of patients, 38,197 (76%), had incomplete smoking history documentation. Out of the patients with incomplete smoking history documentation, many charts were missing documentation of smoking history in pack year, and/or the number of years it has been since the patient quit smoking. **Conclusion:** Data identifies a key weakness in electronic health record documentation of smoking history at RUMC and ROPH. Since the BPA for lung cancer screening only triggers with a documented smoking history of greater than 30 pack years, patients who may be eligible for lung cancer screening are not being identified. By advocating for more thorough documentation of patient smoking history, we can optimize use of the BPA and provide patients with better health management.

Keywords: low dose computed tomography (LDCT), smoking documentation, lung cancer screening

P3.11 SCREENING AND EARLY DETECTION
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.11-09 SHARED DECISION MAKING; A DECISION AID FOR THE PRIMARY PRACTITIONER

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Background: Lung cancer (LC) remains the number one cancer killer of both men and women. Despite general agreement that computerized tomographic (CT) lung cancer screening (LCS) is safe and effective, with first-dollar insurance coverage available from CMS, uptake of LCS among those at risk is currently less than 5%. Centers for Medicare and Medicaid Services (CMS) mandates shared decion making (SDM) using decision aids (DA) providing specific information. Only half of primary care practitioners (PCPs) know USPSTF guidelines and identify multiple barriers to guideline adherence. Although half of PCPs know how to work up positive test results, most prefer to refer such patients to specialists. Compounding these problems, existing DAs provide inaccurate and difficult to understand information. PCPs require accurate information to fulfill their obligation to patients in SDM. **Method:** Research and clinical results from the prospective, international, multi-institutional cohort research project, International Early Lung Cancer Action Program (IELCAP) and National Comprehensive Cancer Network (NCCN) over 20 years was reviewed and distilled into content aimed to provide accurate, up-to-date information for PCPs to use in answering patient questions during SDM consultation. Information is summarized in "stick figure" graphics. **Result:** Multiple current LCS DAs provide gratuitously inaccurate information, e.g. that only 21% with LC in LCS survive 5-years. IELCAP and NCCN research results show that cancer detection rate with adhernce to annual CT screening is 12.5% (1 in 8) / decade in both NCCN risk groups 1 and 2. Baseline false positive rate is 10% at baseline screen; 5% during annual repeat screens. More than 80% of LC are early-stage. 10-year actuarial LC survival exceeds 80%. With guideline adherence, 10% of false positives have biopsy or surgical removal of a benign nodule and overtreatment of slow-growing, pre-invasive LC is avoidable. Screen-detected LC are increasingly treated with minimally invasive operations, often with sub-lobar resection, with equivalent cure rates and lower morbidity. Operative mortality is less than 1%. Radiation therapy is available for treatment of early-stage LC in patients with increased surgical risk. Radiation exposure is smal; there is no evidence of substantial risk of radiation carcinogenesis in adults receiving LCS. **Conclusion:** A new DA, reflecting results in LCS from IELCAP and NCCN centers provides PCPs with accurate information for SDM sessions with patients at risk of LC. PCPs providing accurate, coherent information to patients can play a major role in prevention of many housands of unnecessary LC deaths.

Keywords: lung cancer screening; shared decision making; decision aid

P3.11 SCREENING AND EARLY DETECTION
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P3.11-10 LUNG CANCER SCREENING SHARED DECISION MAKING:DECISION-AID FOR THE PATIENT

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Background: Despite general agreement in the U.S. that lung cancer screening (LCS) is effective and safe, with availability of insurance coverage for those at high-risk, screening uptake is less than 5%. Patients in Medicare and Medicaid (CMS) must participate in "shared decision making" (SDM) with a primary care giver and a "decision-aid" (DA) used. A major potential contributor to low LCS uptake is inaccurate and difficult to understand information on LCS benefits and risks contained in currently-available DAs. A gratuitous example is the statement "4 of 5 patients slip through to die of LC". We offer a new DA that provides information required by CMS, based upon lessons learned from twenty years research and clinical experience in the International Early Lung Cancer Action Program (IELCAP), and reflected in the LCS guidelne of the National Comprehensive Cancer Network (NCCN). **Method:** Currently available DAs used in LCS were reviewed and compared with published results from LCS programs participating in IELCAP and NCCN with findings distilled to provide information required by CMS and understandable by patients of average intelligence. **Result:** When an individual with NCCN risk criteria levels 1 or 2 receives a low-dose CT scan annually, as a participant in a screening program using the IELCAP or NCCN diagnostic guidelines, and reliably follows recommendations for further testing or treatment, benefits and risks described herein may be confidently anticipated. Based on recent data from LCS at the Lahey Clinic, with optimal uptake, 12.5% 1 in 8) of those screened will be diagnosed with LC over a decade, more than 80% in early stage. At baseline screen 10.4% will have a positive test result but not be diagnosed with LC during that screening cycle (false-positive). Subsequent annual repeat scans will have 5% false positives. In IELCAP centers actuarial ten-year LC-specific survival exceeds 80% after diagnosis of LC. Application of IELCAP's algorithm results in invasive biopsy or surgical resection of benign nodules in less than 10%. Patients diagnosed by LCS are increasingly treated with minimally-invasive, sub-lobar resections that offer equivalent survival with less morbidity. Fewer than 1% die after surgery. Benefits of screening will diminish and disappear over time if annual screening stops. Higher risks may be experienced if diagnostic and treatment decisions deviate from those recommended. **Conclusion:** If patients at high risk of LC participate in SDM using the DA presented, it can be confidently anticipated that LCS uptake will increase, with increased future survival and reduced LC mortality.

Keywords: shared decision making, decision aid, lung cancer screening

P3.11 SCREENING AND EARLY DETECTION
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.11-11 IMPROVING TIMELINESS OF LUNG CANCER DIAGNOSTIC SERVICES WITH THE IMPLEMENTATION OF COORDINATED CARE VIA A "NAVIGATION DAY"

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Background: Lung cancer patients often experience stressful wait times and delays throughout the diagnostic phase of care. In an effort to streamline this process, a multidisciplinary team at The Ottawa Hospital (TOH) created a "Navigation Day" whereby patients and their family partake in a day-long visit and receive concurrent coordinated testing. At the Navigation Day, patients have teaching, introduction to social work, access to specialist care for symptom control, and same day appointments via dedicated test slots for positron emission tomography–computed tomography (PET-CT) scans, pulmonary function tests (PFTs) and/or magnetic resonance imaging (MRI) of the head. We evaluated the impact of this program on wait times and patient satisfaction. **Method:** Patients with a suspicion of lung cancer on chest CT who were referred during three time periods relative to the implementation of Navigation Day were included: one year pre-launch, one year post-launch, and two years post-launch. Mean wait times for PET, PFT, and/or MRI tests were calculated for each time period. To specifically assess the impact of dedicated slots on wait times, patients within each time period were stratified according to whether they underwent their test on the same day or different day from their Navigation Day. Student's t-test and ANOVA were used to assess for significance. Patient satisfaction was measured by examining provincially-collected data from a standardized survey used by all diagnostic assessment programs in Ontario, and data from program-specific feedback surveys distributed at TOH. **Result:** At one year post-launch, mean wait times improved from 15.5 to 9.2 days for PET ($p<0.0001$, t-test), from 15.7 to 9.6 days for PFT ($p<0.0001$), and from 16.0 to 10.2 days for MRI ($p<0.0001$). These improvements were sustained at two years post-launch, and MRI wait time improved even further from 10.2 to 6.6 days ($p<0.0001$, t-test). Those patients who underwent tests within a dedicated slot experienced the shortest wait times for all tests, at 5.8 days for PET, 5.8 days for PFT, and 6.3 days for MRI ($p<0.0001$, ANOVA). Wait time dispersion also improved by 11.2%

for PET, 10.1% for PFT, and 19.1% for MRI. Patient satisfaction in the categories of quality of care, rapidity of care, coordination of care, and being informed remained high following the implementation of Navigation Day. **Conclusion:** Implementation of a Navigation Day significantly improved timeliness of diagnostic services (PET, PFT, and MRI) for potential lung cancer patients. This program represents an innovative service delivery model for other lung cancer care centers.

Keywords: lung cancer, timeliness, Diagnostic services

P3.11 SCREENING AND EARLY DETECTION
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P3.11-12 COMPARISON OF CANCER SCREENING ADHERENCE ACCORDING TO SMOKING STATUS: KOREA NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY 2010-2012

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Background: Smokers who are aged 55 to 74 years with 30 pack-years or more of smoking-history are regarded as high risk subjects for lung cancer, and recent study revealed lung cancer screening with low-dose CT (LDCT) could reduce lung cancer mortality of high-risk individuals. The purpose of this study was to compare the general medical checkups and cancer screening practice pattern according to self-reported smoking status. **Method:** Using a representative dataset from the Korea National Health and Nutrition Examination Survey (KNHANES) IV from 2010 to 2012, we compared the adherence of general medical checkups and cancer (gastric, colorectal, breast, and cervical cancer) screening practice of Korean adults (55-74 years) according to self-reported smoking status; heavy smokers (≥ 30PY), non-heavy smokers (< 30PY), and never-smokers. Socio-demographic factors (gender, age group, obesity, education, marital status, income, insurance status), health-related lifestyle behavior (drinking status, exercise), and comorbidities (HTN, DM, hyperlipidemia, and self-reported health status) were also collected. **Result:** For the 5,480 respondents, the weighted prevalence of heavy smokers, non-heavy smokers, and never-smokers was 19.3%, 23.5%, and 57.2%, respectively. The overall screening rate was 70.7% (health), 59.1% (stomach cancer), 58.1% (colorectal cancer), 59.1% (breast cancer), and 48.9% (cervical cancer). The screening rates for colorectal cancer are lower in heavy smokers compared with never-smokers even after adjusting covariates (OR=0.71, 95% CI=0.52-0.95). The adherence of general medical checkups and other cancer (gastric, breast, and cervical cancer) screening were not different according to self-reported smoking status. **Conclusion:** The results of this study suggest that high risk subjects for lung cancer were less likely to be screened for colorectal cancer than never-smokers, however, no difference was observed in the adherence of general medical checkups and other cancer screening. This finding provides a better understanding of the screening practice adherence for this population.

Keywords: lung cancer, Screening, smoking

P3.11 SCREENING AND EARLY DETECTION
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P3.11-13 LIVERPOOL IDENTIFIES THE HARD TO REACH POPULATION AT RISK OF DEVELOPING LUNG CANCER.

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Background: The Liverpool Healthy Lung Programme (LHLP) is an initiative aimed at improving respiratory health and diagnosing respiratory disease at a more treatable stage, taken by the Liverpool Clinical Commissioning Group (CCG) working with communities across Liverpool. Liverpool has one of the highest respiratory morbidity rates in England, with double the national lung cancer incidence, particularly in lower socioeconomic groups. The Liverpool Healthy Lung Programme was initiated in response to both the clinical problem and the health inequality. **Method:** General practice records targeted ever-smokers and subjects with chronic obstructive pulmonary disease (COPD), 58-70y and were invited for 45-minute lung health check. Positive lifestyle messages were promoted; 5-year personal lung cancer risk calculated (www.MyLungRisk.org using LLPv2 risk model). Those who trigger the 5% threshold were offered a LDCT-scan. Spirometry was used to assess lung function (FEV1/FVC); those with abnormal results referred for potentially definitive diagnosis of COPD. Smoking advice and referrals to smoking cessation clinics were provided. Patients CT detected nodules were managed, based on BTS guidelines; referred to MDT for work-up and significant other findings (SoF) were analysed in detail. **Result:** 3,591 Healthy Lung Programme consultations (consented). 11,526 people were invited, 4,566 (40%) attended. 1,853 (52%) were male, 2,897 (81%) in the most deprived IMD quintile. 832 (23%) subjects had an existing diagnosis of COPD and 527 (15%) had a previous diagnosis of cancer. 1,173 (33%) subjects had a family history of cancer. 1,548 (99.3% meeting LLP_{v2} 5% risk criterion) were offered CT scan. 119 (9%) patients required further investigations (follow-up CT scan at 3 or 12 months, or immediate MDT referral), 25 (1.9% undergoing CT scan) were diagnosed with lung cancer (11 have suspected lung cancer, undergoing further investigations). Analysis of a sub-set of the SoF findings were followed up and indicated benefit to participants. **Conclusion:** The results suggest that it is feasible to achieve similar clinical outcome benefits to those observed in the US trial of LDCT screening for lung cancer, with lesser harms in terms of unnecessary diagnostic activity. However, this needs confirmation with extended follow-up, larger numbers of lung cancers diagnosed, and the addition of mortality data. Additional randomised trial results would also add to the precision of estimation of benefits and harms, in particular mortality results from the large European trial, NELSON. In the meantime, the results of LHLP suggest that it is succeeding in early detection of both COPD and lung cancer.

Keywords: Implementation in primary care, CT screening, Risk stratification in CT screening

P3.11 SCREENING AND EARLY DETECTION
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P3.11-14 LOW RATES OF LUNG CANCER SCREENING AMONG DOCTORS IN MEXICO

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Background: Lung cancer represents the leading cause of death from cancer worldwide and in Mexico. Most patients are diagnosed in advanced stages at the time of diagnosis and treatment in these cases is palliative. Lung cancer screening with low-radiation exposure tomography has shown to reduce mortality due to early detection of the disease in high-risk individuals. In Mexico more than 80% of patients are diagnosed in the metastatic stage. Our objective is to know the frequency of screening for lung cancer among neumologists, thoracic surgeons and oncologists in Mexico and the reasons why they do not. **Method:** Transversal, descriptive study, carried-out during the international congress of pneumology and thoracic surgery from April 2-6, 2018, in Guanajuato, Mexico. A survey was conducted in Mexican doctors from different specialties and different public and private institutions, they were questioned if they consider screening for lung cancer useful, if they do it, if the screening can be applied to Mexico and what are the barriers that it finds not to do it. The data were emptied into a database in the SPSS v23 system and descriptive statistics were made for the analysis. **Result:** A total of 147 specialist doctors were interviewed, 49% were oncologists, 43% were neumologists and 8% were chest surgeons. Despite the fact that 86% considered screening to be useful, only 36% performed it within their daily clinical practice. The main barriers they found to implement screening in our country were due to multiple factors according with response of 70% of physicians where lack of CT scan and qualified personnel to interpret image results were the most prevalent. The remaining 30% considered only one factor as the most important where the lack of infrastructure (CT scan) was the most prevalent in 14% of the answers. **Conclusion:** Although the specialists in prevention, diagnosis and treatment of lung cancer in Mexico are aware of the usefulness of screening for lung cancer, the frequency of implementation is low, mainly due to lack of appropriate infrastructure and trained personnel. It is necessary to implement public health policies to promote screening in the majority of patients who meet the high-risk criteria to increase early diagnosis and subsequently improve survival outcomes in this population.

Keywords: diagnosis in latin-america, Screening, Early Detection

P3.11-15 LUNG CANCER SYMPTOM PERCEPTION AND INTERVENTION PREFERENCES IN THE UK'S MOST DEPRIVED COMMUNITIES: A QUALITATIVE STUDY

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Background: People at highest risk for lung cancer- current or former smokers, aged over 40 years, with serious lung comorbidity and living in areas of deprivation- are more likely to prolong presenting to a GP with symptoms, leading to advanced stage diagnosis. This qualitative study sought to understand the influences on early presentation with lung cancer symptoms and intervention preferences in a sample of high risk, highly deprived individuals. **Method:** Semi-structured interviews were conducted with 37 high risk participants recruited purposively according to age, lung comorbidity and smoking status from primary care practices in deprived areas of England, Scotland and Wales. A lung symptom attribution task was used to explore symptom interpretations, symptom presentation and beliefs surrounding lung cancer, underpinned by Leventhal's Common Sense model. Four focus groups with members of the public and local stakeholders (healthcare professionals and community partners) were conducted to explore intervention preferences. Data were analysed using Framework method. **Result:** *Interviews* All participants resided in the most deprived quintile and most were unemployed or seeking benefits, and/or rented social housing. Key themes were: fixation on short term health (chest infections) leading to avoidance of longer term health (lung cancer), and the importance of the relationship with their healthcare professional to facilitate or deter help seeking. Focusing on detecting and managing 'treatable' chest infections led to denial of symptoms of 'inevitable and incurable' lung cancer. For example, participants normalised haemoptysis. Feeling judged by healthcare professionals and unworthy of medical help because of residence in a disadvantaged area or smoking habit deterred help seeking. Some participants, particularly those without caring responsibilities, anticipated refusal of treatment for lung cancer, with some contemplating suicide. *Focus groups* Suggestions for intervention content included information to raise awareness of lung cancer symptoms, modify negative lung cancer beliefs and highlight the importance of earlier diagnosis. Multi-faceted interventions were suggested including talks and stands in community venues, led by a trained, non-judgemental facilitator. **Conclusion:** In the context of difficult life circumstances and stigma, individuals who are high risk for lung cancer manage their lung health in the short term. Fixation on the treatment and detection of immediate health concerns may lead to avoidance and denial of important lung cancer symptoms. Community based multi-faceted interventions are required to empower highly deprived individuals to seek timely help, using a non-judgmental and welcoming approach.

Keywords: Intervention Development, symptom presentation, early diagnosis

P3.11-16 COMPARATIVE ANALYSIS OF HEALTH-CARE RESOURCES AND ECONOMIC COSTS OF LUNG CANCER PATIENTS TREATED MEDICALLY OR SURGICALLY IN CATALUNYA

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Background: To contribute to the debate about the cost-benefit ratio of lung cancer computerized tomography (CT) screening programs, and to support the implementation of large scale lung ancer (LC) screening programs to increase the number of potential LC patients that can benefit from this treatment. **Method:** Observational, comparative, retrospective study includes 13.415 patients who were diagnosed of LC between 2014 and 2016 in Catalunya. All of them were treated medically or surgically. We obtain information from the data bases of the "Health attention area. Information and knowledge unit." of the following variables (both before and after LC diagnosis): vital status and autonomy level, drug dispensation, radiotherapy sessions, use of health-care resources, day-hospital visits, hospitalization events, use of nursing homes, non-urgent sanitary transport, monthly and annual costs (€) per patient (and 3 year/survival) Variables were compared between the group medical treatment vs. the group surgical treatment using unpaired parametric tests. Since this is an observational study, no formal calculation of sample size was pretended. Yet, post-hoc results identified a cohort of 13.415 participants, which should be enough for descriptive purposes. **Result:** 3 year/Survival after LC diagnosis was much higher in surgical patients (78,9% vs 23,3%) (p<0.001). Surgically treated patients achieve a higher level of autonomy earlier before diagnosis. The monthly rate of total drug dispensation, cancer drugs, radiotherapy sessions, opioid and analgesic dispensation before and after LC diagnosis were much higher in medical patients. The rate of dispensation of ansiolitic, sedatives and anti-depressives were similar in both groups. Hospitalization events were slightly higher in the surgical group. There were no significant differences between groups in the rate of primary care or hospital outpatient clinic visits. The use of Health-care resources and non-emergency sanitary transport peaked before diagnosis to a larger extend in medical patients. The average annual cost of medical and surgical patients one year after LC diagnosis and treatment was 67% higher in medical patients (17.495 vs. 10.447 €). **Conclusion:** Surgical treatment of LC offers better clinical outcomes and is cost-efficient. These arguments support the implementation of large scale LC screening programs to increase the number of potential LC patients that can benefit from this treatment.

Keywords: Screening, Early stages, survival

P3.11-17 GENDER COMPARISON IN LUNG CANCER SCREENING

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Background: Persistent underrepresentation of females in lung cancer screening (LCS) trials has raised concerns regarding the accurate perception of differences between the sexes and its generalizability. We examined a balanced cohort of men and women undergoing LCS with the hypothesis that gender does not affect the ability of LCS to successfully detect early-stage lung cancer. **Method:** In an urban, academic medical center, we prospectively collected data on patients referred for LCS from June 2015 to May 2017. We compared age, ethnicity, level of education and smoking history and outcomes of LDCT between men and women. We also measured treatment and complications. **Result:** Two hundred and thirty-six patients underwent LCS. 115 (48.7%) were females and 121 (51.3%) were males. Age did not significantly differ between females (63±5.19) and males (63.93±5.56; p=0.187). There was no gender difference amongst the distribution of ethnicity, education or smoking with 77 (67%) females and 70 (57.9%) males being active smokers (p=0.149). There was a significant difference in the pack years smoked between males (54.8±35.6) and females (43.88±15.54; p=0.024). There was no gender difference in the distribution of LDCT results. 41 (35.7%) females and 56 (46.3%) males diagnosed with Lung-RADs 1, 57 (49.6%) females and 48 (39.7%) males with Lung-RADs 2, 5(4.3%) females and 6 (4.9%) males with Lung-RADs 3 and 8 (6.9%) females and 7 (5.8%) males with Lung-RADs 4 (p=0.542). Three females and 2 males were diagnosed with lung cancer. 4 patients (2 females and 2 males) were treated with surgery and 1 female underwent radiation therapy, all without complications or death.

(See next page)

	(percent)	(percent)	
number of patients 36)	115 (48.7)	121 (51.3)	
	63 (SD 5.19)	63.93 (SD 5.56)	0.187
			0.066
frican American	74 (64.3)	57 (47.1)	
Caucasian	27 (23.5)	42 (34.7)	
Hispanic	13 (11.3)	21 (17.4)	
Asian	1 (0.9)	1 (0.8)	
ation			0.894
8th grade	14 (12.2)	10 (8.3)	
9-11th grade	26 (22.6)	30 (24.8)	
High school	29 (25.2)	37 (30.6)	
Some college	11 (9.6)	10 (8.3)	
ssociate degree	11 (9.6)	12 (9.9)	
achelor degree	6 (5.2)	4 (3.3)	
Graduate	18 (15.6)	18 (14.8)	
ding history			0.149
Active smokers	77 (67)	70 (57.9)	
Ex smokers	38 (33)	51 (42.1)	
years	43.88 (SD 15.54)	54.8 (SD 35.6)	0.024
-RADs			0.542
0	4 (3.5)	4 (3.3)	
1	41 (35.7)	56 (46.3)	
2	57 (49.6)	48 (39.7)	
3	5 (4.3)	6 (4.9)	
4	8 (6.9)	7 (5.8)	

Conclusion: Our study of LCS demonstrates the equal participation of men and women. Gender did not impact early detection and successful treatment of lung cancer. This is an opportunity to advocate for enhanced female participation in LCS research to provide meaningful guidance to women and their physicians.

Keywords: lung cancer screening, Low Dose CT Scan, gender comparison

P3.11 SCREENING AND EARLY DETECTION
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P3.11-18 IMPLEMENTING ONE STOP LUNG CLINIC TO IMPROVE DIAGNOSTIC TIMELINESS IN LUNG CANCER PATIENTS IN THE NORTH OF ENGLAND

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Background: Employing just one modification (early use of endobronchial ultrasound) has been shown to improve survival in a randomised controlled trial (Navani et al. Lancet Respir Med 2015). A new innovation set out to implement One Stop lung clinic to reduce diagnostic times as a part of of the Macmillan Integrated Cancer Care Programme on the Lung Cancer Pathway maping started in 2014, which pre-dates the National Optimal Lung Cancer Pathway. Aim of the study was to demonstrate shorter time to diagnosis for patients with suspected lung cancer referred from general practice on a '2 week wait' referral pathway in the UK. **Method:** Data relating to diagnostic intervals of the patient's attending One Stop clinic collected and interim analysis performed. The diagnostic intervals were analysed using descriptive analysis to establish the timeliness of intervals from first seen to diagnosis and discussion at the Multi-Disciplinary Team (MDT) meeting. **Result:** 33 patients attended One Stop clinic and received a CT and then either bronchoscopy, endobronchial ultrasound or pleural aspiration on the same day. 48% (n=15) of patients were diagnosed with a primary lung cancer, 16% (n=5) - with other malignancies including myeloma, lymphoma and colorectal cancer and 32% (n=10) - with non-malignant conditions. The diagnostic intervals from first seen in a lung clinic to diagnosis were in range between 9 and 37days. 39% (n=13) of patients attending the clinic were worked up for the lung MDT discussion within 9 days, 24% (n=8) of patients - within 16 days, 6% (n=2) of patients - within 23 days. In 9% (n=3) of the cases the work up took 30 days or over. 15% (n= 5) were taken off the pathway and 6% (n=2) - were referred for best supportive care. **Conclusion:** Diagnostic intervals for a cohort of patients attending the clinic were shorter in comparison to England's National Cancer Standard of 31 days from referral to diagnosis. It is argued that One Stop clinic which involves a CT, then either a bronchoscopy, endobronchial ultrasound or pleural aspiration completed all on the same day reduces the time to diagnosis and improves organisational performance. Interventions for expediting earlier diagnosis of lung cancer need to focus on the compliance of diagnostic services to be all aligned in a rapid one stop environment to improve the earlier diagnosis of lung cancer.

Keywords: earlier diagnosis, lung cancer

P3.11 SCREENING AND EARLY DETECTION
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P3.11-19 IMPROVING LUNG CANCER SCREENING RATES IN AN UNDERSERVED OUTPATIENT CLINIC

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Background: Lung cancer is the leading cause of cancer death worldwide and in the United States. Despite its massive mortality, no screening method was available until this decade. The National Lung Cancer Screening Trial (NLST) demonstrated in 2011 that lung cancer screening in high risks patients using low dose chest computed tomography (LDCT) resulted in a 20% relative reduction in lung cancer-related mortality compared to chest X-Ray screening. Hence, the USPSTF recommended (grade B) in December 2013 annual LDCT for lung cancer screening in adults age 55-80 years, who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. **Method:** We performed a retrospective review of current and former smokers evaluated by a primary care provider over a six month period in 2017 in our inner city community health center. Patients that met the USPSTF criteria for lung cancer screening were selected and data regarding LDCT ordering and completion was collected. Microsoft Excel was used for data tabulation and analysis. We aim to improve our screening compliance by 20% in 6 months by implementing electronic medical records reminders, staff educational sessions, and telephone reminders to patients. **Result:** 577 patients were identified and total of 108 patients met the USPSTF criteria for screening. A total of 287 patients were excluded as the numbers of pack per year were unable to be calculated. Of the 108 patients, 67% were current smoker and 33% former smokers. The mean age was 65 with 54% male and 46% female. A total of 57% of the patients identified as Hispanic or Latino and 70% of selected English as their primary language. A LDCT was ordered by a physician in 32% (N=35) of cases and completed in only 18 patients, resulting in a net rate of screening compliance of 17%. Among those ordered, 17 patients (48.5%) did not complete their LDCT due to multiple reasons. Appointment no-show was the most common reason reported in 73% of cases. Other reasons included insurance denial in 12%, or patient cancellation or re-scheduling in 12%. **Conclusion:** By highlighting our poor adherence to lung cancer screening guidelines, we hope to provide improve our screening rates and provide a valuable approach for other institutions.

Keywords: lung cancer screening, hispanic, ealy detection

P3.11-20 PATTERNS AND PREDICTORS OF ADHERENCE TO RECOMMENDED FOLLOW-UP AFTER LOW-DOSE COMPUTED TOMOGRAPHY SCREENING FOR LUNG CANCER

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Background: Results from the National Lung Screening Trial support current guidelines to screen high-risk smokers annually for lung cancer with low-dose computed tomography (LDCT) in the United States. Monitoring the screening process, including repeat screening and follow-up, is important to ensure the benefits of screening outweigh its harms. We examined early patterns and predictors of adherence to recommended follow-up care after baseline LDCT screening in a large integrated healthcare system. **Method:** Our cohort study included patients screened for lung cancer during the first year of LDCT screening at selected Kaiser Permanente Northern California facilities, when referrals for screening came directly from primary care physicians (PCPs, instead of dedicated clinician specialists as now implemented). Using electronic administrative and clinical databases, we identified 145 screening-eligible patients who had a baseline LDCT screening exam from July 2014 to June 2015, with continuous health plan enrollment for at least 14 months post-baseline. Adherence to recommended follow-up after the baseline exam was determined according to Lung-RADS classification. We defined adherence as receipt of imaging within 10 to 14 months after a negative exam (i.e., Lung-RADS category 1 or 2) and receipt of imaging or diagnostic evaluation within ±30 days of the recommended follow-up interval after a positive exam (i.e., Lung-RADS category 3 or 4). Among patients with a negative exam, we further examined whether baseline factors, including age, gender, race/ethnicity, prior healthcare utilization, smoking history, and Charlson comorbidity index (CCI), were associated with adherence, using logistic regression. **Result:** Of the 145 patients, 61% were male, 71% were of white race, 76% were current smokers, and 72% had a CCI of 0-1. The median age was 66 years. Baseline exam results were negative for 122 patients and positive for 23 patients. All five patients subsequently diagnosed with lung cancer were classified as Lung-RADS category 4B at baseline. Adherence to recommended follow-up was higher after a positive than negative exam – 61% vs 23% – although low overall. Among patients with a negative exam, adherence was suggestively associated with gender and race/ethnicity, with greater adherence in women than men [odds ratio, OR (95% confidence interval, CI): 1.8 (0.8–4.1)] and patients of white than non-white race/ethnicity [OR (95% CI): 1.8 (0.7–8.3)]. **Conclusion:** Our preliminary results suggest adherence to recommended follow-up is low, particularly after a negative baseline exam, due in part to insufficient patient education and shared decision-making about LDCT screening during PCP visits. Further analyses are underway to interpret these results.

Keywords: lung cancer screening, Adherence

P3.11-21 THE DEVELOPMENT OF A ROBUST RADIOLOGY QUALITY ASSURANCE (QA) PROGRAM IN A PROVINCIAL HIGH-RISK LUNG CANCER SCREENING PILOT (HRLCSP)

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Background: Lung cancer is the leading cause of cancer death in Ontario, with an estimated 7100 patient deaths occurring in 2016 (Canadian Cancer Society, 2016). Based on results from the National Institute of Health's National Lung Screening Trial, Cancer Care Ontario (CCO) implemented the HRLCSP in 2017 to determine feasibility of provincial scale roll-out of an organized lung cancer screening program. An integral component of the HRLCSP is to ensure low-dose computed tomography (LDCT) scans would be performed, interpreted and reported in a standardized, and high-quality manner. **Method:** The HRLCSP project team coordinated with CCO's Cancer Imaging Program (CIP) to gain insight into cancer imaging practices and protocols, and recruited clinical expertise through a Radiology QA Clinical Lead (RQACL). In collaboration with pilot site radiologists, a comprehensive QA program was developed to encompass all aspects of radiology including facility, educational, and reporting standards, in addition to defining quality improvement criteria. **Result:** To ensure pilot centres were able to deliver high-quality LDCTs, the RQACL, site participants and clinical experts collaborated to define and implement quality parameters. Equipment standards were defined in The Radiology QA Program Manual, and agreement from pilot sites was confirmed. Collaboration with reading radiologists led to tailored educational workshops designed to ensure consistency in the reporting of lung nodules based on the Lung-RADS™ scoring criteria, adapted from the American College of Radiology. Scan interpretation considerations, scoring criteria, and reporting templates were implemented. Annual assessments have ensured compliance across pilot sites. A working group aiming to determine an algorithm to examine incidental findings is being created. LDCT scan Double Read minimums and Peer Review adjudication processes were developed to ensure expert opinion availability with radiologist discrepancies to ensure high quality scan interpretation. **Conclusion:** The design of the HRLCSP offered opportunities for implementing high quality standards around the LDCT scans. Implementation of a robust quality assurance program can ensure that the radiology component is delivered in a high-quality manner. Radiologist training programs, centre minimum requirements, and standardized reporting can ensure standards remain high. Lessons learned through the development of this comprehensive radiology QA program in the HRLCSP will allow for adoption of high-quality radiology standards on a larger provincial scale.

Keywords: quality, Sreening, radiology

P3.11-22 THE PATH TO NATIONAL LUNG CANCER SCREENING PROGRAM IN ISRAEL

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Background: 2500 people are diagnosed every year with lung cancer and 2000 die from the disease, the leading cause of death in Israel. The prevalence of smoking is 22.5% above 21 years of age, resulting in about 1.2 million smokers overall. The USPSTF found adequate evidence that annual screening for lung cancer with LDCT in a defined population of high-risk persons can prevent a substantial number of lung cancer–related deaths, therefore the Israeli Lung Cancer foundation (ILCF) decided to advocate for including LC screening program in Israel's medical services. **Method:** The medical services "health basket" in Israel encompasses the entire range of services, drugs, medical equipment and devices that the insured public receives. Every end of year, a health basket committee is appointed to review and approve the new services to be included in the following year health basket. The services are reviewed for their health benefit and then are chosen to fit a limited budget. ILCF have filled twice for the years of 2017 and 2018 to have a national LDCT LC screening program in Israel. **Result:** LC Screening program was filled by ILCF to the 2017 Health basket committee. The committee decided that there is not enough supporting evidence and did not rank the program high enough to be included in the funding debate. Nevertheless, because the issue was raised, the ministry of health decided to gather a special committee to evaluate LC Screening program. The committee decided that there is enough evidence and recommended to have the program be part of the health system in Israel. For 2018-year, LC Screening program was filled by ILCF and the ministry of health LC Screening committee. This time after an additional appeal the program was ranked to enter the funding debate. Unfortunately, it was excluded from the 2018 health basket. As a result, ILCF appealed to the Israeli high court of justice against the health basket committee claiming that the decision was unreasonable. The appeal is being currently discussed. **Conclusion:** Change takes a lot of effort and collaboration. Unfortunately, lung cancer screening is not an industrial initiative, thus does not have strong lobbying power. Therefore, it is the duty of patient advocates and leading oncologists, radiologists and pulmonologists to raise the flag. Here we present a model of collaboration between a patient organization and leading oncologists and radiologists to incorporate LC Screening program in Israel.

Keywords: Screening, advocacy

P3.11-23 ADHERENCE TO ANNUAL LOW-DOSE CT LUNG CANCER SCREENING AT A LARGE ACADEMIC INSTITUTION

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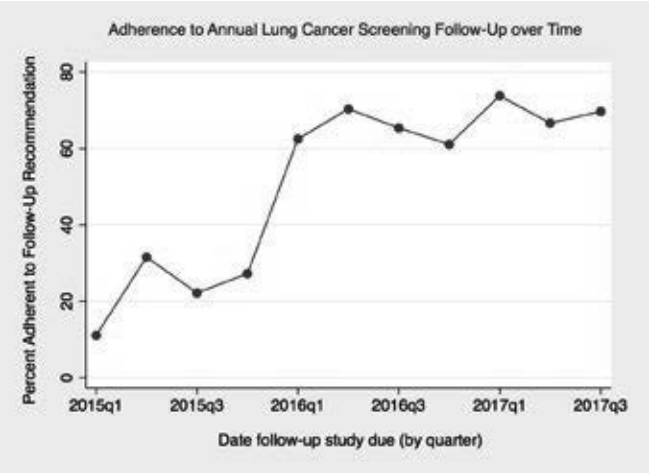
Background: Annual low-dose computed tomography (LDCT) is standard-of-care in the high-risk population for lung cancer screening. We assessed adherence to annual LDCT screening in a large academic institution. **Method:** We assembled a retrospective cohort of patients who underwent LDCT between January 1, 2014 and September 30, 2016. We included patients with baseline LungRads 1 or 2 with 12-month follow-up recommendation. We excluded those who died before the time of recommended follow-up. The time interval between the recommended follow-up study date and the actual follow-up study was calculated. Patient adherence at time of due follow-up was defined by this time interval: <=90 days (adherent) and >90 days (non-adherent). Primary analysis was change in adherence over time. Secondary analysis included descriptive statistics of demographics. **Result:** 395 patients had baseline LDCT screening. We found a persistent, significant increase in adherence: 11% (2/18) in the 1st quarter 2015 and 70% (46/66) in the 3rd quarter 2017 (Pearson's chi-squared test p=.008). We also identified racial disparity in patients enrolling in our Lung Screening Program (93% white).



Conclusion: Adherence to annual LDCT screening significantly increased from 2015 to 2017. Improvement may be due to changes in national policy and/or implementation of a dedicated program physician director and program coordinator. Future work should address racial disparities and barriers to and facilitators of annual LDCT screening.

Keywords: low dose CT, Adherence, lung cancer screening

P3.11-24 "TO KNOW OR NOT TO KNOW .?" PUSH AND PULL IN EVER SMOKERS LUNG SCREENING UPTAKE DECISION MAKING INTENTIONS

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Background: Despite introduction in America and calls for European implementation, lung screening isn't currently endorsed as a UK programme. Whether smokers want to be screened has been raised as an issue. This study explored uptake decision-making with ever-smokers, aged 50-80 as part of the UK's first community based one-stop lung screening pilot service. **Method:** Thirty-three participants (22 ex-smokers; 11 smokers) men and women, aged 50-80 were recruited purposively from community settings and health facilities in Manchester, England. The setting is a city with significant deprivation and high lung cancer incidence. Six semi-structured focus groups were held with separate groups for current and former smokers to facilitate freer expression and comparison but mixed by gender, age, ethnicity and deprivation. Discussions followed semi-structured topic guides were audio-recorded, transcribed verbatim and coded using NVIVO software. Inductive thematic analysis was used to analyse data and identify key themes. **Result:** Lung screening was widely acceptable to participants. It was seen as offering reassurance about lung health or opportunity for early detection and treatment. However, being positive 'in principle' didn't always translate into uptake intention. Factors that impacted participants' desire to know about their lung health included: views about screening benefits; emotions such as worry about a diagnosis and screening tests; practicalities such as service accessibility; and smoking related factors included views about individual smoking risk and smoking stigma. **Conclusion:** Indications were that current smokers faced higher uptake barriers than ex-smokers. The uptake factors identified appeared to motivate some participants to be screened but act as a barrier for others. This factorial 'push and pull' effect is important as it indicates where action can be taken to help reduce participation barriers to lung screening. This is shown in Figure One.

(See next page)

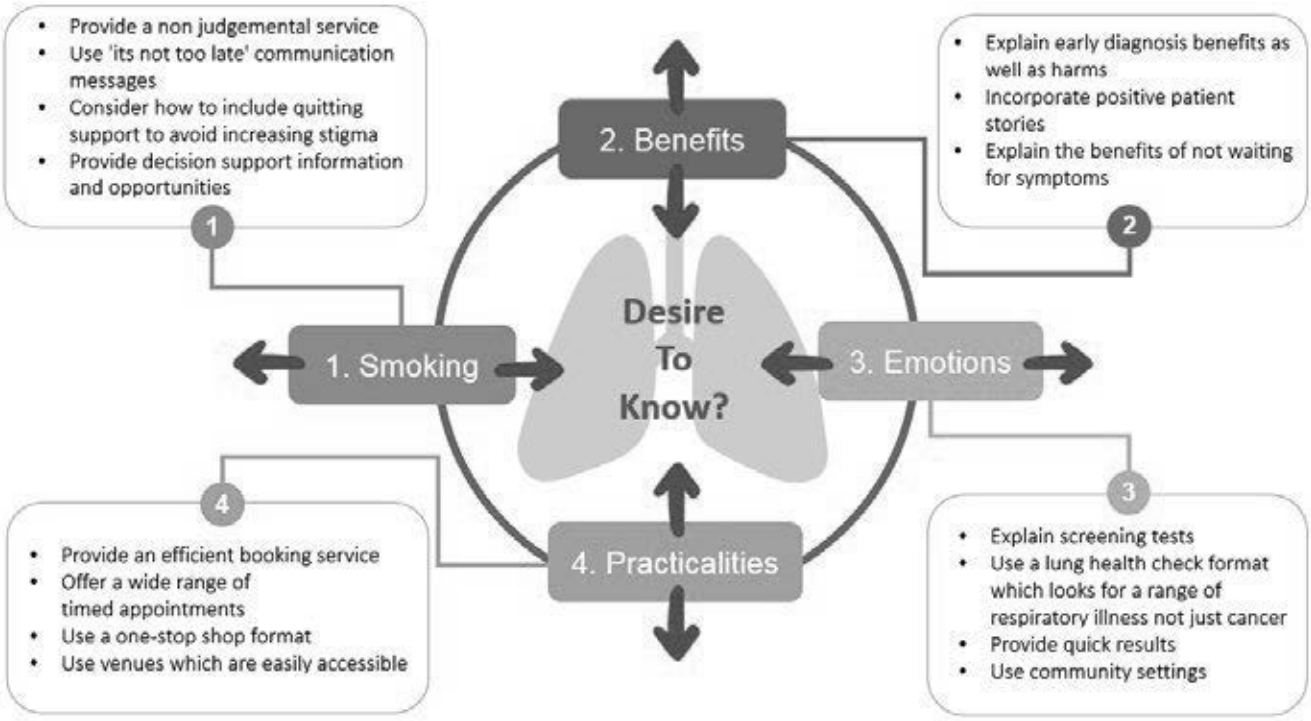

Figure 1: 'Push and Pull' in participants lung screening uptake decision making intentions

Keywords: Screening, Uptake, decision making

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P3.11-25 ANALYSIS INDICATES LOW INCREMENTAL COST-EFFECTIVENESS RATIO FOR IMPLEMENTATION OF LUNG CANCER SCREENING IN ITALY

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Background: Given the potential of early lung cancer detection to improve survival, accurate assessment of the cost-effectiveness of low-dose computed tomography (LDCT) screening is crucial. We report the results of a cost-effectiveness analysis of screening for Italian persons at high risk of lung cancer from the public payer's perspective **Method:** The study built on a mathematical decision model to estimate the cost-effectiveness of annual LDCT screening for 5 years in a high-risk population of smokers (at least 30 pack-years) aged 55-79 years. The stage distribution of patients diagnosed as part of the COSMOS screening study was used for the "screening arm;" the stage distribution of patients in the SEER database was used for the "usual care arm." Treatment costs were determined using detailed individual-level administrative information from our Institutional database of lung cancer patients. Lung cancer survival in screened patients was adjusted for 2 year-lead time bias. The model estimated expected future life years using survival probabilities according to age, sex, and lung cancer stage (or no lung cancer). Quality-Adjusted Life Years (QALYs) gained and Life Years (LY) gained were estimated. **Result:** The base-case incremental cost for each QALY gained was 4747,57 Euro. The incremental cost-effectiveness ratio (ICER) for each LY gained was 4069 Euro. An extensive sensitivity analysis showed that model outcomes were particularly sensitive to lung cancer prevalence, the sensitivity and specificity of screening, and the lead-time bias assumed. **Conclusion:** Our analysis indicates that LDCT screening is associated with a low ICER of 4069 Euro, meaning that this is the yearly incremental cost of saving the life of a patient, and is lower than the ICER accepted by the Italian government. The implication is that implementation of screening throughout Italy can be achieved at a relatively low cost, a finding which should be taken into account by health policy decision-maker.

Keywords: lung cancer screening, Cost-effectiveness, cost-analysis

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P3.11-26 RESULTS OF INITIAL LOW-DOSE COMPUTED TOMOGRAPHIC SCREENING FOR LUNG CANCER FROM A SINGLE-INSTITUTION IN CHINA

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Background: Lung cancer screening using low-dose computed tomography (LDCT) has been reported to reduce lung cancer-specific mortality for smokers at high risk in patients of the United States. However, there are very few LDCT screening results from Chinese patients. We here report the screening findings at the initial round of LDCT screening program from a single-institution population-based cohort in China. **Method:** We conducted a retrospective study of a single-institution population-based LDCT screening program for lung cancer. Patients participated LDCT in Taizhou Hospital of Enze Medical Center were eligible. All noncalcified nodules with long-axis diameters of 4mm or greater in the axial plane were considered to be positive for potential lung cancer according to NLST definition. If more than three nodules were found, one dominant nodules were selected for this analysis. **Result:** From July 2017 through December 2017, a total of 8611 participants with LDCT screening were included in this report. A total of 78 participants with history of cancer and 437 participants were follow-up procedures were excluded in this analysis. Of the remaining 8096 participants, the median age was 51 years (range, 16-97 years). A total of 1516 (18.8%) participants were younger than 40 years, 5264 (65.2%) were 40-64 years and 1316 (16.3%) were greater than 64 years. The total proportion of positive nodules was 21.8%, slightly higher in females (535/2258, 23.7%) than males (1233/5838, 21.1%). Lung cancer was diagnosed in 26 participants (0.32%) (11 males and 14 females) of the 1768 positive nodules. The comprehensive demographics of 26 lung cancer patients (included one patients with multiple metastases tumor from pancreas) is shown table 1.

(See next page)

Table 1 Comprehensive demographics of 26 lung cancer patients

No.	Sex	Age (y)	Smoking	Type of nodules	Histology	Type of EGFRm	TNM	Treatment
1	M	70	Never	8mm GGN, RUL	ADC in situ	Wild	pT1isN0M0	Wedge resection
2	M	47	Current, 40 pack-year	16mm solid, RUL	ADC	19-del	pT1aN0M0	Lobectomy
3	M	70	Never	Multiple nodules; 12mm solid, RLL	Metastatic ADC from pancreas	unknown	pT1bN0M0	without
4	M	53	Current, 60 pack-year	21mm sub-solid, LLL	ADC	unknown	pT1cN0M0	Lobectomy
5	M	49	Never	6mm GGO, RLL	ADC	L858R	pT1aN0M0	Wedge resection
6	M	62	Former, 45 pack-year	30mm, LLL	SCC	unknown	cT2aN2M0	chemotherapy
7	M	62	Former, 24pack-year,	32mm solid, RLL	ADC	19-del	pT4N0M0	Lobectomy
8	F	44	Never	12mm GGO, LUL	ADC	unknown	pT1bN0M0	Segmental Resection
9	F	68	Never	8mm GGO,RML	ADC	unknown	pT1aN0M0	Lobectomy
10	M	74	Current, 60 pack-year	14mm solid, RUL	ADC	L858R	pT1aN0M0	Wedge resection
11	M	74	Former, 40 pack-year	15mm sub-solid, LLL	SCC	unknown	pT1bN2M0	Lobectomy
12	F	55	Never	12mm GGN, RUL	ADC	unknown	pT1aN0M0	Lobectomy
13	F	64	Never	11mm GGO,RUL 8mm GGO, RUL	ADC ADC	Wild	pT3N0M0	Lobectomy
14	F	78	Never	18mm solid, RLL	ADC	19-del	cT1bN0M0	Gefitinib
15	F	67	Never	14mm GGO, RUL 12mm GGO, RUL	ADC; ADC	unknown	pT3N0M0	Lobectomy
16	F	73	Never	18mm GGO, LUL	ADC	unknown	pT1bN0M0	Wedge resection
17	M	75	Never	10mm sub-solid, RUL	ADC	unknown	pT1aN0M0	Lobectomy
18	M	71	Current, 60 pack-year	30mm solid, LLL	NSCLC	unknown	cT2aN2M	Lobectomy
19	F	60	Never	8mm solid, RLL	ADC	19-del	pT1aN0M0	Lobectomy
20	F	78	Never	17mm solid, RUL	ADC	L858R	pT1bN0M0	Wedge resection
21	F	56	Never	11mm GGN,RUL	ADC	unknown	pT1bN0M	Lobectomy
22	F	58	Never	13mm solid, RUL	ADC	L858R	pT1bN0M0	Lobectomy
23	F	46	Never	13mm sub-solid, LUL	ADC	Wild	pT1bN0M0	Lobectomy
24	M	65	Current, 40 pack-year	50mm solid, LUL	SCC	unknown	pT3N0M0	Lobectomy
25	F	67	Never	9mm solid, RUL 5mm solid, RUL	ADC; ADC in situ	L858R	pT3N0M0	Wedge resection
26	F	47	Never	7mm GGO, RUL	ADC	20-INS	pT1bN0M0	Wedge resection

GGO=Ground-glass opacity; GGN=ground glass density nodule; RML=right middle lobe; RLL=right lower lobe; RUL=right lower lobe; LUL=left upper lobe; LLL=left lower lobe; tis=carcinoma in site; EGFRm= EGFR mutation

Conclusion: The overall rate of positive nodules is similar to previous reports, and the overall cancer detection rate by LDCT in our cohort was lower than previous reports from others (0.36-3.3%).

Keywords: lung cancer, Low-Dose Computed Tomography (LDCT) screening, Pulmonary nodles

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P3.11-27 LUNG CANCER DIAGNOSED AT AGE 50-54 YEARS: SURVIVAL AS POOR AS OLDER PATIENTS

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Background: The United States Preventive Services Task Force (USPSTF) recommends lung cancer screening with low-dose computed tomography among people aged 55-80 years with a 30 pack-year cigarette smoking history and, if stopped smoking, quitted within 15 years. We previously identified a prominent subpopulation that would have been too young (i.e., 50-54.9 years) yet otherwise met the USPSTF criteria and were diagnosed with lung cancer. We assessed survival outcomes in these younger patients compared to those eligible for USPSTF lung cancer screening. **Method:** We studied two cohorts of 7,390 primary lung cancer patients: a Hospital Cohort from Mayo Clinic Rochester (n=6,554) and a Community Cohort from the Olmsted County population (n=836, Minnesota, USA). All patients were diagnosed between age 50 and 80 years, had >30 pack-year smoking history and had quitted <15 years if they had stopped smoking. Two cohorts were analyzed independently to evaluate the impact of younger age (50-54.9 years) on overall survival using Cox Proportional Hazard models by hazard ratio (HR) and 95% confidence interval (CI). Known prognostic factors (age, sex, tumor stage and treatment) were adjusted. To control for age gap, the USPSTF group was subdivided into a 55–69 age subgroup (lower age USPSTF subgroup) and a 70–80 age subgroup (higher age USPSTF subgroup). **Result:** In both cohorts, the younger age group had at least the same risk of death as patients who met the USPSTF criteria; HR=1.16 for both cohorts; p=0.08 for the Hospital Cohort and p=0.52 for the Community Cohort. Age-group stratified analyses did not change the results in either cohort. **Conclusion:** People who are 50-54.9 years of age and otherwise meet the USPSTF screening criteria for lung cancer, once diagnosed, experience a similar or potentially worse survival outcome as older patients. Benefit of screening in this younger population deserves consideration and futher study.

Keywords: Screening, Younger age, survival

P3.12 SMALL CELL LUNG CANCER/NET
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P3.12-01 TARGETING MITOCHONDRIAL METABOLISM AS A SELECTIVE THERAPEUTIC APPROACH IN SMALL CELL LUNG CANCER (SCLC)

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Background: SCLC accounts for 13% of new lung cancer diagnoses and is the most aggressive form of the disease. Altered cellular metabolism is considered a hallmark of cancer and a target for therapeutic intervention. Mitochondria represent an important cellular compartment and selectively targeting mitochondrial bioenergetics may be an effective therapeutic approach for SCLC. Nicotinamidephospho-robosyltransferase (NAMPT) is a key enzyme in the mitochondrial nicotinamide adenine dinucleotide salvage pathway. Recent high-throughput drug screens identified SCLC as the most sensitive cancer subtype to NAMPT inhibitors like FK866. Genomic studies of SCLC have also suggested the constitutive activation of the PI3K/AKT/mTOR pathway in a significant portion of SCLC cases. Idelalisib a phosphatidylinositol-3-kinase-delta inhibitor is approved for the treatment of B-cell malignancies. We hypothesize that the inhibitors FK866 and idelalisib will alter SCLC mitochondrial bioenergetic profiles and function, and that combination therapy may enable lower drug doses in clinical use. **Method:** Mitochondrial bioenergetics profiles at baseline and in response to drug were assessed in SCLC cell lines H69, DMS79, and H209 using a high resolution Oroboros Oxygraph 2K. Corresponding cell survival was determined using ATP glow and flow cytometry. Western blot analysis was used to evaluate cell death pathways. **Result:** Cell survival and mitochondrial bioenergetics parameters i.e. basal respiration, maximal respiration, spare respiratory capacity, and respiratory control ratio were measured in a dose-dependent manner for FK866 (0.5 – 2.5 nM) and idelalisib (1 – 50 μM) at 24 and 48 hours in SCLC. The IC_{50} for cell survival with FK866 in the 3 lines ranged between 1 and 8 nM. FK866 did not induce apoptosis as measured by Caspase 3 cleavage, but induced γH2X phosphorylation suggesting a role for DNA damage at lethal doses. Mitochondrial bioenergetics was inhibited as low as 0.5 nM dose of FK866 and 6.25 μM of idelalisib. Our preliminary data also demonstrate that the combination of 1 nM FK866 and 6.25 μM idelalisib significantly decreases the major mitochondrial bioenergetic parameters compared to FK866 alone after 24 or 48 hours treatment. **Conclusion:** Both FK866 and idelalisib affected bioenergetics profile in SCLC cells and the combined effect of both drugs is on the mitochondrial bioenergetics profile is greater than the impact of single agents. The combined use of these drugs at lower doses targeting mitochondrial metabolism may allow for a greater therapeutic index in clinical trials.

Keywords: NAMPT inhibition, mitochondrial bioenergetics, small cell lung cancer

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P3.12-02 DYNAMICS OF DLL3 AND ASCL1 EXPRESSION IN SCLC OVER DISEASE COURSE

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Background: SCLC is a high-grade neuroendocrine malignancy highly responsive to first-line therapy, etoposide plus platinum (EP), but increasingly resistant to subsequent lines of therapy. Because SCLC is rarely biopsied following the initial diagnosis, the dynamics of expression of therapeutically relevant biomarkers in relapsed disease are poorly understood. ASCL1 is an oncogenic driver of SCLC and directs transcription of delta-like protein 3 (DLL3), an atypical Notch receptor family ligand involved in neuroendocrine tumorigenesis and the target of the antibody drug conjugate rovalpituzumab tesirine (Rova-T™). We investigated ASCL1 and DLL3 expression in SCLC patient (pt) tumor biopsies and patient-derived xenografts (PDXs) collected serially from time of diagnosis (pre-treatment) and after progression following ≥1 lines of therapy. **Method:** Fresh cut, formalin fixed, paraffin embedded tissue from primary SCLC tumors and PDXs was sectioned and stained with mouse monoclonal antibodies against DLL3 (SC16.65) and ASCL1 (SC72.201) on the Dako platform. ASCL1 and DLL3 expression were scored as a percent of positive cells and correlated with each pt's treatment history. **Result:** Among biopsies and/or PDXs derived over serial time points, 6 cases had baseline positive DLL3 expression ranging from 15-80% of cells with a mean of 50% pre-EP. All 6 remained positive following progression after EP, with DLL3 expression ranging from 10-100% of cells with a mean of 66%. Up to 7 serial tissue or PDX samples were available over the course of multiple treatments for 2 pts, and DLL3 and ASCL1 expression remained consistent over time, being strongly positive in 1 case and negative in the other. Among biopsies and PDXs established at matched time points, ASCL1 and DLL3 expression were consistent in 7/7 and 7/8 cases, respectively. **Conclusion:** ASCL1 and DLL3 expression remain mostly consistent pre- and post- chemotherapy in pts with SCLC, suggesting that expression of these biomarkers in archival tissue likely accurately estimates expression even after intervening treatments. Furthermore, PDXs derived both from biopsies and circulating tumor cells maintain ASCL1 and DLL3 expression that reflects the pt tumor, supporting use of PDXs to model pt tumor biology.

Keywords: DLL3, small cell lung cancer, Patient-derived xenograft

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P3.12-03 TARGETING DLL3 WITH AMG 757, A BITE® ANTIBODY CONSTRUCT, AND AMG 119, A CAR-T, FOR THE TREATMENT OF SCLC

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Background: Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine tumor with a poor prognosis and limited therapeutic options. Redirecting the potent cytotoxic potential of T cells via bi-specific T cell engager (BiTE®) antibody constructs and chimeric antigen receptor T cells (CAR-T) represents a promising new approach in the treatment of cancer, with durable complete responses observed in the clinic. **Method:** Differential expression profiling of SCLC tumors and normal tissues was performed using RNAseq and immunohistochemistry. BiTE® and CAR scFv constructs were converted from fully human

antibodies. BiTE® and CAR redirected T cell activity was evaluated in vitro and in vivo. **Result:** Analysis of gene expression in SCLC tumors versus normal tissues identified Delta-Like Ligand 3 (DLL3) as a highly specific tumor associated antigen for SCLC. Expression of DLL3 in normal tissues was detected at very low levels in the brain, pituitary, and pancreatic islets, and showed a cytoplasmic staining pattern by IHC. We have developed a novel BiTE® antibody construct, AMG 757, with prolonged serum half-life relative to that of canonical BiTE® molecules. AMG 757 showed low picomolar potency against SCLC cell lines in vitro and also demonstrated significant inhibition of tumor growth in vivo. Pharmacokinetic analysis showed AMG 757 demonstrated a serum half-life predicted to support Q2W dosing in humans. Furthermore, AMG 757 was well tolerated in a repeat-dose 28-day GLP toxicology study, with no AMG 757-related adverse findings at doses as high as 4.5 mg/kg QW. Exposures were dose-proportional and with no evidence of tissue damage. We have also advanced AMG 119, a CAR-T targeting DLL3, into clinical development. AMG 119 demonstrated robust ablation of target cells in vitro and significant anti-tumor activity in an in vivo mouse model. AMG 119 CAR T cells showed robust cytokine production and proliferation when cultured in the presence of DLL3-positive cells, indicating appropriate T cell signaling as a function of antigen engagement. **Conclusion:** The expression pattern of DLL3, with prevalent membranous expression in the majority of SCLC tumors and no detectable cell surface expression in normal cells, makes it an ideal target for BiTE®- and CAR-redirected T cell cytotoxicity. High potency against DLL3-positive tumor cells, coupled with an excellent preclinical safety profile suggest that AMG 119 and AMG 757 may provide a new therapeutic option for SCLC patients with DLL3-positive tumors. AMG 757 (NCT03319940) and AMG 119 (NCT03392064) are currently enrolling in Phase 1 studies for the treatment of relapsed/refractory SCLC.

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P3.12-04 LINC00173 MODULATES CHEMORESISTANCE OF SMALL CELL LUNG CANCER BY BINDING HNRNPA2B1 AND HNRNPI TO REGULATE CHK2 LEVEL

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Background: Small-cell lung cancer (SCLC), the most aggressive type of lung cancer, accounts for approximately 15% of all lung cancers. Long non-coding RNAs (lncRNAs) with length over 200 nucleotides, have been identified to play crucial regulatory roles in cell differentiation, proliferation, migration, invasion and apoptosis. Long intergenic non-protein coding RNA 173 (Linc00173) which was first identified in small cell lung cancer, and was found to be involved in chemoresistance in our previous array analysis. In this study, we aimed to explore the biological role of Linc00173 and its possible molecular mechanism in SCLC chemoresistance. **Method:** Linc00173 was examined in 60 SCLC patient samples by quantitative RT-PCR (qRT-PCR). The functional roles of Linc00173 in SCLC were studied by overexpression and RNA interference approaches in vitro and in vivo. The localization of Linc00173 was studied by separating cytoplasmic and nuclear RNA fractions from SCLC cells. RNA pulldown and mass spectrum experiments were performed to find the RNA-binding proteins that interact with Linc00173. RNA sequencing of RNA-binding proteins-immunoprecipitated RNA and coexpression profiles of Linc00173 and mRNAs were used to identify the gene that was regulated by Linc00173 with the RNA-binding proteins. **Result:** Linc00173 expression was significantly associated with chemoresistance and the shorter survival time in SCLC patients. Upregulation of Linc00173 promoted the proliferation and cell-cycle progression and also induced multidrug resistance, whereas downregulation of Linc00173 expression had opposite effects both in vitro and in vivo. Linc00173 increased the expression of hnRNPA2B1 and hnRNPI in the nucleus and formed an RNA-protein complex, which further bound to the target mRNA of CHK2 that is implicated in cell-cycle progression. This interaction made the CHK2 mRNA fragile and decreased its protein level. **Conclusion:** Linc00173 was first identified to promote proliferation and chemoresistance in SCLC. It interacts directly with hnRNPA2B1 and hnRNPI to regulate levels of CHK2. Overexpression of Linc00173 represents a biomarker of poor prognosis and chemoresistance in SCLC patients.

Keywords: Linc00173, Small cell lung cancer (SCLC), chemoresistance

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P3.12-05 THE PATTERN OF PD-L1 EXPRESSION IN THORACIC NEUROENDOCRINE TUMORS

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Background: Immunotherapy has assumed a pivotal role in the treatment of a number of cancers including lung cancer through up-regulation of tumor-specific cytolytic T cell activity. The level of expression of programmed death-ligand 1 (PD-L1) on tumor cells play an important role in determining the first-line of therapy in non-small cell lung cancer (NSCLC) with immunotherapy. Large cell neuroendocrine carcinoma (LCNEC) of the lung has an adverse prognosis, with small numbers of patients suitable for surgical resection at diagnosis. While PD-L1 expression is shown to be an overall negative prognostic factor, it is associated with a positive outcome when PD-1/PD-L1 blocking antibodies are used. In this study, we investigated PD-L1 expression in LCNEC using immunohistochemistry. **Method:** Thirty-six patients with LCNEC diagnosed between 2007 and 2013 at the University of Cincinnati Medical Center were included. PD-L1 IHC 22C3 expression was analyzed by immunohistochemistry on formalin fixed, paraffin embedded (FFPE) tissue samples using anti-PD-L1 antibody PD-L1 expression in the tumor and surrounding stromal cells was quantitated based on staining intensity (0 to 3+) and stained surface area (0-100%). A grade cutoff of PD-L1 of ≤5% was used to decide positive or negative. **Result:** We found that 11 of 36 patients showed stromal expression of PD-L1, but only 6 out of 36 patients demonstrated PD-L1 expression on the tumor, and 3 patients were positive for PD-L1 expression in both tumor and surrounding stromal cells. **Conclusion:** In conclusion, PD-L1 expression on stromal cells appears to be higher in patients with LCNEC compared to the PD-L1 expression on the tumor cells. Prior studies have shown that patients with small cell lung cancer, another aggressive neuroendocrine tumor exhibited greater levels of PD-L1 expression on stromal cells and tumor-associated macrophages suggesting a possible alternative predictive marker.

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P3.12-06 SLFN11 EXPRESSION AND EFFICACY OF PARP INHIBITOR THERAPY IN EXTENSIVE STAGE SMALL CELL LUNG CANCER: ECOG-ACRIN 2511 STUDY

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Background: Veliparib (V),an oral small molecule inhibitor of poly (ADP) ribose polymerase (PARP) enhanced cytotoxic chemotherapy in preclinical models of small cell lung cancer (SCLC). The combination of V with cisplatin/etoposide (CE) doublet showed efficacy improvement as first-line therapy of extensive stage SCLC (ES-SCLC) with adjusted PFS HR: 0.63 1-sided p=0.01. There was differential treatment effect by strata (adjusted treatment HR comparing CE+V: CE: 0.34; 80% CI: 0.22 - 0.51; 1-sided p<0.001 for male patients with high tumor burden versus adjusted HR: 0.81 80% CI: 0.60 - 1.09; 1-sided p=0.18 for other patients subsets) highlighting the need to identify patient subset most likely to benefit. SLFN11 expression was previously shown to be associated with benefit of V when combined with temozolomide in relapsed SCLC and also predicted benefit of CE in preclinical models. We assessed the utility of SLFN11 as a predictive biomarker in the context of E2511 frontline clinical trial. **Method:** Archival tissue samples collected from patients with ES-SCLC enrolled and treated on E2511 study was employed for biomarker analysis looking at SLFN11 expression by immunohistochemistry. The study has 88% power to detect a PFS hazard ratio of 0.5 comparing SLFN11 (+) and (-) patients using a one-sided 0.025 level logrank test. **Result:** There was an imbalance between control and experimental arms in the Male/abnormal LDH stratum (in strata) with respect to Age: p=0.006; malignant pleural effusion: p=0.095 and T stage: p=0.02. Median PFS was 5.1 mos on CE (95% CI 4.1-6.1) vs. 6.2 mos on CE+V (95% CI 5.9-8.8); HR=0.32, p=0.002 (unadjusted); median OS on CE was 8.8 mos (95% CI 6.6-11.1) vs. 9.5 mos on CE+V (95% CI 7.8-12.8); HR=0.76, p=0.39.

Clinical outcome differences based on SLFN11 expression is ongoing and will be presented at the meeting. **Conclusion:** Pending ongoing analysis of correaltion of biomarker with clinical outcomes

Keywords: small cell lung cancer; biomarker; SLFN11

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P3.12-07 MICRORNA DEREGULATION IN A TYPICAL CARCINOID TUMOR: POTENTIAL ROLE OF IMMUNE RESPONSE AND INVASION IN TUMORIGENESIS.

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Background: Lung carcinoid tumors comprise an uncommon type of neuroendocrine cancer, and are classified as typical or atypical according to their histological characteristics. Typical carcinoid tumors are more common and usually not associated with metastasis at diagnosis. To date, genetic and epigenetic changes, as well as regulatory mechanisms mediated by non-coding RNAs and their association with the development and progression of lung carcinoid tumors are not understood. Considering that microRNAs (miRNAs) are potent gene expression regulators associated with several cancer types, our goal was to determine global miRNA expression changes in a rare case of typical lung carcinoid tumor and its corresponding metastasis from the same patient. **Method:** RNA was isolated from two fragments of the same tumor and its paired lymph node metastasis, using the RecoverAll Total Nucleic Acid Isolation Kit for FFPE tissues (Ambion/Thermo Fisher). miRNA profiling was performed using the TaqMan Array Human microRNA card A v.3.0 platform (Life Technologies/Thermo Fisher). miRNA expression was analyzed in the Expression Suite software using the global normalization algorithm provided. Furthermore, we applied bioinformatic methods for prediction of miRNA target genes, using microRNA data integration portal, mirDIP, and to determine validated targets in lung tissue as well as molecular pathways, using miRTarBase and ToppGene Suite. **Result:** 16 miRNAs were commonly deregulated in the two fragments of tumor and the corresponding lymph node metastasis from the same patient. Of these, 15 miRNAs were significantly down-regulated (FC>=2 and p<0.01). Pathways identified were enriched for miRNA target genes associated with immune response, invasion and metastasis. Notably, many of the identified miRNAs, which were consistently down-regulated, are known to have a suppressor role in tumorigenesis. **Conclusion:** Down-regulated miRNAs may be associated with metastatic progression of typical carcinoid tumors, since a subset of 15 miRNAs were down-regulated in paired primary tumor and metastasis samples. Our results contribute to improve our understanding of miRNA regulation and disease pathogenesis in lung carcinoid tumors.

Keywords: Typical carcinoid tumor, MicroRNAs, Bioinformatics

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P3.12-08 THE ROLE OF CONTACTIN 1 ON ACQUIRED RESISTANCE TO PEGYLATED ARGINASE IN SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) accounts for about 15% of all lung cancer cases. SCLC is characterized by easy to relapse, and current treatment lacks tumor specificity. Arginine is an important amino acid in human, but some tumors lose the ability to synthesize it. So arginine deprivation has become a targeted therapy in certain tumors. BCT-100 is a pegylated arginase with anticancer activity in arginine auxotrophic tumors, such as human melanoma, hepatocellular carcinoma and acute myeloid leukemia. Contactin 1 (CNTN1) is a cell adhesion molecule which plays an important role in drug resistance. The aim of this study is to determine the effects of CNTN1 on BCT-100 acquired resistance in SCLC. **Method:** BCT-100 resistant (BR) cells, H446-BR and H526-BR cells, were developed by incubating with serially increasing concentration of BCT-100 with parental H446 (adherent cell line) and H526 (suspension cell line) cells respectively. Gene chip assay was employed to fish out the potential targeted biomarkers in BR cell lines. MTT assay was used to detect cell viability on BR cell lines. Western blotting was employed to evaluate the protein expression. Knockdown of CNTN1 was performed using specific shRNA. Wound healing assay was used to evaluate the cell migration ability in H446 and H446-BR adherent cell lines. Flow cytometry was applied to detect the related biomarkers in BR cells. **Result:** The protein expression of CNTN1 in H446-BR and H526-BR cells was 2.7 folds and 5.3 folds higher than that in parental cells respectively. Cell migration ability in BR cells was stronger than parental cells: wound healing rate was greatly increased from 48.5% to 69.9% in H446-BR cells. Epithelial-mesenchymal transition (EMT) progression and AKT activation were observed in both BR cell lines. Knockdown of CNTN1 re-sensitized BR cells to BCT-100 treatment and reversed the EMT progression via inhibiting AKT pathway. **Conclusion:** Contactin 1 modulates BCT-100 resistance through induction of EMT by activating AKT pathway in SCLC.

Keywords: Contactin 1, small cell lung cancer, pegylated arginase (BCT-100)

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P3.12-09 SMAD4 MUTATION CONFERS ACQUIRED NEUROENDOCRINE PHENOTYPE IN TRANSFORMATION OF LUNG ADENOCARCINOMA TO SMALL CELL LUNG CANCER

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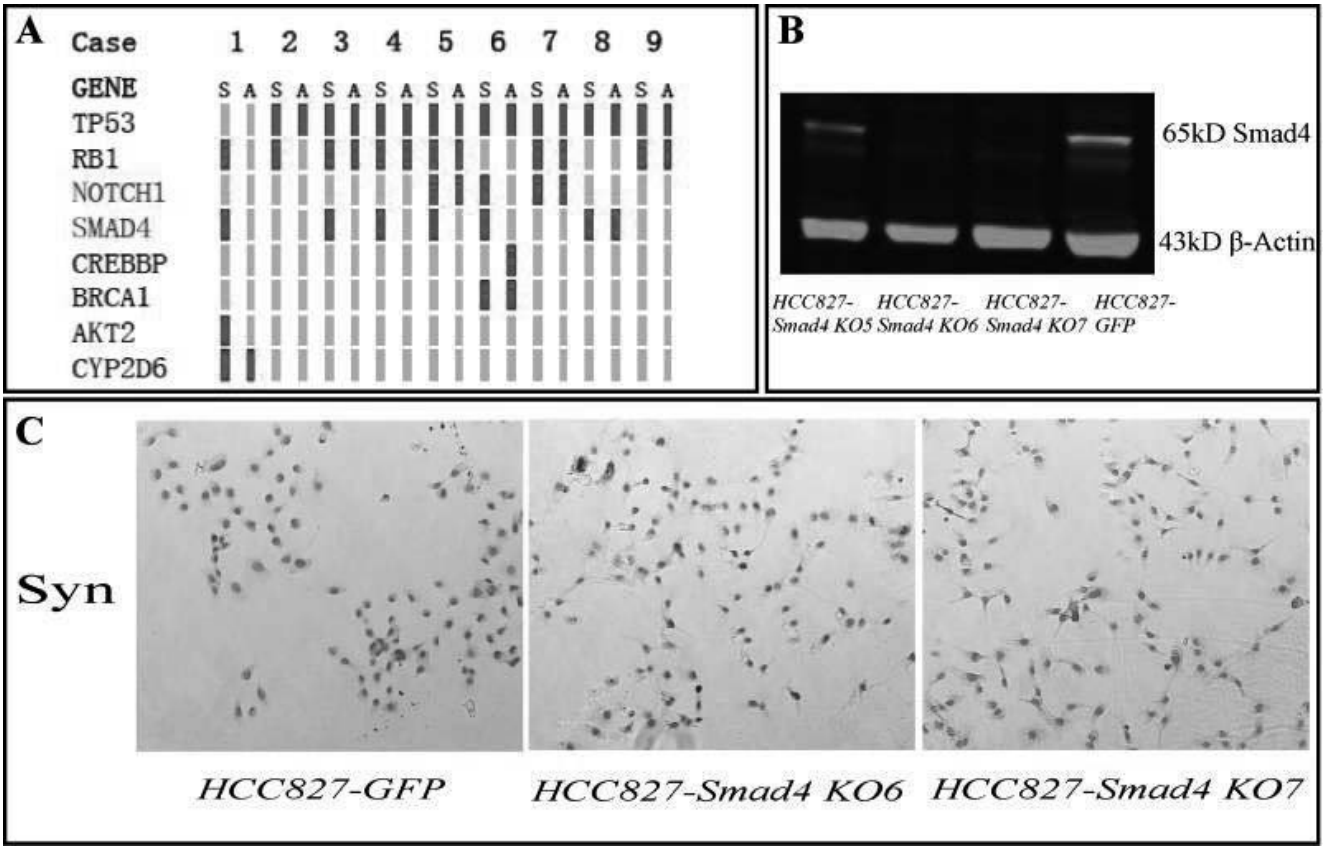
Background: Along with the widely use of EGFR-TKI therapy, transformation from lung adenocarcinoma (LAC) to small cell lung cancer (SCLC) has been recognized and accepted as a reason of drug resistance , but the mechanism remains unclear . **Method:** At first, we detected mutated genes in LAC and SCLC component from 9 combined SCLC cases independently by NGS, and analyzed the gene expression in pairs to find the targeted genes. And then, we knocked out the putative gene in HCC827 cell line by CRISPR/Cas9 to detect the changes of classic neuroendocrine markers (CgA, Syn, CD56). **Result:** A high mutation rate of Smad4 gene is observed in SCLC component from 9 combined SCLC cases (66.7%, 6/9, Figure 1A), which is much higher than that in pure SCLC (1.8%, available on http://www.cbioportal.org) samples. HCC827-Smad4$^{-/-}$ cell line is successfully established (Figure 1B), and by IHC assay, the expression of Syn is obviously enhanced in HCC827-Smad4$^{-/-}$ cells when compared with HCC827-GFP cells (Figure 1C).

(See next page)



Conclusion: The dysfunction of Smad4 protein confers the neuroendocrine phenotype of LAC, which plays a potential role in transformation to SCLC.

Keywords: small cell lung cancer, SMAD4 mutation, transformation

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P3.12-10 IMMUNOGENOMIC CHARACTERISTICS OF SCLC AND LCNEC REDEFINED MOLECULAR SUBGROUPS

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Background: While small-cell lung cancer (SCLC) and large-cell neuroendocrine carcinoma (LCNEC) are distinct classes of high-grade neuroendocrine carcinomas, the differential diagnosis between SCLC and LCNEC remains challenging. In fact SCLC and LCNEC overlap in clinical, histopathologic, cytologic, morphologic and genetic characteristics. Molecular profiling with microarray or next-generation sequencing has provided growing evidence suggesting that both SCLC and LCNEC are biologically heterogeneous and a great part of them are borderline neuroendocrine carcinomas falling between typical SCLC and LCNEC. On account of accumulated knowledge, we speculated that immunogenomically characterizing SCLC and LCNEC collectively as one group, or rather morphologically or cytologically separating SCLC from LCNEC has superior clinical value. **Method:** We analyzed gene expression profiles of 44 SCLCs, 56 LCNECs and 25 normal lung samples obtained from Gene Expression Omnibus. Unsupervised and supervised analyses were performed to understand molecular characteristics of samples. Pathway and CIBERSORT analyses were employed to obtain immune landscape of SCLC and LCNEC. **Result:** Unsupervised clustering with 1189 differentially expressed genes revealed 2 distinct molecular subgroups (G1 and G2) of SCLC and LCNEC, which is not associated with histopathology. Targeted pathway analysis found that G1 was marked by activated IL-17, MAPK and Hippo signaling pathways. In contrast, transcriptional factors, such as ASCL1, INSM1, SOX2, and NKX2-1 were significantly up-regulated in G2, but not in G1. Moreover, in silico analysis of cellular composition and expression of immune genes disclosed unique immunoprofiles for G1 and G2. G1 was characterized by enriched CD4 memory cells, M1 macrophages and activated dendritic cells. While G2 was composed of high fractions of memory B cells and naïve CD4 cells. Strikingly, expression of both immunoinhibitors (IL10, PDL1, IDO1) and immunomodulators (OX40L, BAFF, GITR, IL6), as well as MHC class I and II molecules was higher in G1 compared to that in G2. **Conclusion:** We identified the common intrinsic features and molecular subgroups of SCLC and LCNEC, which are beyond conventional histopathology and better associated with immunogenomics of tumors. Further research is warranted to identify potential clinical implication of SCLC and LCNEC molecular subgroups.

Keywords: immunogenomic, molecular subgroup

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P3.12-11 ASSOCIATION OF THE LUNG IMMUNE PROGNOSTIC INDEX (LIPI) WITH OUTCOMES FOR IMMUNE CHECKPOINT INHIBITORS IN DIFFUSE SCLC PATIENTS

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Background: Pretreatment LIPI (Lung Immune Prognostic Index), based on derived NLR (neutrophils/[leucocytes-neutrophils] ratio) and lactate dehydrogenase (LDH) has been associated with outcomes for immune checkpoint inhibitors (ICI) in advanced NSCLC patients. We tested whether LIPI has the same role in diffuse small cell lung cancer (SCLC) patients. **Method:** Baseline dNLR and LDH and clinical data were retrospectively collected in SCLC patients, treated with ICI (PD1 inhibitor, PDL1 inhibitors +/- CTLA4 inhibitor) from April 2014 to Jan. 2018 (N=66) from 6 European centers. LIPI was calculated combining dNLR and LDH, stratifying 3 risk groups: good (dNLR<3+LDH<upper limit of normal (ULN), intermediate (dNLR>3 or LDH>ULN), poor (dNLR>3+LDH>ULN). The primary endpoint was overall survival (OS), and secondary endpoint was progression-free survival (PFS). **Result:** Fifty-three patients (80%) were males, 58 (88%) smokers and all patients had PS ≤1, with median age 63 years (41-82). PDL1 was ≥ 1% by immunohistochemistry in 6 patients, and unknown in 60 patients. The median of prior lines was 1 (0-6). Platinum-based therapy was the prior line in 63 (95%) patients, with ORR of 88%. The median PFS and OS with ICI were 2.7 months (m) [95% CI 1.87-4.43] and 10.3 m [95% CI 5.8-12.6]. dNLR was greater than 3 in 16 (25%) and LDH> Upper Limit of Normal (ULN) in 33 (50%) patients. Based on both, LIPI stratified the population in 3 groups: 26 patients as good (40%), 29 (45%) as intermediate and 10 (15%) as poor LIPI risk groups. LIPI was an independent factor for OS (HR 2.77, 95% CI 1.07-7.14, *P*=0.03) and PFS (HR 3.13, 1.37-7.16, *P*=0.01). Median OS for good, intermediate, and poor risk groups were 11.4 m [95% CI 5.5-27.3], 11 m [95% CI 6.8-not-reached (NR)] and 2.3 m [95% CI 0.7-NR], respectively (*P*=0.004). Median PFS for good, intermediate, and poor risk groups were 3 m [95% CI 1.9-12.6], 2.8 m [95% CI 1.6-6.0 and 1.2 m [95% CI 0.47-NR], respectively (*P*=0.004). **Conclusion:** Baseline LIPI poor risk group is associated with poor outcomes for ICI in diffuse SCLC patients. LIPI effect in a validation cohort is currently evaluated.

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P3.12-12 GENOMIC PROFILING OF PULMONARY LARGE-CELL NEUROENDOCRINE CARCINOMA (LCNEC) REVEALS DISTINCT MUTATIONAL LANDSCAPE

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Background: The controversial classification of lung neuroendocrine tumor has been amended a few times since recognised as a separate entity. LCNEC shares clinical features with small cell lung carcinoma (SCLC) and they were both classified as lung neuroendocrine carcinoma according to the 2015 WHO lung primary pathology classification, numerous studies have revealed barely satisfactory outcomes when it was treated as SCLC. However the underlying molecular basis for such commonalities and discrepancies are poorly understood. In this study, we interrogated the genomic landscape of LCNEC and SCLC along with their histologically related subtypes: carcinoids and atypical carcinoids to define the molecular pattern of LCNEC. **Method:** We performed targeted sequencing in 35 tissue samples using a panel covering 520 cancer related genes, spanning 1.6MB of human genome, with an average sequencing depth of 1,418x. Among them, 15 were diagnosed with SCLC, 9 with LCNEC, 6 with carcinoid and 5 with atypical carcinoid. **Result:** On average, LCNEC exhibited 13.5 mutations per million base pairs (Mb) and a C:G>A:T transversion rate of 34%, which is indicative of tobacco exposure. LCNEC had SCLC (16.7 Mb) had comparable TMB (p=0.18), which is significantly higher than carcinoids (1.2/Mb, p<0.001) and atypical carcinoids (2.4/Mb, p<0.001). The most frequently mutated gene in LCNEC is *TP53* (89%, 8/9), followed by *NOTCH1* (33%), *KEAP1* (22%), *RB1* (22%) and a few chromatin modifiers, including *KMT2D* (33%), *KMT2C* (33%). Co-mutation in *TP53* and *RB1*, a hallmark of SCLC, was found in 22% (2/9) of LCNEC patients; in contrast, 80% of SCLC patients harbored concurrent mutation. 67% carcinoid (4/6) and 20% (1/5) atypical carcinoid patients had no mutation identified from this panel. No classic lung adenocarcinoma driver mutations were found in any subtype. Copy number analyses revealed significantly higher copy number variation (CNV) in SCLC and LCNEC comparing with carcinoids and atypical carcinoids, which yield virtually no CNV. Our analysis revealed a comparable CNV status of SCLC and LCNEC (p=0.158), with an enrichment in amplification of chromatin modifiers. **Conclusion:** Our study, comprehensively characterized 4 subtypes of neuroendocrine tumors, revealed a high TMB and CG:AT transversion rate in LCNEC patients as well as a distinctive mutation landscape, with an enrichment of mutations occurring at chromatin remodelers. Furthermore, LCNEC has comparable TMB and CNV status as SCLC, which are significantly higher than carcinoid and atypical carcinoids.

Keywords: lung neuroendocrine carcinoma, large-cell neuroendocrine carcinoma, targeted sequencing

P3.12 SMALL CELL LUNG CANCER/NET
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.12-13 EXPRESSION OF THE IMMUNE CHECKPOINT AXIS-PVR/TIGIT IN SMALL CELL LUNG CANCER

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Background: The poliovirus receptor (PVR) is an immune checkpoint protein expressed on tumor cells. It has been reported to mediate activation of T cells via CD226 or inhibition through binding to T-cell Ig and ITIM domain (TIGIT). TIGIT competes with CD226 for binding to PVR, and exhibits stronger affinity for PVR. Recently we have found that PVR is highly expressed in SCLC cell lines. Characterizing the expression and significance of the PVR-TIGIT axis in SCLC will help us to better understand the immunology of SCLC and may lead to novel therapeutic strategies to combine checkpoint blocking agents for improved SCLC immunotherapy. **Method:** Immunohistochemistry (IHC) was performed to evaluate PVR protein expression in a TMA of 39 SCLC cell lines and a cohort TMA of 77 limited stage SCLC patients with clinical data. We analyzed both PVR and TIGIT in an independent cohort of 27 resected, limited-stage SCLC tumors. **Result:** Thirty-seven cell lines (95%, 37/39) demonstrated staining for PVR and of those, 4 cell lines (10.3%, 4/39) showed strong staining (H-score ≥ 270). In the 77 SCLC patients cohort, PVR expressed predominantly in the membrane of tumor cells, with minimal expression observed on immune cells. PVR expression in the SCLC patient cohort was 82% with an arbitrary H-score cut-off of ≥ 50. Higher PVR expression was found for male patients (P=0.040). The expression of PVR increased with the tumor progressing from stage I to stage III (p =0.007). SCLC patients who had higher PVR expression demonstrated poorer prognosis and the difference was near statistically significant (p=0.050). Using the same cut-off (H-score ≥ 50) in the independent SCLC cohort, the prevalence of high PVR expression was 89% (24/27). In the independent SCLC cohort, TIGIT was found to be expressed membranous or cytoplasm on the immune cells with weak to moderate staining. Immune cells with TIGIT staining were typically seen as variable size and aggregated toward the periphery of the tumor nest. TIGIT protein staining was demonstrated in 20 cases (74%). No association was found between PVR H-score and TIGIT expression by Fisher's test (p=0.093). **Conclusion:** PVR is broadly expressed in SCLC cell lines and tumor tissues. The expression of TIGIT protein was also found in SCLC patients with weak to moderate staining. Blockade of the PVR-TIGIT pathway may represent a possible future target to immunotherapy in SCLC patients.

Keywords: small cell lung cancer, PVR-TIGIT immune checkpoint axis

P3.12 SMALL CELL LUNG CANCER/NET
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P3.12-14 GENOMIC PROFILING OF CHINESE SMALL CELL LUNG CANCER AND THE IMPLICATIONS FOR THERAPY

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Background: Small cell lung cancer (SCLC) is one of the deadliest malignancies and accounts for nearly 15% of lung cancers. The 5-year survival rate for SCLC is very low. Previous study had revealed the genomic characterization of SCLC in Western patients. However, little is known about that in Chinese SCLC patients. **Method:** FFPE tumor and matched blood samples of 79 Chinese SCLC patients, including 60 males (median age of 60 years old) and 19 females (median age of 59 years old), were collected for next generation sequencing to detect 450 cancer related genes. All histological diagnoses were confirmed by independent pathologists. Genomic alterations including single nucleotide substitutions (SNV), short and long insertions/deletions (Indel), copy number variations (CNV), and gene rearrangement in selected genes were assessed. **Result:** The most frequently altered genes in 79 Chinese SCLC patients were *TP53* (94.9%), *RB1* (83.5%), *LRP1B* (22.8%), *KMT2D* (13.9%), *NOTCH1* (12.7%), *FAM135B* (11.4%), *FAT1* (11.4%), *KDR* (11.4%), *SPTA1* (10.1%) and *STK24* (10.1%). Four of the patients harbored *EGFR* alterations including one *EGFR* fusion. Copy number variation analysis revealed that the most frequent variations occurred in the long arm of chromosome 13, including amplifications of *STK24*, *FGF14*, *IRS2* and *TNFSF13B* (10.1%, 8/79, located at 13q32~13q34) and deletion of *RB1* and *BRCA2* (59.5%, 47/79, located at 13q13~13q14). Compared to the previously reported 25% mutational frequency in Western cohort reported previously, 31.6% (25/79) of our patients exhibited alterations in NOTCH signaling pathway related genes (*NOTCH1*, *NOTCH2*, *NOTCH3*, *NOTCH4*, *EP300* and *CREBBP*). Around 15.2% (12/79) patients had PI3K/AKT/mTOR signaling pathway alterations (*PIK3CA*, *MTOR*, *PTEN*, and *TSC2*). Homologous Recombination Deficiency (HRD) related genes altered in 17.7% (14/79) patients, suggesting the potential clinical benefits from PARP inhibitors. The genomic alterations of FGF family members occurred in 25.3% (20/79) of patients. Other targetable genes included *KIT* (7.6%, n = 6), *PDGFRA* (5.1%, n = 4) and *DDR2* (2.5%, n = 2). **Conclusion:** In this study, we characterized the genomic alteration profile of Chinese SCLC patients. Our discovery of CNV in the long arm of chromosome 13 might be helpful in understanding the pathogenesis of SCLC. Consistent with previous report, high mutation rates of *TP53* and *RB1* are the most important genomic features of SCLC [PMID: 26168399]. In addition, we also found several targetable gene variations including HRD, FGF family, *KIT*, *PDGFRA* and *DDR2*, which might provide potential targeted therapy options for SCLC patients. Further association analyses of these genomic alterations with clinical features in SCLC are still needed.

Keywords: small cell lung cancer, genomic profiling, Chinese population

P3.12 SMALL CELL LUNG CANCER/NET
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P3.12-15 68 GA DOTA PET/CT IN STAGING OF BRONCHO-PULMONARY CARCINOID TUMORS. IS THERE A REAL BENEFIT?

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Background: The staging of well differentiated bronchopulmonary neuroendocrine tumours (carcinoids) is complicated by the unpredictable incidence of nodal and distal metastases. PET CECT, which has become the standard for staging of lung cancers has proven ineffective in the staging of carcinoid tumours. 68 Ga DOTA NOC PET/CT which depends on radio-tracer uptake in somatostatin receptors appears to be an attractive modality for the staging of these neuroendocrine tumours **Method:** We performed a retrospective analysis of patients who underwent 68 Ga DOTA NOC PET/CT followed by surgical resection from October 2014 to March 2018. Data was retrieved regarding demographics, standardized uptake value (SUV), surgery performed and final histopathology report including degree of differentiation, nodal positivity and Mib index. The study included only patients who underwent resection since the focus of the study is on correlation with histopathological features. An attempt was made to correlate the SUV with diagnosis of typical vs atypical carcinoid, nodal metastases and Mib index **Result:** During the study period 42 patients underwent surgical resection following DOTA PET. All details of imaging including SUV were available for 38 patients, while complete histopathological details was available for 42 patients. DOTA PET was not able to differentiate between typical and atypical carcinoids (35 vs 3) based on SUV. The mean SUV of typical carcinoids was 45.2(SD-42.77) whereas that of atypical carcinoids was 34.3(SD-39.7) and the difference was not statistically significant (p=0.6). 6/42 cases had nodal metastases of which DOTA PET could corrrectly identify only 1. There were 2 false positive reports and 5 false negative reports, (sensitivity 16.6% and specificity 94.1%). The mean SUV of the false positive nodes(n= 2 cases) was 7 which calls into question the specificity of the tracer. No corelation between SUV and Mib index could be demonstrated, p=0.8 **Conclusion:** In this study 68 Ga DOTA NOC PET CECT could not help in predicting the histopathological nature of carcinoid tumours, atypical vs typical, presence of nodal metastases or Mib index. This study is limited by the small numbers enrolled, a larger series may help us in coming to a more definitive conclusion

Keywords: broncho pulmonary carcinoid, 68 Ga DOTA NOC PET CT

P3.12 SMALL CELL LUNG CANCER/NET
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P3.12-16 PROGNOSTIC IMPACT OF M DESCRIPTORS OF THE 8TH EDITION OF TNM CLASSIFICATION FOR EXTENSIVE DISEASE-SMALL CELL LUNG CANCER

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Background: The International Association for the Study of Lung Cancer proposed the eighth edition of TNM classification of lung cancer on the basis of a new database in 2015. One of the most significant change in new criteria was that M descriptors has changed from three (M0, M1a and M1b) to four (M0, M1a, M1b and M1c). Although the 8th TNM classification is strong in the related with non-small cell lung cancer (non-SCLC) management, association between the 8th TNM classification and prognosis of SCLC patients remains unclear. In this study, we evaluated the applicability of the 8th TNM staging system to SCLC patients, especially whether prognosis of extensive disease (ED)-SCLC was related to the M descriptors. **Method:** We performed a retrospective study of consecutive 277 SCLC patients who had treated at our hospital between January 2008 and December 2016. The SCLC patients classified based on the 8th TNM classification and evaluated clinical factors and survival. **Result:** 186 (65.7%) of 277 SCLC patients were classified ED-SCLC based on the two-stage system, classically. Among the ED-SCLC patients, 10 (5.3%), 38 (20.4%), 32 (17.2%) and 106 (57.0%) were categorized into stage M0, M1a, M1b and M1c based on the 8th TNM classification, respectively. All ED-SCLC patients received systemic chemotherapy and median overall survival (OS) was 13.7 months. There were significant differences in OS [7.3 months; 95% confidence interval (CI), 5.7–8.9 months vs. 16.0 months; 95% CI, 13.2–18.8 months; p<0.001] according to the M descriptors (M0, M1a, M1b vs. M1c) and the TNM stage groups (III and IVa vs. IVb). Multivariate survival analyses showed that the M descriptor was one of prognostic factors (hazard ratio 1.50; 95% CI, 1.26–1.78 months; p<0.001) in addition to known prognostic factors such as ECOG performance status and pretreatment serum level of LDH. **Conclusion:** In this study, the 8th TNM classification had prognostic value in the SCLC patients treated with systemic chemotherapy. We suggested that ED-SCLC patients was divided into two subgroups based on the TNM classification. In ED-SCLC as well as non-SCLC, treatment development should be considered based on the TNM classification.

Keywords: Prognosis, small cell lung cancer, Staging

P3.12 SMALL CELL LUNG CANCER/NET
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P3.12-17 A RETROSPECTIVE STUDY EXAMINING THE ROLE OF PET-CT IN THE 8TH TNM STAGING SYSTEM OF SCLC

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Background: We have recently performed a validation of the 8th TNM system in SCLC. The aim of the present study is to perform a subgroup analysis on patients (pts) who underwent a PET/CT scan, to furhter assess potential utility of this method in SCLC pts, since PET/CT is usually performed primarily to identify potentially curable cases. **Method:** Between January 2008 and February 2016, a total of 706 pts with SCLC were diagnosed in the Stockholm and Gotland region. A multivariate model adjusted for basic patient characteristics and PET-CT was performed. **Result:** One third of the patients had performed a PET/CT scan (n=204). Pts were classified according to the 8th TNM. The table

shows patient distrubution according to clinical variables and stage (8th TNM), as well as HR for multivariate survival analysis. Many pts (48%) were classified to stage I-III disease, while the rest had stage IV. Pts with stage I-III were treated with Surgery (n=13), Radiotherapy+ Chemotherapy (CT) (n=80) or Stereotactic body radiation (n=7). The patients who were diagnosed with stage IV disease were treated with palliative CT or did not receive any oncological therapy. In pts that did not perform PET/CT, the majority (87%) were treated with CT or did not receive treatment. The percentage of pts diagnosed with M1b-disease was slighlty higher in those who performed a PET/CT vs those who did not (7% vs 3%, respectivley).

Multivariate analysis with PS, Age, Gender, Stage for those patients who performed PET/CT.

	# of pts	8th TNM	
		p-value	HR
Gender		0.055	
Male	83		1.0
Female	122		1.00 (0.84-1.18)
Age		0.01	
<70	115		1.0
>70	90		1.25 (1.06-1.49)
PS		0.0002	
0-1	176		0.25(0.20-0.32)
2	23		0.56(0.44-0.73)
3-4	6		1.0
Stage		<.001	
IA	-		-
IA2	7		0.09 (0.02- 0.49)
IA3	6		0.29 (0.08-0.96)
IB	2		0.92 (0.15-8.26)
IIA	3		NA
IIB	7		0.21 (0.08-0.53)
IIIA	32		0.44 (0.26-0.73)
IIIB	27		0.27 (0.15-0.47)
IIIC	16		0.23(0.11-0.50)
IVA	30		0.47 (0.25-0.82)
IVB	74		1.0

Conclusion: The 8th TNM edition has a strong prognostic impact in SCLC. Incorporating a PET/CT scan in the diagnostic workup of SCLC is relevant to distinguish potentially curable pts (stages I-III) from pts with stage IV disease, and may be of value to indentify single extra-thoracic metastases (M1b cases).

Keywords: SCLC, PET/CT

P3.13 TARGETED THERAPY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.13-01 DETECTING ALK REARRANGEMENTS IN NSCLC PATIENTS: IHC, FISH OR NGS FUSION?

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Background: Rearrangements of the anaplastic lymphoma kinase (*ALK*) gene in non-small cell lung cancer (NSCLC) represent a novel molecular target in a small subset of patients. Although *ALK* rearrangements are usually assessed by immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH), molecular approaches have recently emerged as relevant alternatives in routine laboratories. Previous studies that compared FISH and IHC considered FISH the gold standard, although there are emerging data on *ALK* fusion variants that question the role of FISH. **Method:** Here, we report our personal experience with the use of the IHC, FISH and next-generation sequencing (NGS) analyses in a group of *ALK* rearranged NSCLC patients treated within our institution **Result:** A total of 13 patients with NSCLC was positive for *ALK* rearrangements on IHC and was subsequently tested with FISH. Interestingly 5 out of 13 patients were negative on FISH but all the patients received first line *ALK* inhibitors. The response rate (RR) was 79% (10/13), the progression free survival (PFS) was 19 months for the total population. Among the non-responders 2/13 were FISH negative but 1/13 was IHC and FISH positive. We are going to retrospectively perform NGS analyses to further assess the role of NGS fusion in the context of ALK patients. **Conclusion:** Our study suggests that IHC is a valid, quick and reliable assay for the detection of *ALK* gene rearrangements. It also shows that FISH should not be considered the gold standard on its own for the detection of *ALK* gene rearrangements. We are going to present the data on NGS fusion in this group of patients at the next conference (WLLC November 2018) with the view of seeing if NGS fusion could and should be a valid alternative and replace FISH as the gold standard.

Keywords: ALK, IHC, NGS fusion

P3.13 TARGETED THERAPY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.13-02 LYMPHOCYTIC PLEVRAL EFFUSION DUE TO CRIZOTINIB USAGE: FIRST CASE IN LITERATURE

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Background: Crizotinib is an ALK inhibitor and used for treatment in advanced stages lung adenocarcinoma patients with ALK (+). Most common side effects are; gastrointestinal disorder and visual side effects. Drugs are one of the reasons of effusion. For accurate diagnosis patients' drug history should be questioned in details. To the best of our knowledge pleural effusion due to crisotinib treatment does not exist in current literature. **Method:** 41 years old female patient's admitted to outpatient clinic with chest pain. There was a right hilar lesion and pleural effusion on right hemithorax (Figure 1A). Thorax tomography revealed 5 cm mass lesion in right middle lobe. Transthoracic needle aspiration biopsy reported as adenocarcinoma. Tissue was positive for ALK-rearrangement and first line *crizotinib* initiated. In the third month of treatment bilateral pleural effusion more in the right was occurred (Figure 1B and 1C). Primary lesion was regressed (Figure 1D). Efusion on left hemithorax was serous and exudate. Any malignant cells were observed. It was drained with pleural catheter and performed talk pleuredesis. There were lymphocytic cell predominance. Others reasons were excluded. Crizotinib treatment was interrupted, in 15th day of crizotinib free observation fluid's amount decreased. To increase the rate of recovery methylprednisolone 40 mg/day is added. **Result:** Crizotinib started again with frequent clinical, radiological follow-up. Fluid's amount did not increase when steroid dose was tapered. While patient take 16 mg/day crizotinib, it has been seen that left pleural fluid disappeared and right pleural thickening appeared due to talc pleuredesis (Figure 1E and 1F).

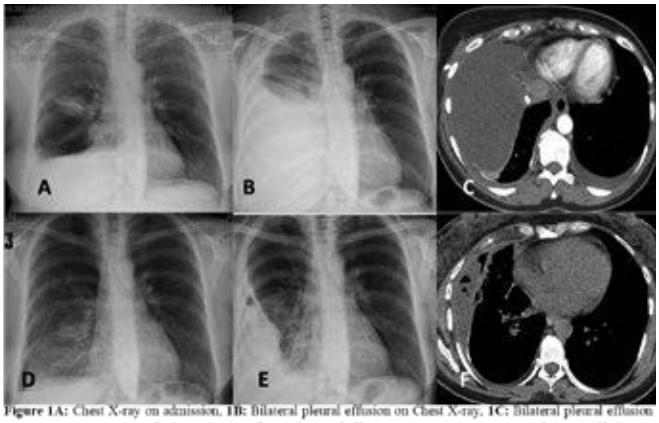

Figure 1A: Chest X-ray on admission. **1B:** Bilateral pleural effusion on Chest X-ray. **1C:** Bilateral pleural effusion on CTT. **1D:** Regression of primary lesion after drainage of effusion. **1E:** Complete response of pleural effusion on left side and organized effusion on right side. **1F:** Regression of pleural effusion on CTT

Conclusion: To the best our knowledge there is not case report with pleural effusion related to ALK TKI treatment. Our case is the first to demonstrate the relationship between ALK TKI treatment and pleural effusion. The case which response to the treatment newly formed pleural effusion's source may have thought as medication.

Keywords: crisotinib, lung cancer, pleural effusion

P3.13-03 REAL-WORLD ANAPLASTIC LYMPHOMA KINASE TESTING PRACTICES: RESULTS FROM A SURVEY IN THE UNITED STATES

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Background: Anaplastic lymphoma kinase (*ALK*) translocation is a clinically validated predictive biomarker in multiple cancer types including non-small cell lung cancer, and widespread adoption of diagnostic assays permits a review of test performance. This analysis presents ALK and epidermal growth factor receptor (EGFR) testing rates, expediency, and results from 4 large national laboratories. **Method:** Deidentified data from January 2013 to December 2015 were compiled from 40 states and Washington DC and included in the final analysis. ALK status was evaluated with the Vysis ALK Break Apart FISH Probe Kit; EGFR status was evaluated by *therascreen* EGFR RGQ PCR Kit, cobas EGFR Mutation Test, or Sanger sequencing. Results from the most recent conclusive test were used. Collection to order (time from date of biopsy to date of biomarker test order), order to results (time from date of biomarker test order to date of available results), and overall turnaround times (collection to order + order to results) were evaluated. Results were analyzed by laboratories and US regions (Northeast, Midwest, South, and West). Data were summarized with descriptive statistics. **Result:** s of 59,058 ALK and 50,992 EGFR tests were collected; 50,023 patients were tested for both ALK and EGFR, 9035 had results for ALK only, and 969 for EGFR only. Mean patient ages at ALK-positive (ALK^+) and EGFR-positive ($EGFR^+$) diagnoses were 62.5 and 69.0 years, respectively. Overall ALK^+ and inconclusive rates were 2.8% and 6.5%, respectively, vs 10.4% and 6.2% for EGFR testing. ALK^+ (2.3–5.1%) and inconclusive (1.1–17.4%) rates varied between test centers. In the western US, the ALK^+ rate (3.3%) was comparably greater than in other regions (2.4–2.7%). The median turnaround time was 15 days, with a median of 10 days for collection to order and 4 days for order to results; some regional variation was seen in turnaround time (14–18 days). No correlation was seen between age and turnaround time. **Conclusion:** $EGFR^+$ and ALK^+ rates and age distributions were consistent with prior reports. An interesting geographic difference in ALK rates was seen that warrants further investigation. The average turnaround time was longer than current guidelines recommend, suggesting an opportunity to improve current testing practices.

Keywords: ALK-positive NSCLC, FISH, molecular diagnostic testing

P3.13-04 LORLATINIB IN ANAPLASTIC LYMPHOMA KINASE AND PROTO-ONCOGENE TYROSINE-PROTEIN KINASE ROS-POSITIVE NON-SMALL CELL LUNG CANCER

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Background: In this case series we present ten patients with anaplastic lymphoma kinase (ALK)-rearranged or ROS proto-oncogene 1 (ROS1)-rearranged non-small-cell lung cancer (NSCLC) treated with lorlatinib. **Method:** Lorlatinib is highly potent and selective third generation ALK and ROS1 tyrosine kinase inhibitor (TKI) with known activity against most resistance mutations. In a phase 1 study, lorlatinib showed intracranial and systemic activity in ROS1-positive and ALK-positive patients with advanced NSCLC. **Result:** Thus far, we treated 6 ALK- and 4 ROS1-positive stage IV NSCLC patients with lorlatinib in a compassionate use program. Best response was complete remission in two of our patients. One ROS1-positive patient with CNS metastases has now ongoing complete response for 27 months; the other patient with a ALK-positive NSCLC with CNS metastasis has now been treated with lorlatinib for 16 months. Three patients showed a partial response with an ongoing progression free survival of respectively 3, 5 and 8 months. Two of our patients (one ALK-positive and one ROS1-positive NSCLC) showed progressive disease as best response. In three patients response data is not (yet) available. There were no significant side effect apart from hypercholesterolemia, which occurred in four of our patients. **Conclusion:** Lorlatinib shows promise in the treatment of ROS1-positive and ALK-positive patients with advanced NSCLC.

Keywords: Anaplastic lymphoma kinase, ROS proto-oncogene 1, lorlatinib

P3.13-05 USE OF CRIZOTINIB IN A PATIENT WITH A ROS MUTATION CAUSING ELEVATED CPK AND RESULTING IN DOSE LIMITING: CASE REPORT

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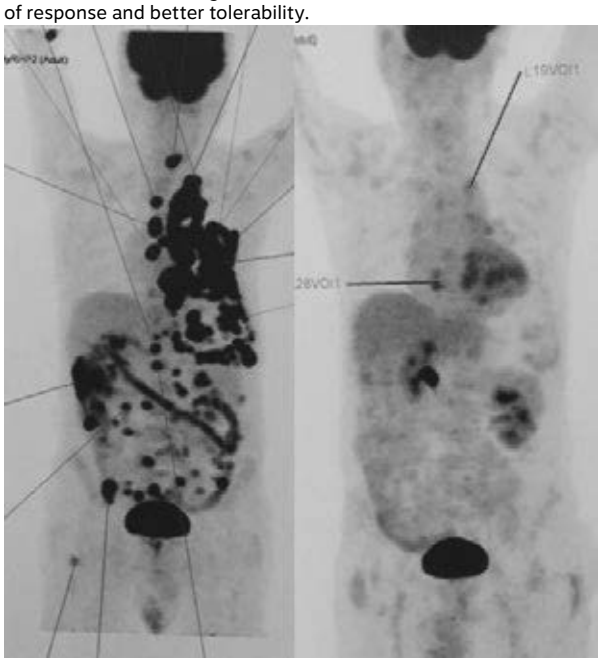
Background: The use of target therapy in lung cancer has changing the story of this disease. However, the toxicity sometimes can be a challenge. **Method:** We report a clinical case in a patient with advanced lung cancer with mutation in ROS 1 that had an excelent response with Crizotinib, but developed high levels of CPK. **Result:** Man, 75y, with an adenocarcinoma of the right lung with lesions in pleura. Tumor was assessed for EGFR mutation and ALK translocation, but were not found. We started chemotherapy with Carboplatin and Pemetrexed with partial response and, after four cycles, we continued treatment with Pemetrexed isolated. After thirteen cycles, he had bone progression and the chemotherapy was changed to Docetaxel. After that, he was submitted to three more lines of chemotherapy and immunotherapy with Nivolumabe. After four years of metastatic disease, a new bone progression with a sternal mass. new biopsy was made and found a mutation in the ROS 1 gene. He was very symptomatic, limitted performance status (ecog 4) and was admmited in the hospital. We started treatment with Crizotinib 250 mg twice daily and he had a dramatic response. After two months, ECOG was one and a PET-CT showed almost a complete response. However, the patient started cramps in the abdomem and laboratory showed a CPK of 4500 u/l. the dose of the Crizotinib was adjusted to 250mg/day and the levels of cpk started to fall. We tried to reintroduce the full dose, but the levels of CPK increases to 4800 u/l again. So, we reduced the dose with maintenance of response and better tolerability.



Conclusion: The increased levels of CPK with inibithors of alk is described with Alectinib. This relation with Crizotinib is not well estabilished. In this case, there was an excellent response, but the dose was limited by the increase of CPK.

P3.13-06 ANALYSIS OF ALK REARRANGEMENT NON-SMALL CELL LUNG CANCER CELL BLOCKS FROM PLEURAL EFFUSION

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Background: Anaplastic lymphoma kinase (ALK) rearrangements occur in 1% to 7% of non-small-cell lung cancers (NSCLCs). Crizotinib, an ALK

inhibitor, has been demonstrated to provide dramatic clinical benefits in ALK rearrangement advanced NSCLC. The aim of this study is to investigate the clinical value of ALK rearrangement NSCLC blocks cell from pleural effusion. **Method:** Two hundred and fifteen cases of ALK rearrangement non-small cell lung cancer (NSCLC) blocks cell from pleural effusion, Four hundred and four cases of tissues were detected by reverse transcription polymerase chain reaction (RT-PCR) method. The consistency of ALK rearrangement was examined in 74 cases of patients with tissues and cell blocks. **Result:** ALK rearrangement was found in 26 of 215 cell blocks (positive detection rate of 12.09 %). ALK rearrangement was detected in 25 of 404 tissue blocks (positive detection rate of 6.19%). There were 67 cases in the 74 (90.54%) cases had the same consistency as tissue block. ALK rearrangement was detected in 11 of 74 (14.86%) cell blocks, and 14 of 74 (18.92%) tissue blocks. **Conclusion:** The rate of ALK rearrangement in cell blocks of NSCLC is higher than in matched tissue blocks. The patients with malignant pleural effusion are likely to tend ALK rearrangement.

Keywords: non-small cell lung cancer, cell block, ALK

P3.13 TARGETED THERAPY
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P3.13-07 THE EFFECT OF CRIZOTINIB IN PATIENTS OF NON SMALL CELL LUNG CANCER WITH BRAIN METASTASES: A RETROSPECTIVE ANALYSIS

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Background: Crizotinib is a tyrosine kinase inhibitor targeting the anaplastic lymphoma kinase gene (ALK) and exhibited a prominent effect in treating ALK-positive non-small cell lung cancer (NSCLC). This retrospective study aimed to evaluate therapeutic effects of crizotinib in patients with brain metastasis (BM) from ALK-positive NSCLC. **Method:** Patients diagnosed with BM caused by ALK-positive NSCLC from November 2010 to October 2015 and treated initially by crizotinib were enrolled and reviewed. The median and 95% confidence interval (CI) of the intracranial and whole-body progression-free survival (PFS) and the overall survival (OS) were calculated by Kaplan-Meier approach. And the candidate prognosticator of the survivals was checked by a log-rank test. **Result:** Totally 41 patients were eligible for analysis. The median whole-body PFS, intracranial PFS and OS were 8.00 (95% CI, 6.96-9.04), 8.00 (95%, CI 6.99-9.01) and 23.0 (95% CI, 15.8-30.2) months, respectively. Compared with multiple BM, single BM seemed to lead to a better OS when crizotinib was administered (P = 0.029). Totally 5 patients (12.2%) developed crizotinib-related adverse events. Except 1 patient terminated crizotinib treatment because of interstitial pneumonia, the other 4 cases exhibited only adverse events of grade 1. **Conclusion:** Crizotinib could bring an ideal control on BM from ALK-positive NSCLC and were well tolerated. It might be a feasible treatment for patients with this kind of disease.

Keywords: ALK-positive NSCLC, brain metastasis, crizotinib, survival

P3.13 TARGETED THERAPY
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P3.13-08 ASSESSMENT OF EGFR GENE MUTATIONS IN CF-DNA IN MONITORING OF RESPONSE TO EGFR TKIS IN PATIENTS WITH LUNG ADENOCARCINOMA

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Background: Molecular analysis of cf-DNA in NSCLC patients enables detection and monitoring of EGFR mutations. It allows for detection of the acquired resistance for 1st and 2nd generation of EGFR-TKIs caused Thr790Met substitution. The third generation of EGFR-TKIs (osimertinib) could overcome the resistance in patients with Thr790Met mutation. **Method:** The studied group included 23 Caucasian patients (8 male and 15 female, median age 71±9) with diagnosed lung adenocarcinoma and with EGFR mutations detected in tumor samples. Blood samples were collected before administration of EGFR-TKIs in all patients, and re-collected repeatedly from 10 patients during therapy. EGFR mutations and content of mutated cf-DNA were analyzed using ctEGFR Mutation Analysis Kit (Entrogen, USA) in Rotor-Gene Real-Time PCR device (Qiagen, Germany). **Result:** Analysis of EGFR activating mutations in cf-DNA showed 82.61% concordance/sensitivity (19/23) with tumor samples. The mean content of mutated cf-DNA was 7.44% and it was significantly lower (p<0.000035) than in tumor samples (34.54%). Concentration of mutated cf-DNA positively correlated with advanced stage of the disease. Monitoring of EGFR status in cf-DNA showed reduction and stabilization of mutant DNA content with the emergence of response to EGFR-TKIs treatment. Primary Thr790Met substitution was undetectable in cf-DNA and in tumor samples. Acquired resistance in Thr790Met mechanism during EGFR-TKIs treatment was detected only in one patient (1/10). This patient responded to osimertinib therapy. **Conclusion:** Analysis of EGFR mutations in cf-DNA shows lower sensitivity than in DNA isolated from tumor samples. Multiple evaluations of EGFR status may be useful in monitoring of therapy and allows for early detection of acquired resistance.

Keywords: EGFR-TKIs, liquid biopsy, NSCLC

P3.13 TARGETED THERAPY
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P3.13-09 ALTER-0303 STUDY: TUMOR MUTATION INDEX (TMI) FOR CLINICAL RESPONSE TO ANLOTINIB IN ADVANCED NSCLC PATIENTS AT 3RD LINE

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Background: Anlotinib is an effective multi-targeted receptor tyrosin kinase inhibitor (TKI) for refractory advanced Non-Small Cell Lung Cancer (NSCLC) therapy at 3rd line. ALTER-0303 clinical trial has been revealed that Anlotinib significantly prolongs progression free survival (PFS; Anlotinib: 5.37 months vs Placebo: 1.40 months) and overall survival (OS; Anlotinib: 9.63 months vs Placebo: 6.30 months) with the objective response rate (ORR) of 9.18% and the disease control rate (DCR) of 80.95%. Here, we sought to understand the gene mutation determinants for clinical response to Anlotinib via next generation sequencing (NGS) upon cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA) at baseline. **Method:** Totally 437 advanced NSCLC patients enrolled in ALTER-0303 study, and 294 patients received Anlotinib therapy. Of the 294 patients, 80 patients were analyzed in the present study. Capture-based targeted ultradeep sequencing was performed to obtain germline and somatic mutations in cfDNA and ctDNA. Response analyses upon discovery cohort (n = 62) and validation cohort (n = 80) were performed by use of germline and somatic (G+S) mutation burden, somatic mutation burden, nonsynonymous mutation burden, and unfavorable mutation score (UMS), respectively. Based on the above independent biomarkers and their subtype factors, tumor mutation index (TMI) was developed, and then used for response analysis. **Result:** Our data indicated that the patients harbouring less mutations are better response to Anlotinib therapy (G+S muatation burden, cutoff = 4000, Median PFS: 210 days vs 127 days, p = 0.0056; somatic mutation burden, cutoff = 800, Median PFS: 210 days vs 130 days; p = 0.0052; nonsynonymous mutation burden, cutoff = 50, Median PFS: 209 days vs 130 days; p = 0.0155; UMS, cutoff = 1, Median PFS: 210 days vs 131 days; p = 0.0016). TMI is an effective biomarker for Anlotinib responsive stratification (Median PFS: 210 days vs 126 days; p = 0.0008; AUC = 0.76, 95% CI: 0.62 to 0.89) upon discovery cohort and validation cohort (Median PFS: 210 days vs 127 days; p = 0.0006). Lastly, integrative analysis of TMI and IDH1 mutation suggested a more promising result for Anlotinib responsive stratification upon validation cohort (Median PFS: 244 days vs 87 days; p < 0.0001; AUC = 0.90, 95% CI: 0.82 to 0.97). **Conclusion:** This study provide a biomarker of TMI to stratify Anlotinib underlying responders, that may improve clinical outcome for Anlotinib therapy on refractory advanced NSCLC patients at 3rd line. Clinical trial information: NCT02388919.

Keywords: NSCLC, Anlotinib, Responsive biomarker

P3.13-10 FACTORS ASSOCIATED WITH LONG-TERM SURVIVAL OF STAGE IV NSCLC PATIENTS ON FIRST-LINE EGFR-TARGETING THERAPY

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Background: To determine factors associated with long term survival in Stage IV, non-small cell lung cancer (NSCLC) patients receiving EGFR-targeting agents (EGFR-TA) as systemic anti-cancer treatment in the first-line setting at a Canadian tertiary cancer centre. **Method:** Retrospective analysis was conducted on patients diagnosed with Stage IV (AJCC 7th edition) NSCLC between 1999 and 2014, and receiving EGFR-TA as first-line treatment. Demographic, clinical, histopathological, treatment and outcome data was extracted from the large, population-based institutional Glans-Look Lung Cancer Database. Long-term survivors (LTS) were defined as those surviving ≥ 18 months post EGFR-TA initiation. Correlates of survival were investigated via univariate analysis, Kaplan-Meier analysis using the log-rank test, and multivariate Cox regression. **Result:** We identified 117 eligible patients. Median age was 65 (IQR 54.5-74) years, 61% female, 91% adenocarcinoma, 60% never smoking history, and 80% were identified as EGFR-mutant (remainder were untested and accessed EGFR-TA before routine testing was performed). Most common ethnicity (by place of birth) was North American (47%), followed by Asian (37%). 21% survived ≥ 18 months post-EGFR-TA initiation, with a median overall survival (mOS) of 46 vs. 13 months in those surviving < 18 months post-EGFR-TA initiation (p <0.001). LTS were more likely to be over the age of 65 years at diagnosis (76% vs. 46%, p=0.012), receive palliative radiation therapy (72% vs. 27%, p<0.001), and possess Asian ethnicity (60% vs. 30%, p=0.044), although impact of age and radiation therapy did not retain prognostic significance in multivariate analysis after controlling for other measured confounders; Asian ethnicity was retained as a favorable prognostic factor for survival [HR: 0.5, 95%CI 0.3-0.8, p=0.005)]. Patients with Asian ethnicity revealed no significant demographic or clinical characteristics (notably gender, smoking status and EGFR mutation type) between LTS and non-LTS, with the exception of age. Asian LTS were significantly more likely to be ≥ 65 years of age at diagnosis (87% vs. 32%, p<0.001), a factor which retained significance as a favorable prognostic factor in multivariate analysis [HR: 0.3, 95% CI 0.2-0.7), p=0.004)]. **Conclusion:** Analysis of this population-based cohort identifies Asian ethnicity, and within this ethnic group, older age at diagnosis, as favorable prognostic factors for patients with Stage IV, NSCLC accessing EGFR-TA in the first-line setting. These findings help identify patients who derive the most benefit from EGFR-TA, and suggest that older, Asian patients represent a unique sub-population within metastatic NSCLC, who may possess different biological underpinnings of NSCLC, outside of a propensity to harbor EGFR mutations.

Keywords: EGFR-targeting agents, long-term survival, Asian ethnicity

P3.13-11 ADVANCED NSCLC TREATED WITH GEFITINIB OR ERLOTINIB FOR FIVE YEARS OR LONGER - RETROSPECTIVE SLOVAKIAN STUDY

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Background: Median PFS in the key phase III trials with gefitinib or erlotinib for advanced NSCLC with EGFR sensitizing mutations was less than 12 months. There are only a few data about the treatment results and toxicity of long-term treatment lasting 5 years or over. Purpose of this study was to find patients treated with either gefitinib or erlotinib for at least 5 years and to evaluate the treatment results in this group of patients. **Method:** Retrospective multicentre study, approved by the Ethical Committee of the Specialised Hospital of St Zoerardus Zobor, Nitra. All thoracic oncology centres in Slovakia were involved. Data regarding patients were obtained from the databases of participating institutions and patient files. Descriptive statistics was used for the data analysis. **Result:** Seven patients were included. Patients characteristics and the treatment results are summarised in the Table. Median PFS in this exceptional group was not reached, but it will be over 75 months. There was only one patient with the decreased dose of erlotinib (from 150 to 100 mg QD) due to skin toxicities. All the other patients had the common and manageable grade I – II toxicities only, and there were no unexpected drug-related AEs. **Conclusion:** In our group of patients with advanced NSCLC treated with gefitinib or erlotinib for over 5 years the treatment was safe and effective.
The NGS analysis of the available samples will be retrospectively done to assess the specific genetic features of these long-term responders.

Keywords: erlotinb, gefitinib, long-term treatment

Table: Patients characteristics and treatment results

Gender (M/W)	Age (yrs)	Smoking status	PS	Histology, cytology	NSCLC Stage	EGFR mutation	Treatment line/TKI	Response	PFS (mo)
W	72	Ex	2	AC	IV	Del 19*	1st/gefitinib	SD	63+
W	53	Smoker	1	AC	IV	NK	1st/erlotinib	SD	100+
W	58	Never	1	AC/SQ	IIIB	NK	2nd/erlotinib	PR	83+
W	69	Never	1	AC	IV	NK	2nd/erlotinib	SD	75+
W	72	Never	1	AC	IV	Del 19	2nd/erlotinib	PR	63+
W	59	Never	1	AC	IV	L858R	1st/erlotinib	PR	61+
M	64	Never	1	AC/SQ	IV	NK	2nd/erlotinib	PR	96+

*Del 19 and T790M

Conclusion: In our group of patients with advanced NSCLC treated with gefitinib or erlotinib for over 5 years the treatment was safe and effective. The NGS analysis of the available samples will be retrospectively done to assess the specific genetic features of these long-term responders.

Keywords: erlotinb, gefitinib, long-term treatment

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P3.13-12 A LUNG ADENOCARCINOMA WITH CONCOMITANT EGFR AND DE NOVO MET AMPLIFICATION RESPONSE WELL TO COMBINATION OF TKI AND BEVACIZUMAB

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Background: Patients with NSCLC who are carrying concomitant *de novo* EGFR and MET amplification were commonly reported to have poor response to therapy. Here, we presented a case of a patient harboring concomitant *de novo* MET and EGFR, who obtained favorable response to combinatorial therapy of TKI and bevacizumab. **Method:** We presented a lung adenocarcinoma patient harboring dual EGFR-MET alterations, and evaluated his response to combinatorial therapy of TKI and bevacizumab. In vitro experiments were performed in HCC827(EGFR-19del) and HCC827-GR (EGFR-19del+MET amplification) cells to validate the effect of bevacizumab on MET pathway. **Result:** A 44-year-old male stage IV lung adenocarcinoma with left lung tumor was detected harboring of EGFR-19del and MET amplification using PCR and FISH. The patient was treated with erlotinib+bevacizumab and achieved partial response (PR) with a PFS with 13 months. After PD, NGS performed on both tissue and plasma biopsies revealed that the patients obtained first-generation resistant mutation EGFR-T790M, concomitant with EGFR-19del. The patient was treated with osimertinib+bevacizumab and achieved PR. He developed PD again with a PFS of 10.2 months, and repeated biopsies sequencing identified concomitant EGFR-19del and MET amplification. Then, the patient was treated with crizotinib+bevacizumab and the best curative effect was stable disease. Four months later, he developed PD and the third biopsy still revealed positive EGFR-19del and MET amplification. The patient received osimertinib+crizotinib+bevacizumab and he achieved PR one month after treatment initiation. He is still under the treatment and the PFS is more than eight months. In vitro data revealed that, under gefitinib treatment, cell viability was higher in HCC827(EGFR-19del) than HCC827-GR (EGFR-19del+METamp). However, the patient harboring dual EGFR-MET alterations in this study obtained a PFS of 13 months to erlotinib, similar with patients with EGFR-19del only (mPFS was 13 months to erlotinib as reported), suggesting the efficacious treatment of EGFR-TKI and bevacizumab than TKI alone. We observed that VEGFR-2 was expressed at relatively high levels in HCC827-GR than other cell line without METamp, and VEGF pathway inhibition by bevacizumab resulted in decreased phospho-c-Met in HCC827-GR cell lines. This result provided *in vitro* evidence that bevacizumab can reduce MET pathway activation. **Conclusion:** This study provided basic knowledge and evidence for patients harboring concomitant EGFR and *de novo* MET amplification who may obtain favorable response to combinatorial treatment of TKI and bevacizumab. Encouraging antitumor activity of TKI+bevacizumab support further development of this combination for patients with advanced NSCLC and other solid tumors.

Keywords: EGFR, de novo MET, bevacizumab

P3.13 TARGETED THERAPY
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P3.13-13 AFATINIB IN LUNG ADENOCARCINOMA HARBORING DE NOVO EGFR EXON 20 INSERTIONS.

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Background: NSCLC, particularly adenocarcinoma, has been successfully treated with upfront targeted therapies according to respective oncogenic mutations in a tailor-made model. EGFR-TK inhibitors (TKi) have exhibited major responses, improving PFS, RR and even mOS (a subset treated with afatinib). This drug has emerged as the best option for those with uncommon mutations, but until now is broadly unknown its action in exon 20 mutations, which accounts for nearly 3% of all and, classically, is associated to worse response to 1st-generation TKi. **Method:** Here, in this retrospective analysis, is reported the past medical history and clinical outcomes of two patients who presented with *de novo* EGFR exon 20 insertions: D770_N771insSVD and Ser768_Asp770dup. The patient were treated in two differents Cancer Centers in Brazil and the mutations were identified with Next Generation Sequencing (NGS) by Illumina HiSeqs of Foundation Medicine (FM) and the other by a local certified laboratory using Ion Torrent-PGM Thermo Fischer v5.0. Analysis were performed in tissue samples extracted from FFPE. The follow-up was obtained from electronic charts. **Result:** Patient 1: never-smoker 66 y/o lady, without comorbidities, presented 12 mo ago with dry cough, thoracic pain and -10% of weight. CT scan revealed extensive ground-glass infiltration area and multiple bilateral pulmonary nodules. Lung biopsy pointed out a mod. differentiated adenocarcinoma of predominantly lepidic pattern (IHC: AE1/2+, CK20-, CK7+, Napsin A+, TTF1+). With this, rtPCR (Cobas Mu test v.2) detected an exon 20 insertion, thus ineligible to upfront EGFR-TKi. However, was chosen to re-analyze it using NGS (FM). After a TAT of only 2 weeks, we retrieved the result which showed a poorly described mutation: EGFR exon 20 insertion D770_N771insSVD. Afatinib 30mg/day was started and, only three days after the initiation, the patient decreased the dry cough and fatigue. CT scans showed stable disease after 45 days of continuous use. Patient 2 had a more extensive past medical history: 1L chemo, followed by nivolumab and docetaxel. Lastly, NGS revealed an uncommon EGFR exon 20 insertion (Ser768_Asp770dup). Rapid clinical improvement was observed (less fatigue and dyspneia), but occured liver progression in the first control, 4w after initiation. **Conclusion:** This study confirms that rare mutations have been increasingly seen due to the employment of improved sensitivity genetic techniques, like NGS. Furthermore, reveals two rare examples of rapid clinical response to afatinib in patients harboring EGFR exon 20 insertions. Finally, despite it could be an option for management of this broadly unknown situation, it suggests caution because of the short-lasting benefit in some.

Keywords: exon 20 insertions, EGFR, Afatinib

P3.13 TARGETED THERAPY
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P3.13-14 IDENTIFICATION OF NOVEL MUTATIONS BY HIGH-THROUGHOUT SEQUENCING IN T790M WILDTYPE/CMET UNAMPLIFIED NSCLC WITH ACQUIRED RESISTANCE TO EGFR TKIS

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Background: Lung cancer remains the leading cause of cancer-related death worldwide. Though most patients with EGFR activating mutations are sensitive to EGFR tyrosine kinase inhibitors (TKIs), tumors will inevitably acquire resistance to first generation EGFR TKIs. *EGFR* T790M mutation and *cMET* amplification are common mechanisms. Further study is needed to explore unknown genomic alterations contributing to drug resistance. **Method:** In the screening period of ASTRIS (D5160C00022) study of single center, tumor and blood samples from 69 stage IIIB-IV NSCLC patients defined as acquired resistance to first generation EGFR TKIs (Gefitinib, Elortinib or Ecotinib) were collected. The cobas® and Droplet digital PCR (ddPCR) were used to detect T790M mutations in tumor samples and plasma ctDNA. *cMET* amplification were evaluated by Fluorescence *in situ* Hybridization (FISH). Exome sequencing were performed in four T790M wildtype/*cMET* unamplified samples. **Result:** The T790M mutation rate of FFPE tissue cobas, plasma cobas and plasma ddPCR testing were 54.5%, 21.3% and 30.4% respectively. Taking all testing methods into account, the T790M positive rate was 52.2%. In 21 samples which tumor re-biopsy was performed, 14 were T790M positive (66.7%). *cMET* amplification were identified in 3 out of 7 T790M negative samples. Exome sequencing in 4 T790M wildtype/*cMET* unamplified samples and paired white blood cells identified a cohort of candidate key mutated genes including *BRAF*, *FGFR1*, *PAK1*, *PCNT*, *PEBP4* and *SOX3*. **Conclusion:** EGFR T790M mutation and cMET amplification are main mechanisms leading to EGFR TKI resistant in lung adenocarcinoma. These key mutated genes identified in the present study would need further functional study validation.

Keywords: exome sequencing, cMET, T790M

P3.13-15 FIRST-LINE AFATINIB DOSE INITIATION AND ADJUSTMENT IN PATIENTS WITH EGFR MUTANT ADVANCED NON-SMALL CELL LUNG CANCER

C. Liam[1], G. Ho[2], C. Chai[3], A. Bt Alip[2], Y. Pang[1]

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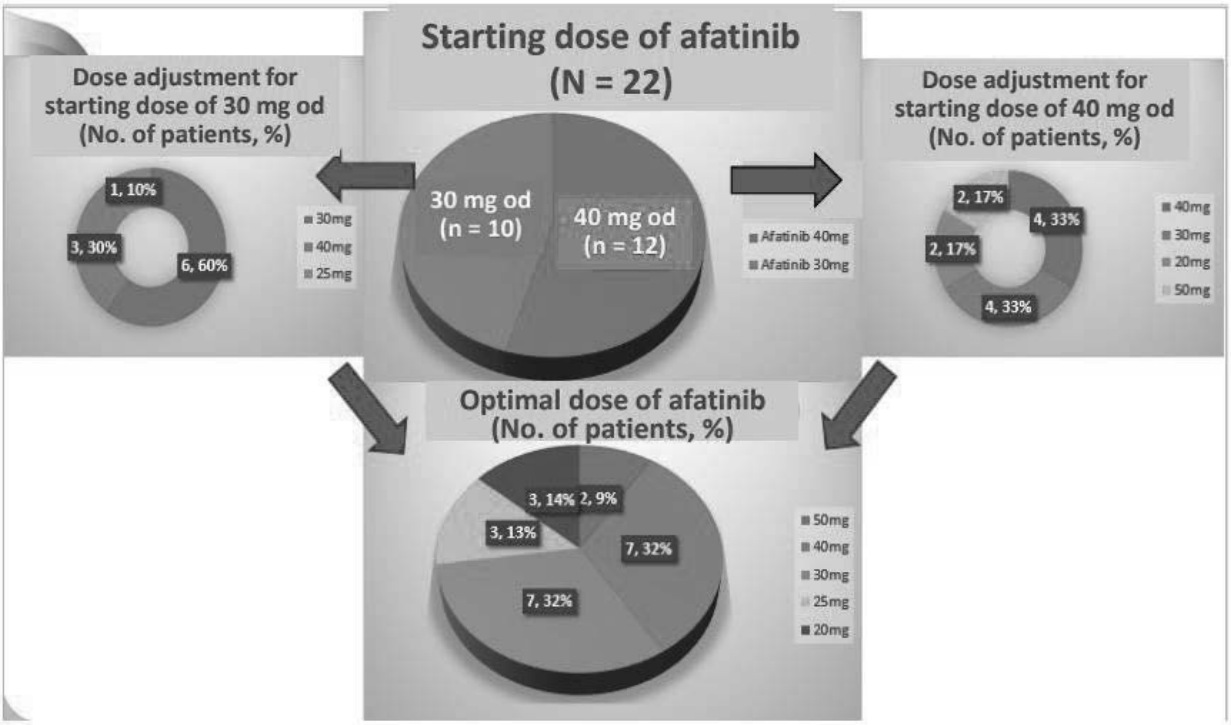
Background: The recommended starting dose of afatinib is 40mg od with 20mg, 30mg and 50mg tablets available for dose adjustment. **Method:** This is a retrospective observational study of starting dose, dose adjustment and optimal dose of first-line afatinib in patients with *EGFR* mutant advanced non-small cell lung cancer in University Malaya Medical Center from 1st December 2014 to 30th April 2018. **Result:** Of 22 patients on first-line afatinib, the starting dose was 40 mg od in 12 patients and 30 mg od in 10 patients (Figure 1). Among the 12 patients started on afatinib 40mg od, 4 (33.3%) did not require dose adjustment, 4 (33.3%) needed dose reduction to 30mg od, 2 (16.7%) needed dose reduction to 20mg od, and 2 (16.7%) had dose escalation to 50mg od. Among 10 patients started on afatinib 30mg od, 6 (60%) did not require dose adjustment, 1 (10%) needed dose reduction to 25mg od and 3 (30%) had dose escalation to 40mg od. Dose reduction was to reduce the cost of treatment in 1 patient and to reduce drug-related side-effects in the rest. Dose escalation was exclusively to improve disease control. The overall response rate and disease control rate was 80% (8/10) and 90% (9/10) in patients who did not require dose adjustment; while the respective rates were 85.7% (6/7) and 100% (7/7) in patients who had dose reduction. The optimal dose of afatinib defined by good disease control and tolerable side-effects was 50mg od in 9.1% (2/22), 40mg od in 31.8% (7/22), 30mg od in 31.8% (7/22), 25mg od in 13.6% (3/22) and 20mg od in 13.6% (3/22) of patients. **Conclusion:** We suggest starting afatinib at 30mg od and adjust the dose accordingly because dose adjustment is not required in most cases on this starting dose and it is the commonest optimal dose.

Keywords: afatinib, dose adjustment, Optimal dose

Figure 1 First-line afatinib starting dose, dose adjustment and optimal dose



P3.13-16 CONCOMITANT EML4-ALK REARRANGEMENT AND EGFR MUTATION IN NON-SMALL CELL LUNG CANCER PATIENTS: DATA FROM EASTERN INDIAN HOSPITAL.

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Background: Clinical guidelines recommend routine testing for genetic mutations in all adenocarcinoma of lung, including ALK EML4 gene rearrangement. The coexistence of EGFR mutations and EML4- ALK rearrangements have been described as extremely rare. Perhaps this is due to its low prevalence and the sensitivity of available diagnostic modalities. All India Institute of Medical Sciences, Bhubaneswar, is an upcoming institute of national importance situated in eastern India. No report on EGFR mutation and EML4- ALK rearrangement has been published so far from this region of India. **Method:** We retrospectively analysed the available data of patients from June 2014 to April 2018. Genetic testing was done from tissue block specimens immediately after establishing the histology. EGFR mutation analysis were done using commercially available Real Time PCR and ALK-positivity was assessed with immunohistochemistry (IHC) by VENTANA ALK (D5F3) CDx Assay. We investigated the course of disease with the efficacy of targeted therapy in EGFR/ ALK co-altered NSCLCs **Result:** Out of 251 NSCLC cases, 198 had adenocarcinoma and only four patients (1.6%) had concomitant EGFR/ALK co-alterations. Of the EGFR mutations, two were positive for Exon 19 and other two were positive for Exon 21. Mean age for Exon 19 and Exon 21 positive patients were 40 and 63 respectively. All four patients were male and had advanced stages of lung cancer. Mutation in all the four patients were detected from initial tissue biopsy and they were negative for ROS1. Three patients had received platinum based doublet regimen followed by EGFR-TKI and one patient received Erlotinib. None had received Crizotinib yet. **Conclusion:** The coexistence of EGFR mutations and EML4- ALK rearrangements is low but higher than other geographical areas. Since the two alterations may coexist from the beginning of diagnosis, future perspective in management could be finding potential efficacy of a double inhibition of both ALK and EGFR mutations.

Keywords: EGFR, ALK, NSCLC

P3.13 TARGETED THERAPY
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P3.13-17 A RETROSPECTIVE STUDY: CENTRAL NERVOUS SYSTEM RESPONSE TO OSIMERTINIB IN PATIENTS WITH ADVANCED NSCLC

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Background: Central nervous system (CNS) metastases are common in patients with non-small-cell lung cancer (NSCLC). More than 30% of patients who progress during or after treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have CNS metastases. Osimertinib, a third-generation EGFR-TKI, has been demonstrated promising intracranial efficacy in patients with advanced NSCLC from several large scale randomized control trials. We aimed to explore clinical impact of osimertinib for patients with CNS metastases, advanced NSCLC in real world setting. **Method:** Patients with advanced NSCLC who received osimertinib after progression of prior EGFR-TKIs and CNS metastases on baseline brain scan were retrospectively collected from Cancer Hospital Chinese Academy of Medical Sciences. Primary outcome was objective response rate (ORR) and secondary objectives were disease control rate (DCR), progression-free survival (PFS), time to tumor response, median best percentage change from baseline in CNS target lesion (TL) size and safety. **Result:** Between Apr 1, 2017, and Dec 30, 2017, 22 patients met selection criteria, 15 with ≥1 measurable CNS lesion (RECIST 1.1) were included in CNS evaluable for response (cEFR) set. The median duration of follow-up was 6.5 months. For overall 22 patients, ORR and DCR were 40.9% and 86.4%, respectively, with median PFS of 8.5 months (95% CI 4.1, 13.0). Of 15 patients in cEFR set, CNS ORR was 53.3% with complete responses reported in 3 patients (20.0%). Median best percentage change from baseline in CNS TL size was -40% (range: -100% ~ +60%) and median time to CNS tumor response was 1.3 months. CNS DCR was 80.0%. Median CNS PFS was not reached. Safety profile was acceptable and no new unexpected findings were found.

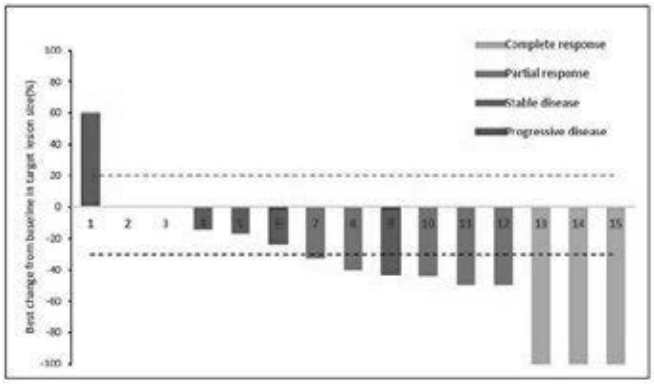

Figure 1 Waterfall plot for best percentage change in CNS target lesion

Conclusion: This real world analysis further confirmed that osimertinib was indeed demonstrated clinically meaningful efficacy against CNS metastases in Chinese patients with advanced NSCLC.

Keywords: central nervous system, non-small cell lung cancer, Osimertinib

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P3.13-18 MECHANISMS OF ACQUIRED RESISTANCE TO AFATINIB CLARIFIED WITH LIQUID BIOPSY

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Background: While the elucidation of the mechanisms of acquired resistance to 1st and 3rd generation EGFR-TKI progresses, there have been few clinical investigations into the mechanisms of acquired resistance to 2nd generation EGFR-TKI, afatinib. **Method:** We analyzed 20 patients with advanced lung adenocarcinoma who acquired resistance to afatinib including EGFR-TKI re-challenge. We examined *EGFR* T790M, C797S, *BRAF* V600E, *MET* amplification by MBP-QP method and droplet digital PCR using ctDNA and re-biopsy samples at pre and post afatinib treatment. **Result:** Just before afatinib treatment, 15 patients were T790M negative, and 5 were positive with ctDNA. Among T790M negative patients, 40.0% (6/15) turned to positive at PD to afatinib. T790M positive patients showed synchronous change of T790M allele frequency with treatment efficacy of afatinib. C797S was not detected just before afatinib treatment, and it appeared in 3 patients with very low level of allele frequency. Two of 3 patients were both C797S and T790M positive, who achieved PR to osimertinib. However, PFS with these patients was a trend shorter than T790M only. *BRAF* V600E was detected in one patient at PD to afatinib. *MET* amplification was never detected in this study. **Conclusion:** T790M was related with acquired resistance to afatinib like 1st generation EGFR-TKI, but the frequency is relatively lower. The influence of C797S for resistance to afatinib would be less than T790M, but existence of C797S possibly causes shorter PFS of osimertinib.

Keywords: afatinib, Acquired resistance, T790M

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P3.13-19 SURGERY FOR CIIIB LUNG ADENOCARCINOMA AFTER RESPONSE TO ERLOTINIB, SURVIVAL AND MANAGEMENT OF POSTOPERATIVE OLIGOPROGRESSIONS

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Background: Down-staging of epidermal growth factor receptor (EGFR) activating mutation-positive (EGFR M+) advanced non-small-cell lung cancer (NSCLC) after first-line EGFR tyrosine kinase inhibitor (TKI) therapy may lead to primary tumor resection. Unfortunately, most patients' disease will progress postoperatively even with the use of adjuvant TKI therapy mainly due to EGFR T790M mutation. Osimertinib, a third-generation inhibitor of EGFR T790M mutation, is with reduced toxicity profile as compared to non-selective EGFR TKI. Our aim is to assess a survival benefit of salvage lung resection in Stage IIIB lung adenocarcinoma after response to TKI and a management of oligoprogressions in the postoperative period. **Method:** A Caucasian age 56 female lung adenocarcinoma patient (ECOG PS-0) was initially staged as cT2aN3M0 on October 10, 2015. Pretreatment biopsy specimens from ipsilateral scalene lymph node harbored EGFR mutation (exon 19 E746-T751insI deletions). After six months of first-line treatment with erlotinib150 mg/daily, which patient tolerated very well, a FDG-PET scan showed a 21/16 mm formation of the left upper lobe with SUV-2 without other abnormalities, down-staging with cT1cN0M0. Radical left upper lobectomy with 20 negative dissected mediastinal lymph nodes was carried out (May 17, 2016). Postoperative pathomorphological and mutational studies of residual tumor revealed adenocarcinoma and EGFR exon 19 mutation. **Result:** Adjuvant erlotinib therapy was started for 3 months. Four months after its discontinuation by patient decision a 3 cm left supraclavicular mass (SUV-2.0 on FDG-PET) was diagnosed and totally resected. Adenocarcinoma involvements of 3 lymph nodes, as well as EGFR exon 19 mutation, were confirmed. The patient continued on erlotinib, but after 6 months on FDG-PET scan 2 left cervical lymph nodes (SUV 4.6 and 6.1 on FDG-PET) were diagnosed. Systematic left cervical dissection was performed with resection of four metastatic lymph nodes. Again adenocarcinoma histology was confirmed, but EGFR T790M mutation was identified as well. Three months later, even without signs of residual tumor mass on computerized tomography scan, Osimertinib therapy in dose 80 mg orally once daily was administered. The last follow-up FDG-PET scan revealed no signs of progression (April 30, 2018). The patient is with ECOG PS-0 and perfect quality of life without drug-related adverse events. **Conclusion:** Radical surgery of oligoprogression following salvage surgery for Stage IIIB (EGFR M+) lung adenocarcinoma after response to TKI, while continuing to use TKIs (specifically osimertinib in EGFR T790M mutation), can result in prolonged overall survival. The pending question is whether the EGFR-TKI therapy can be discontinued in these patients.

Keywords: adenocarcinoma, target therapy

P3.13-20 FREQUENCY OF EGFR MUTATIONS IN PATIENTS WITH ADENOCARCINOMA LUNG CANCER. COMPARATIVE STUDY BETWEEN PUBLIC AND PRIVATE MEXICAN HEALTH SERVICES

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Background: The frequency of the EGFR mutation in pulmonary adenocarcinoma varies between 15-40% depending of population reported. Study descriptive, observational, retrospective and multicentric was conducted to determine the frequency of this mutation in public and private centers service in Mexico **Method:** They were selected patients with diagnosed of pulmonary adenocarcinoma between January 2011 and January 2016 from three oncology centers, two private centers (ABC Medical Center and the Spanish Hospital) and one public (National Institute of Respiratory Diseases). The total sample was 328 patients, subdivided by the presence or not of EGFR mutations. The primary objective was the mutation in EGFR and the secondary the type of mutation, frequency by sex, type of treatment and clinical stage at the time of diagnosis. **Result:** The sample was formed by 136 (41%) men and 195 (59%) women, the average age of diagnosis was 62.4 years, the clinical stage in 75.7% was IV at the time of diagnosis. The total frequency of the EGFR mutation was 42.7% (140 patients), the most prevalent being Del19 (66.4%) and L858R (30%). These mutations were present in 113 patients of INER (34.5%) and by both private centers was 27 patients (8.2%), this difference was significant when comparing hospital types (public vs. private, p 0.033). Men showed a protective factor for the EGFR mutation compared to women with HR 0.88 (p 0.028), there were differences between the possibility of presenting the EGFR mutation in patients with lung cancer, with less possibility of presenting it if medical attention was done in a private medium compared to the public medium with a HR 0.81 (p .001). **Conclusion:** There is a significant difference in the frequency of mutations in EGFR between the public and private hospital, probably associated with ethnic, genetic, environmental and social differences between the two populations.

P3.13-21 APATINIB PLUS ICOTINIB AS FIRST-LINE THERAPY FOR EGFR CO-MUTATIONS NSCLC IN CHINESE PATIENTS: AN EXPLORATORY STUDY

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Background: To date, the phenomenon of *EGFR* co-mutated with other genes in untreated NSCLC patients was common, which might be the reason of *EGFR*-TKI primary resistance. In our previous research, samples from 81 NSCLC Chinese patients were tested with next-generation sequencing (NGS) based targeted panel assay, 49% (40/81) patients had *EGFR* co-mutations,the top-ranked co-mutant genes were TP53 (35%, 28/81) and cell cycle pathway related genes (19%, 15/81). Clinical data indicated that antiangiogenic drug combination with *EGFR*-TKI might reverse *EGFR*-TKI acquired resistance. Apatinib is a new antiangiogenic drug targeting vascular endothelial growth factor receptor 2 (*VEGFR2*), and Icotinib is a potent and specific *EGFR*-TKI, which were both made in China. In this study, we aim to assess the efficacy and safety of Apatinib plus Icotinib as first-line therapy for **EGFR co-mutations** NSCLC in Chinese patients, and compare the differences of curative effect among **EGFR co-mutant subgroups. Method:** This single-arm, open-label exploratory study will recruit 50 Chinese patients with stage IIIB/IV NSCLC who have never received any anti-tumor treatment previously. Tumor tissue and matched blood of each patient will be collected for NGS-based 450 cancer related genes panel assay, designed to comprehensively assess *EGFR* mutation and co-mutations. Meanwhile, ctDNA extracted from blood samples will be collected for NGS-based 329 cancer related gene before treatment as baseline, and every 2 months after enrollment until disease progression, to evaluate the evolution of genomic variation and effects of drug efficacy. The analysis of genomic alterations including single base substitution, short and long insertions/deletions, copy number variations, gene rearrangement in selected genes and also tumor mutation burden (TMB) calculated as total somatic substitutions and indels per megabase. Patients with *EGFR*-sensitizing mutations accompanied with other genomic alterations will receive Apatinib 250mg, qd, po and Icotinib 150mg, tid, po until disease progression, or unacceptable toxicity. The primary endpoint of this study is progression free survival (PFS), and the secondary endpoints include objective response rate (ORR), disease control rate (DCR), overall survival (OS), quality of life (QOL) and drug-safety. **Result:** Not applicable **Conclusion:** Not applicable

Keywords: Co-Mutations, ctDNA detection, Targeted therapy

P3.13-22 REAL WORLD STUDY OF AFATINIB IN FIRST-LINE OR RE-CHALLENGE SETTING FOR PATIENTS WITH EGFR MUTANT NON-SMALL CELL LUNG CANCER.

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Background: Afatinib is the second generation epidermal growth factor receptor (EGFR) - tyrosine kinase inhibitor (TKI) for mutant non-small cell lung cancer (NSCLC), and approved in Japan in 2014. This study evaluated clinical outcomes of afatinib in real world practice. **Method:** Patients who received afatinib for advanced EGFR-mutant NSCLC in 5 institutions in Aomori, Japan from October 2014 to January 2017 were included into the analyses. **Result:** In total, 128 patients were analyzed. Seventy-six patients received afatinib as first-line setting and 52 as re-challenge setting (i.e., prior first generation TKIs used and third generation TKI were not adapted). In first-line setting, patient characteristics were as follows: a median age 68 yrs (42- 88 yrs), 67% female, and 88.1% PS 0/1. The median progression-free survival (PFS) was 17.8 months (95% CI: 13.7- 21.5 months). The overall survival (OS) was 39.5 months (95% CI: 34.4- not reached). There was no difference in median PFS and OS according to age (< 74, 75 ≦). Though 58 patients (76.3%) had to reduce the dose due to adverse events, it did not affect its efficacy in terms of OS (39.5 months in the reduction group vs. not yet reached in the no reduction group) (P= 0.37). Moreover, the reduction group showed even longer PFS than the no reduction group. (18.0 months in the no reduction group vs. 7.9 months in the reduction group) (P= 0.016). The response rate (RR) was 64% (CR/PR/SD/PD/NE: 1/48/16/1/10). Twenty-eight patients among 48 who had PD underwent re-biopsy, and 16 patients (57.1%) were T790M positive. In re-challenge setting, patient characteristics were as follows: a median age 65 yrs (37- 90 yrs), 78% female, and 90.3% PS 0/1. The median PFS was 8.0 months (95% CI: 4.9- 9.5 months). The RR was 24% (CR/PR/SD/PD/NE: 1/12/29/6/4). Most common adverse events leading to dose modification and treatment discontinuation were diarrhea, paronychia, and oral mucositis in both settings. Interstitial lung disease occurred in 5.4% (7/128). **Conclusion:** In the real practice in Japan, afatinib in first-line and re-challenge settings showed comparable or better efficacy compared with previous clinical trials.

Keywords: afatinib, first-line, re-challenge

P3.13-23 EGFR-TKIS COMBINED HYDROXYCAMPTOTHECIN IMPROVED OUTCOMES IN EGFR-MUTANT NSCLC PATIENTS WHO HARBORING PERICARDIAL EFFUSION.

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Background: Pericardial perfusion of hydroxycamptothecin (PCPH) is the effective treatment for malignant pericardial effusion(MPCE). Epidermal growth factor receptor tyrosine kinase inhibitors(EGFR-TKIs) have shown greater efficacy in clinical trials than chemotherapy in patients with EGFR-mutant non-small cell lung cancer (NSCLC), but little

information is available on EGFR-mutant NSCLC patients who harboring MPCE. We therefore investigate the advantage of EGFR-TKIs with PCPH for these patients. **Method:** We enrolled patients with MPCE, stage IV, EGFR-mutant (exon 19 deletion or exon 21 Leu858Arg) NSCLC. These patients were divided into 2 groups by different treatments: EGFR-TKIs in combination with PCPH and chemotherapy combined with PCPH. Retrospectively analyzed the survival of different treatment programs and their prognostic factors. **Result:** Between January 1, 2010, and December 31, 2016, 644 patients were screened. MPCE occurred more frequently in patients with EGFR-mutant than those with EGFR wild-type (10.62% vs. 5.20%; p = 0.046). 29 patients were enrolled, 15 to EGFR-TKIs/HCPT group and 14 to chemotherapy/HCPT group. The progression free survival (PFS) was significantly longer with EGFR-TKIs/HCPT group (360 days) than chemotherapy/HCPT group (90 days; P=0.003). The effusion control rate for pericardial lesions showed statistical difference between two groups (93.33% vs. 71.43%, P = 0.038). Toxicity of EGFR-TKIs/HCPT groups were characterized by skin rash (40.0% vs. 7.1%; P=0.039), whereas the proportions of patients with leucopenia (42.9% vs. 6.7%; P=0.023) and thrombocytopenia (42.9% vs. 6.7%; P=0.023) were higher in chemotherapy/HCPT group. **Conclusion:** EGFR-TKIs combined with PCPH is preferable for advanced NSCLC patients with EGFR-mutant and MPCE.

Keywords: malignant pericardial effusion, hydroxycamptothecin, EGFR-TKIs

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P3.13-24 EFFICACY OF EGFR-TKIS COMPARED WITH CHEMOTHERAPY AS FIRST-LINE THERAPY IN PATIENTS WITH EGFR RARE MUTATION ADVANCED LUNG ADENOCARCINOMA

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Background: Clinical activity of epithelial growth factor receptor tyrosine kinase inhibitors or platinum-based chemotherapy as firstline therapy in patients with EGFR rare mutation advanced lung adenocarcinoma remains unknown, This retrospective study assesses the activity and long-term survival of the two treatment regimens. **Method:** 3856 patients diagnosed with lung adenocarcinoma from Henan Cancer Hospital received EGFR gene detection during January 2, 2012 to November 1, 2017. 1643 patients with EGFR mutation and phase IIIB/IV were identifed. Among them, 130 cases (7.9%) with EGFR rare mutations, excluded 64 patients(4 cases of patients coexist with uncommon mutations and common mutations, 17 cases of insertions in exon 20, 42 cases of T790m and T790m complex mutations, and 1 loss of follow-up), 66 cases of EGFR uncommon mutations(G719X, L861Q, S768I and compound mutations) enrolled in the evaluation of efficacy, of whom 34 patients received EGFR-TKIs alone and 32 patients received platinum-based chemotherapy as frstline therapy. All EGFR-TKIs were first-generation drugs, details were gefitinib (250 mg/day), erlotinib (150 mg/day) and eclectinib (125 mg tid/day), all patients received at least 4 weeks of EGFR-TKIs. All chemotherapy drugs were third-generation in combination with platinum, details were pemetrexed (500 mg/m2), vinorelbine (25 mg/m2 d1, 8), or gemcitabine (1000 mg/m2 d 1, 8) platinum-based chemotherapy, every 3 weeks as a treatment cycle. **Result:** Regardless of whether EGFR-TKIs or chemotherapy, the objective response rate (ORR: 28.6% vs 36% P>0.05) and disease control rate (DCR: 82.1% vs 84% P>0.05) were similar. EGFR-TKIs showed superior progression-free survival than chemotherapy group (7.1 vs 4.9 mts; HR=0.717, P=0.166), but there was not statistically difference. However, compared with chemotherapy, we found that overall survival (OS: 14.6 vs 20.3 mts; HR=1.879, P=0.019) was significantly lower in patients with EGFR-TKIs, which was statistically significant. In multivariate analysis, first-line use of targeted therapy (HR = 0.447 P = 0.006) and smoking history (HR = 3.824 P = 0.003) were found to be a signifcant independent prognostic factor for OS in lung adenocarcinoma patients with EGFR uncommon mutation. **Conclusion:** Compared with chemotherapy, first-line use of the first generation of EGFR-TKIs can improve the short-term efficacy of patients with EGFR rare mutation advanced lung adenocarcinoma, but longer survival in patients with first-line platinum-based chemotherapy.

Keywords: lung adenocarcinoma, rare mutation, Epithelial growth factor receptor tyrosine kinase inhibitors

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P3.13-25 DEVELOPMENT OF A COMPREHENSIVE GENOMIC PROFILING SYSTEM TO DETECT ACTIONABLE GENETIC ALTERATIONS AND TUMOR MUTATION BURDEN

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Background: Current non-small-cell lung cancer (NSCLC) treatment includes targeted therapies for *EGFR*, *ROS1*, *BRAF* and *ALK*. Patients treated with immunotherapies have shown both high and durable response rates. Tumor mutational burden (TMB) has emerged as a promising biomarker, with multiple clinical studies correlating high TMB with better response to immunotherapy. However, in order for widespread adoption to be successful, the community needs more clarity and guidance around TMB analytical performance before implementation into routine diagnostic practice. First, analytical accuracy across a broad dynamic range of mutation burden is critical. Second, comparison to a common reference and standardization of reporting TMB is also required for clinicians to translate results across different technologies and methods. Here, we describe the development and analytical validation of a decentralized comprehensive gene profiling kit to determine TMB and other clinically relevant somatic variants from a 507-gene next-generation sequencing panel. **Method:** Identification of somatic mutations with sufficient accuracy is critical for inferring mutational load from a targeted gene panel. We developed a machine learning algorithm to optimize sensitivity and specificity for somatic mutation detection across the entire coding sequence of a 507-gene panel. We compared the overall accuracy of this approach using simulated and experimentally validated whole-exome and targeted gene analyses. We then assessed the accuracy of the 507 gene panel for prediction of TMB *in silico* across a wide dynamic range using several cohorts of publicly available NSCLC whole exome sequencing datasets. Then, cases from an independent NSCLC cohort were experimentally evaluated and compared to whole exome sequencing results to demonstrate the analytical accuracy across a spectrum of tumor mutational loads. Finally, sensitivity and specificity of clinically relevant genetic alterations in NSCLC were determined using both contrived and clinical samples compared to orthogonal methods. **Result:** Our results indicate that the 507-gene system, combined with proprietary software leveraging machine learning algorithms, accurately identifies somatic mutations, and achieves high analytical accuracy for determining TMB across a broad dynamic range. In addition, this system has the capability to detect somatic genetic variants that are important for therapeutic stratification in NSCLC. **Conclusion:** This 507-gene decentralized system provides accurate results for the determination of TMB across a broad range of mutational burden, and detects clinically relevant genetic alterations important in NSCLC.

Keywords: Tumor mutation burden, next-generation sequencing, Decentralized Solution

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P3.13-26 OUTCOMES OF PATIENTS WITH METASTATIC LUNG CANCER PRESENTED IN A MULTIDISCIPLINARY MOLECULAR TUMOR BOARD

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Background: With the adoption of broad genomic profiling, interpretation of genomic data in NSCLC has become increasingly complex. Approved targeted therapies against oncogenic driver mutations have improved clinical outcomes for patients whose lung cancers harbor these genomic alterations. However, for other patients, the benefit of broad genomic sequencing is not fully proven. Multidisciplinary molecular tumor boards (MTB) may improve clinical outcomes by appropriately matching targeted treatments. **Method:** We retrospectively reviewed clinical, pathologic, and molecular data of metastatic lung cancer patients presented at the UC Davis MTB from January 2016 through May 2017. Genomic alterations were identified by hybrid capture-based comprehensive genomic profiling

to a median coverage depth of >500X for 315 cancer-related genes (FoundationOne®). **Result:** Out of 48 patients presented, 19 (39.6%) had lung cancer. Fourteen patients (73.7%) had adenocarcinoma, 1 SCLC, 1 squamous, 2 neuroendocrine, and 1 mixed histology. Seventeen patients were available for follow-up. Median number of prior treatments was 2 (range: 0-7) and median number of prior targeted therapies was 2 (range: 0-5). On average, each tumor sample had 5.3 genomic alterations (range 2 – 14). Every sample had ³1 actionable mutation, in that matched targeted therapy was available in the form of an FDA-approved drug for NSCLC, FDA-approved drug in another tumor type, or genomically informed clinical trial. Tumors harbored an *EGFR* mutation (N=7), *HER2* amplification (N=2), BRAF V600E (N=2), or mutation in *BRCA1* (N=1), *KIT* (N=1), or *PTCH1* (N=1). All 7 patients with an *EGFR* mutation had previously received EGFR-targeted therapy, six with progressive disease (PD) on prior EGFR-TKI. Thirteen patients (76.5%) received targeted therapy, including FDA-approved therapy for NSCLC (N=4), FDA-approved therapy for another tumor type (N=6), or a genomically informed clinical trial (N=3). The other four patients were either on an immunotherapy clinical trial (N=2) or could not tolerate treatment (N=2). Out of the 13 patients who received targeted therapy, 4 patients had a partial response (31%) (3 EGFR, 1 BRAF V600E), all other patients had stable disease or PD. Median PFS on MTB-selected treatment was 4.8 months (range: 25% 2.2 – 75% 10.7 months). **Conclusion:** MTB at an academic medical center matched a high percentage of patients to either a targeted treatment or clinical trials with targeted therapies or immunotherapy. A subset of patients had clinical benefit to targeted therapies in this pretreated population. Multidisciplinary expertise at MTB can guide treatment for NSCLC, but new targeted treatments are needed to improve clinical outcomes.

Keywords: Molecular Tumor Board

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P3.13-27 CLINICAL OUTCOMES OF PATIENTS WITH LUNG ADENOCARCINOMA HARBORING CONCOMITANT DRIVER MUTATIONS IN A BRAZILIAN CANCER CENTER

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Background: NSCLC, particularly adenocarcinoma, has been successfully treated with upfront targeted therapies according to respective oncogenic mutations in a tailor-made model. It has led to improvement in clinical outcomes (CO) and QoL, however, some evidences sugest that the occurrence of concomitant driver mutations (OCDM) is responsible for poorer results than expected. Questions, thus, have emerged regarding the best strategy to this population. **Method:** In this retrospective study, we reviewed lung cancer patients treated in our institution in the last four years in order to identify the OCDM. The vast majority of patients performed Next Generation Sequencing (NGS) using Illumina HiSeqs of Foundation Medicine (FM). The f/u was obtained from our electronic charts. **Result:** From apr/14 to apr/18, 5 patients were elegible for this analysis, 2M / 3F, mean 59y/o. **Patient 1**: treated with crizotinib because of MET amplification harboring concomitantly ATM deletion exons 11-50. Died after pneumonia before first radiologic evaluation. **Patient 2**: osimertinib for EGFR T790M harboring BRCA-2 c1528G>T. Derived partial response (PR) with PD after 9 mo. **Patient 3**: immunotherapy because of TMB 18 + PD-L1 e PD-L2 amplification, harboring STK11 Q159fs*2 as well. Curiously, the previous report of PD-L1 (22C3) by IHC had been negative. Still in PR, lasting 14 mo. Germline analysis (to Peutz-Jeghers) will soon be performed. By FM, Everolimus or Temsirolimus were sugested. **Patient 4**: crizotinib and alectinib for ALK-EML4 fusion harboring concomitantly BRCA2 S1074R. Had PR lasting 9 mo and only 6 mo respectively. Curiously, previous FISH had not identified the translocation. **Patient 5**: treated with crizotinib because of ALK-EMLA4 translocation harboring concomitantly Kras mutation. This is a rare condition and, until recently, *de novo* rearrangements of ALK was thought to be mutually exclusive to Kras. Not surprisingly, and in line with some reports of literature, the patient experienced rapid progression, saw already in the first control in 8 weeks. **Conclusion:** This study confirms that the OCDM has been increasingly seen due to the employment of improved sensitivity genetic techniques, like NGS. Additionally, provides the clinical outcomes of patients with lung adenocarcinoma harboring more than one of those mutations, which is broadly unknown yet. Finally, previous reports account that, particularly, patients with concomitant ALK fusion and Kras mutation carry poorer results with anti-ALK than expected. This study reinforces this observation and argues that the best management of these patents is still to be clarified.

Keywords: KRAS, concomitant driver mutations, ALK

P3.13 TARGETED THERAPY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.13-28 HETEROGENEITY, PREVALENCE AND PROGNOSTIC SIGNIFICANCE OF PDL1 EXPRESSION IN EARLY RESECTED NSCLC

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Background: The interaction between the programmed death protein-1 receptor (PD1) and its membrane-bound ligand (PDL1) is one mechanism by which tumor cells evade the immune system. Cancer immunotherapies target this interaction by blocking the function of either protein, allowing for T-cell activation and destruction of the tumor. Because PDL1 expression in tumor is used to identify patients who might benefit from immune-modulating treatment, its detection plays a key role in clinical recommendations. Our objectives are to assess the prevalence of PDL1 expression in early stage non-small cell lung cancer (NSCLC) patients, determine its association with clinical outcomes using the Glans-Look Research (GLR) database (Calgary, AB), and validate these findings using a cohort from the Manitoba Tumor Bank (MBTB). **Method:** A tissue microarray (TMA) was built using pre-treatment resected and biopsy tissue samples from 459 GLR database patients with early stage NSCLC, diagnosed between 2003 and 2010. Cell lines expressing varying levels of PDL1 were generated, embedded into HistoGel™ and co-mounted onto the GLR and MBTB arrays. Fluorescence immunohistochemistry was performed using anti-PDL1 E1L3N (Cell Signaling Technology), and PDL1 expression was evaluated as percent-positive and intensity scores in the cytoplasmic compartment of tumor and stromal cells using HALO™ automated image analysis software. Cell line PDL1 intensity scores served as on-slide reference standards to normalize PDL1 expression in patient specimens using R Programming software. PDL1-percent-positive tumor scores were generated to assess the cut-points of ≥50%("PDL1-strong"), ≥1%-to-49%("PDL1-weak"), and <1%("PDL1-negative"), indicated by the FDA-approved companion diagnostic anti-PDL1 22C3 (Dako) for pembrolizumab. Clinicopathological outcomes were analyzed, and overall survival was assessed using the Kaplan-Meier method and compared using the log-rank test. **Result:** Preliminary analyses indicate PDL1-weak/negative GLR patients with adenocarcinoma experienced higher median OS (3.50yrs) compared to PDL1-strong patients (1.91yrs) (p=0.0043). This trend was not significant over all histologies, or when using mean scores. The opposite trend was found with the MBTB cohort (2.52yrs vs. 1.76yrs OS, PDL1-strong vs. PDL1-weak/negative maximum scores, p=0.0410). **Conclusion:** Variations across datasets illustrate the difficulty in harmonizing PDL1 testing. Heterogeneity of protein expression, TMA sampling error, and differences between study cohorts can translate into variable correlations between PDL1-positivity and survival estimates. Increased survivorship in GLR adenocarcinoma patients with PDL1-weak/negative staining could challenge the notion of using PDL1 as a prognostic biomarker. Comparisons between the E1L3N and 22C3 anti-PDL1 assays will be performed, E1L3N percent-positive cut-points will be refined according to the lowest intensity-based statistical p-value, and further outcome findings will be presented and discussed.

P3.13-29 PATIENT-DERIVED XENOGRAFT MODELS(PDX) OF LUNG SQUAMOUS CELL CARCINOMA(SCC) FOR PRECLINICAL STUDIES

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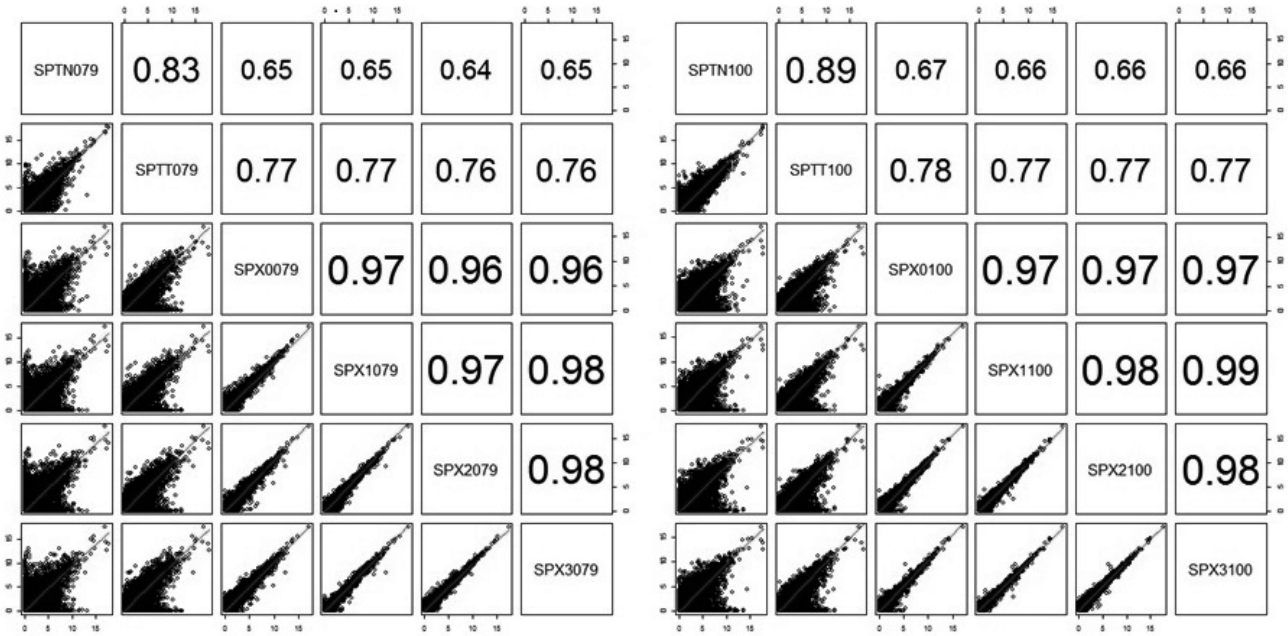
Background: Non-small cell lung cancer is the most prevalent type of lung cancer, and one of its subtype, squamous cell carcinoma has limited targeted therapeutic options in comparison with adenocarcinoma. For this reason, we established the patient-derived xenograft models of primary lung cancer and then focused on the SCC PDX models to be used for the discovery of target mutations through the molecular profiling of lung tumors and their association of therapeutic responses **Method:** PDX models were established using the tissues of patients who underwent surgery as primary lung cancer at Samsung Medical Center during the period between October, 2014 and September, 2017. Briefly, tumor tissues from patients were subcutaneously engrafted and passaged two more times in NOD-scid-IL2Rγnull mouse. Then we are analyzing histological characteristics and molecular profiles of established SCC PDX by whole exome sequencing and whole transcriptome sequencing. **Result:**

Mutation profiles of squamous cell carcinoma Patient Tumors and their PDX models

	Patient tumor			PDX		
ID	Gene	Mutation	Frequency	Gene	Mutation	Frequency
PDL-040				HRAS JAK1 PTEN TP53 GNAQ U2AF1	G13V N136fs -78fs Y236C T96S/M59L G167C	1.000 0.397 0.488 1.000 0.143/0.080 0.080
PDL-041				CTNNA2 FRG1	M672I C159Y	0.278 0.042
PDL-089	EP300 AMER1 RB1	EP300 AMER1 RB1	0.473 0.576 0.500	AMER1 RB1 EP300	R142K I425fs G438V	0.851 0.472 0.479
PDX-073						
PDX-079	DNMT3A BRAF TP53 FRG1	F571L V600E R249S Q137K	0.606 0.524 0.571 0.521	BRAF TP53 FRG1 DNMT3A	V600E R249S Q137K F571L	0.377 1.000 0.026 0.444
PDX-100	DDR2 BRAF GNAS TP53	E757D G469A Q286P 156_157RV>L	0.484 0.388 0.583 0.671	BRAF DDR2 TP53 GNAS	G469A E757D 156_157RV>L Q286P	0.941 0.212 0.500 0.180
PDX-114						
PDX-186				KEAP1 PIK3R1	L281M M200fs	1.000 0.464
PDX-190						
PDX-205						
PDX-207	TP53 ATRX	C176F S1944R	0.617 0.537	TP53	C176F	1.000
PDX-231	MET STK11 KEAP1 RPSAP58 GNAS	L829V D115N G333C Q113H V57M	0.494 0.410 0.551 0.426 0.488	KEAP1 MET STK11 GNAS RPSAP58 SMO	G333C L829V D115N V57M Q113H R138L	1.000 0.485 1.000 0.318 1.000 0.400
PDX-252				HLA-A HLA-A HLA-A HLA-A HLA-A HLA-A TSC1 FRG1 ATRX EEF1B2	R38W G80R A114D S129P T187P T187R S487C Q137K Q929E R122H	0.500 0.267 0.617 0.611 0.091 0.231 0.293 0.026 0.870 0.227
PDX-271				TSC1 KDR	M322T V297I	0.357 0.300
PDX-302	JAK1 TP53	E667Q N268I	0.514 0.488			
PDX-318				ARID1A NF1 TP53 FRG1 SMO SOX17 TRRAP	H203Q R2556T LRK-KGEPHH289fs A151G F332fs R147L A598V	0.125 0.168 0.472 0.048 0.456 0.200 0.349
PDX-364				TSC2	T927I	0.575
PDX-366	KDR TP53 NOTCH1 FRG1	A1103D V173L L107F Q137K	0.494 0.609 0.600 0.496	NOTCH1 TP53 FRG1 CHD4 KDR	L107F V173L Q137K R1825L A1103D	0.160 1.000 0.035 0.061 0.270
PDX-372	CDKN2A TP53	D33H A161fs	0.377 0.534	CDKN2A TP53	D33H A161fs	1.000 0.461
PDX-402	PIK3CA FRG1 FRG1 FRG1	V344G L150S A151T C159Y	0.503 0.443 0.445 0.455	PIK3CA GNAQ FRG1	V344G T96S C159Y	0.173 0.098 0.050
PDX-409	DNMT3A KEAP1 KMT2D	F511L G158C P1912fs	0.653 0.467 0.669	KEAP1 KMT2D GNAQ FRG1 DN-MT3A	G158C P1912fs T96S C159Y F511L	0.917 0.446 0.063 0.043 0.460
PDX-410	TP53 KEAP1 KEAP1	C124G G480V G186R	0.564 0.585 0.737	KEAP1 KEAP1 TP53	G480V G186R C124G	0.298 0.656 1.000
PDX-415	DNMT3A NFE2L2 NFE2L2 CREBBP TP53 APC CDKN2A	I247F R18Q D11N S2356F R337L ENDNG1530fs R52fs	0.494 0.584 0.568 0.600 0.469 0.559 0.531	AMER1 AMER1 APC CDKN2A CREBBP NFE2L2 NFE2L2 TP53 DNMT3A FLT3	H619R H619N -1530fs R52fs S2356F R18Q D11N R337L I247F M799I	0.703 0.698 0.478 0.462 1.000 0.364 0.250 1.000 0.628 0.076
PDX-420				HLA-A NOTCH1 TP53	K292E G427C H179R	0.067 0.575 1.000

PDX-434	NOTCH2 RRAS2 KEAP1 KMT2D TP53	V968L Q72L Y54F D4400fs P301fs	0.366 0.422 0.512 0.509 0.482	IGF1R KEAP1 NOTCH2 TP53 RRAS2	P266S Y54F V968L P301fs Q72L	0.204 1.000 1.000 0.477 0.792
PDX-454	TNFAIP3	R52T	0.431	NF1 TNFAIP3 TP53	LTTILKN58fs R52T P152fs	0.476 0.458 0.455
PDX-473				CREBBP FLT3	Q913R I920V	0.410 1.000
PDX-480	TSC2 NF1 NF1 NF1 TP53 RRAS2 EEF1B2	V1695E N793S K798Q F1287L R158L Q143R R122S	0.831 0.169 0.160 0.210 0.828 0.034 0.166	NF1 TP53 TSC2	W784L R158L V1695E	0.838 0.875 0.516



Conclusion: In PDX models of 49 patients, successful lung SCC PDX engraftment and identical histomorphology was achieved. And the 30 sets of exome sequencing analyses showed that the somatic mutations were relatively preserved. Among them, some interesting targetable mutations including BRAF(V600E) were identified. We identified consistency of transcriptome profiles of PDX models during the passages.

Keywords: Patient derived Xenograft, Squamous cell lung cancer, molecular profiling

P3.13 TARGETED THERAPY
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P3.13-30 DRIVER MUTATION IN HEAVY SMOKER PATIENT WITH SQUAMOUS CELL CARCINOMA METASTATIC LUNG CANCER: CASE REPORT

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Background: Nowadays, guidelines recommend to assess the presence of a driver mutation in tumors that contains an element of adenocarcinoma regardless of the clinical characteristics of the patient or squamous cell carcinoma in a patient that never smoked. **Method:** We reported a clinical case of a pacient that had a squamous cell carcinoma with a driver mutation in EGFR, despite the fact that he was a heavy smoker. the case occured in our service in the northeast of Brazil. **Result:** Woman, 63 years old, current smoking, presented in a public health service in Brazil with history of cought and dyspneia 3 months earlier. In the investigation, CTS showed mass hilar in the right lung and enlarged lymphonodes in the mediastinum IPSI and contralateral, but there was no evidence of secondary lesios in other organs. She was submitted to a core biopsy CT guided that confirmed squamous cell carcinoma. The planned treatment was radiotherapy and concomitant chemotherapy. As in our service the time to start the radiotheraphy is about 3 months, we started a platin based chemotherapy and made sequencial radiotherapy. After that, she was submitted to new CTS that showed partial response in the lung and lymphnodes, but there was evidence of bone metastatis in the sacrum and left iliac. In our service, there was a trial in which all patients diagnosed with lung cancer had it's tissue avaliated for driver mutation, and we received the results with a driver mutation in exon 19 of EGFR. So, we started a treatment with Erlotinib with a great response and, now, after 9 months, it's still responding. **Conclusion:** This case represent a rare case of a squamous cell carcinoma with a driver mutation in a current smoking, and maybe justified by the fact that the tumor had an adenosquamous component. If the patient wasn't tested for driver mutations, she would never received an target therapy. Thus, maybe we should assessed all non small lung cancers for the driver mutations.

Keywords: driver mutation in scc lung cancer, target therapy

P3.13 TARGETED THERAPY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.13-31 CREATING A PRECISION MEDICINE PIPELINE FOR LUNG CANCERS.

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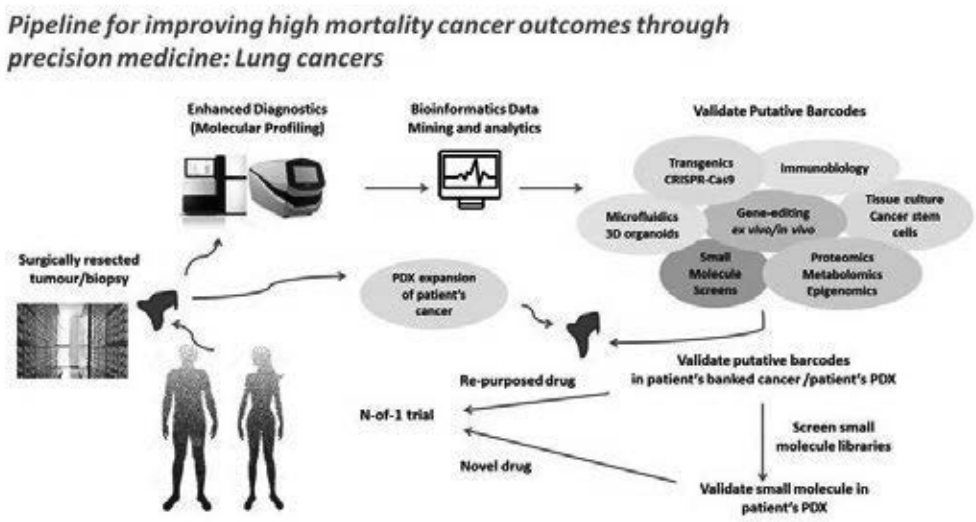
Background: The vision of High Mortality Cancer Precision Medicine Pipeline (HMCPMP) *is to improve high mortality cancer outcomes.* Our mission of HMCPMP *is to establish precision medicine pipelines for high mortality cancers that start with the patient and ends with precise treatments for the patient based on their lung cancer's unique molecular profile.* HMCPMP leverages expertise areas of i) single-cell gene-discovery that allows for the identification of new barcodes and therefore new targets, ii) animal models that recapitulate human cancers, and patient-derived xenographs that allow for pre-clinical trials in mouse models to test novel drugs and drug development, iii) immunology and

cancer stem cell biology to explore the role the immune system and stem cell niche impact tumourigenesis, iv) single-cell fluidics/3D organ systems that allow for understanding the heterogeneity of cancers and vi) data mining that allows for better treatment choices and the discovery of new treatment options based on their lung cancer's barcodes. **Method:** We have created a patient-centered precision medicine pipeline that moves resected lung cancers from the surgical suite to banking, through to single cell molecular diagnostics to validation (Figure 1). **Result:** Single-cell genomic profiling of resected lung cancers were prepared using a microfluidics platform Fluidigm C1 followed by transcriptome sequencing per single cell. We identified differentially expressed genes (DEGs) for stage, sex, and smoking status, followed by validation by quantitative PCR. We are currently pursuing new barcodes that differentially distinguish between the stratified subgroups of patients.

Conclusion: The significance of HMCPMP research is improved health, survivorship, and quality of life for people living with lung cancer. Although the economics of lung cancer are important and likely drivers of federal, provincial and regional research initiative, HMCPMP considers the human when faced with the diagnosis of lung cancer. *PAM is funded by the Dalhousie Medical Research Foundation and the Canadian Cancer Society*

Keywords: precision medicine, early stage lung cancer, single cell genomics



P3.13 TARGETED THERAPY
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P3.13-32 DRUG SENSITIVITY OF LUNG ADENOCARCINOMA TOWARDS INDUCERS OF EPIGENETIC MODIFICATIONS

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Background: Over the last decade, epigenetic regulation of gene expression emerged as a central mechanism in tumorigenesis and metastasis. In contrast to DNA mutations, epigenetic modifications are reversible and therefore suitable targets for pharmacological therapy. To understand which patients will benefit the most from which drug regime remains a challenge in everyday clinical practice. The aim of this study is to characterize the tumor drug sensitivity and epigenetic modifications on a molecular level induced by different compounds, in order to improve tumor-specific treatment for patients. **Method:** We tested a total of 40 epigenetically active compounds (partly known and partly unknown/unpublished) in two different concentrations in 56 lung adenocarcinoma cell lines and 3 control cell lines for cell viability. **Result:** The resulting 14000 data points were split according to sensitivity of the tumor cells to the compounds into three different groups (high sensitivity: < 25% viable cells, medium sensitivity: 25%-75 viable cells and low sensitivity: >75% viable cells). Six compounds showed broad effectiveness with high sensitivity in more than half of the cell lines while 15 compounds inhibited proliferation in only a few cell lines and are therefore of special interest for the discovery of new predictive biomarkers. The remaining compounds did not show high sensitivity in any cell line. Notably, we found that different compounds targeting the class of histone acetyltransferases (HAT) can have very different impacts on the survival of the tumor cells, and that the epigenetic modification of opposing mechanisms (e.g. HAT- and HDAC-inhibitors) may give rise to similar results **Conclusion:** Taken together, we demonstrate the differential effectivity of drugs inducing epigenetic modifications in lung adenocarcinoma cells *in vitro*. By combining the sensitivity data with molecular profiles of RNA and protein expression which we have generated, we are identifying molecular determinants for the individual sensitivity of the tumor to the respective drugs, which could be further developed *in vivo*into predictive biomarkers for drug response.

Keywords: lung adenocarcinoma cell lines, Drug sensitivity, Epigenetic modifications

P3.13 TARGETED THERAPY
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P3.13-33 LUNG ADENOCARCINOMA HARBORING RET FUSION AND DRAMATIC RESPONSE TO COMBINATION OF VANDETANIB (VAN) AND EVEROLIMUS (EVE): A CASE REPORT FROM BRAZIL

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Background: The identification of oncogene addicted NSCLC and the development of target therapies lead to improvement in survival rates and quality of life. In addition to other *drugable* targets such as EGFR mutation and ALK translocation, RET fusion has been shown to be an oncogenic driver in 1 to 2% of patients with NSCLC. **Method:** Here we report a 23-year old never-smoker male patient (Pt) diagnosed with lung adenocarcinoma, metastatic to lymph nodes, bones and lungs. Tumor biopsy was performed during broncoscopy. Tissue molecular testing was negative for EGFR (cobas) and ALK (FISH), and PDL-1 tumor proportional score (22C3) was 5%. Pt presented rapid disease progression after one cycle of cisplatin and pemetrexed, with pleural effusion and respiratory distress. Since initial tissue biopsy paraffin had been exhausted, next generation sequencing in cell-free tumor circulating DNA in plasma was performed (Guardant360). CCDC6-RET fusion and TP53 mutation (T256I) were identified. **Result:** Based on promising activity of the combination

of VAN with EVE previously reported, and the lack of clinical trials in this setting in Brazil, Pt started oral target therapy with VAN 300 mg and EVE 10 mg daily. He had unequivocal clinical improvement over the following weeks, with discontinuation of pain medications and relief of respiratory symptoms. After 30 days on treatment, restaging CT scans demonstrated a dramatic response. Adverse events were grade (G) 1 cutaneous rash, G1 stomatitis and G1 diarrhoea. Pt also presented G1 pneumonitis that resolved rapidly with EVE temporary discontinuation. He remained without disease progression at 4+ months. After 5 months, he presented pneumonitis recurrence with respiratory failure. VAN is a multi-targeted tyrosine kinase inhibitor of EGFR, VEGFR and RET, with limited activity in RET-rearranged NSCLC phase 2 trial. However, the concurrent inhibition of RET and the mammalian target of rapamycin (mTOR) has shown promising activity for RET-rearranged tumors in preclinical models. Among the 6 evaluable NSCLC patients with *RET* fusions treated with VAN and EVE in phase I trial, 5 achieved partial responses (83%) and 1 stable disease (16%). In particular, it has been suggested that *CCDC6-RET* subtype shows higher sensitivity to VAN. **Conclusion:** This case report corroborates the promising activity of combination of VAN and EVE in RET-rearranged NSCLC.

Keywords: Everolimus, Vandetanib, RET fusion

P3.13 TARGETED THERAPY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.13-34 RET GENE, A NEW CHOICE FOR NSCLC

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Background: RET gene, accounting for 1-2% of non-small cell lung cancer (NSCLC), has been identified as a novel target molecule which has been reported that could not coexist with other gene mutations such asrejected with the other mutation like KRAS, EGFR, BRAF, MEK1, HER2 and ALK.The emerging targeted agents Cabozantinib and Vandetanib have been recommended by NCCN guidelines for non-small cell lung cancer with RET fusion, based on a series of clinical trials. **Method:** We presented a case of lung adenocarcinoma with KIF5B/RET fusion. The patient was a 50-year-old, male, non-smoker, diagnosed as left upper lobe adenocarcinoma lung cancer. We performed a radical resection of pulmonary carcinoma for two years ago. Subsequently,he completed four cycles of chemotherapy with gemcitabine and cisplatin. However, half years later, pleural metastasis made him have to receive systemic treatment but no chemotherapy due to his worse tolerance. We then performed a gene examination with the PCR method using the intraoperative specimen, and finally found positive KIF5B/RET fusion gene. From then on June 10,2017, he started to take cabozantinib for treatment. **Result:** He started to take cabozantinib (140 mg orally, once daily) for about nine months. His disease sustained SD during that period (please see Figure 1). No serious adverse events (AEs) except rash (II grade) occurred in the whole treatment process. **Conclusion:** We found that the RET gene is a new alternative for lung adenocarcinoma patients without common mutations such as EGFR, ALK, ROS1 and so on. This case report supports a useful reference for the therapy of lung adenocarcinoma patients with RET mutation and may provide a new choice for this kind of NSCLC patients.

Keywords: RET gene mutation, cabozantinib, Targeted therapy

P3.13 TARGETED THERAPY
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.13-35 ANTITUMOR EFFECT OF NERATINIB TARGETING HER2-ALTERED LUNG CANCER

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Background: Human epidermal growth factor receptor 2 (HER2) plays an important role in the pathogenesis of various cancers. *HER2* alterations have been suggested to be a therapeutic target in non-small-cell lung cancer (NSCLC), as in breast and gastric cancers. However, the benefit of HER2-targeted therapy is much less defined. The aim of the study is to investigate the antitumor effect of neratinib, an irreversible pan-HER tyrosine kinase inhibitor (TKI), in NSCLC cells harboring *HER2* alterations. **Method:** We examined the sensitivity of neratinib against normal bronchial epithelial cells BEAS-2B which ectopically overexpressing wild-type or mutant *HER2*. Human cDNAs encoding full-length HER2 (wild-type and its variants A775insYVMA, G776VC, G776LC, P780insGSP, V659E, G660D, and S310F) were inserted into the pIDT-SMART (C-TSC) vector, pCMViRTSC. Furthermore, we examined the antitumor activity of neratinib in several NSCLC cell lines harboring *HER2* alterations *in vitro* and *in vivo* experiments, and investigated the association between their genetic alterations and sensitivity to neratinib treatment. **Result:** BEAS-2B cells ectopically overexpressing wild-type *HER2* or mutants (A775insYVMA, G776VC, G776LC, P780insGSP, V659E, G660D, and S310F) showed constitutive auto phosphorylation of HER2 and activation of downstream signaling by Western blotting. These BEAS-2B cells were sensitive to neratinib, but insensitive to erlotinib, a first generation EGFR-TKI. Neratinib significantly inhibited the growth of *HER2*-altered (H2170, Calu-3, and H1781) NSCLC cell lines with an average IC_{50} value of 0.00347μL, 0.0428μL, and 0.0119μL. Neratinib administration showed strong antitumor effect on tumor growth in mouse xenograft model using *HER2*-altered lung cancer cell lines. **Conclusion:** Our study strongly suggests that neratinib is a promising therapeutic option for the treatment of *HER2*-altered NSCLC.

Keywords: HER2, Neratinib, pan-HER tyrosine kinase inhibitor

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.15-01 LONG-TERM OUTCOMES OF PULMONARY METASTASECTOMY: A 12-YEAR DUAL CENTRE EXPERIENCE

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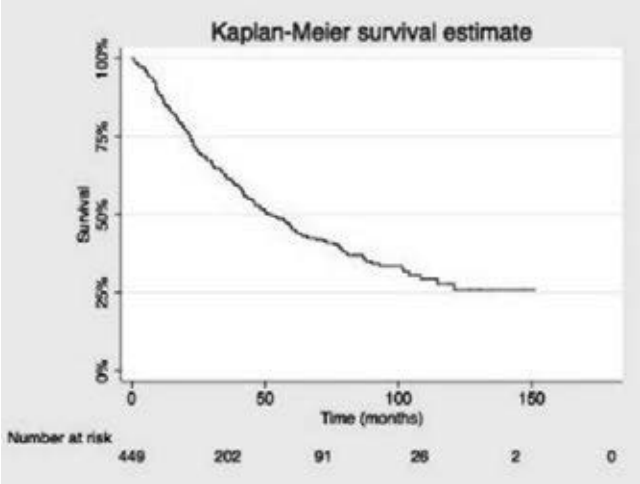
Background: Pulmonary metastases are a common site of spread for many cancers. We describe the long-term outcomes of surgical resection of pulmonary metastases at two major cancer centres. **Method:** The study institutions thoracic surgery databases were searched for all patients who underwent pulmonary metastasectomy between 2005 and 2017. **Result:** There were a total of 489 patients who underwent pulmonary metastasectomy. Mean age at time of surgery was 45.6 ± 11.6 years. There were a total of 658 operations performed with 105 (21.5%) patients having repeat pulmonary metastasectomy. Of these patients 68 (64.8%) had 1 repeat operation, 20 (19.0%) had 2 repeat operations, 11 (10.5%) had 3 repeat operations, 2 (1.9%) had 4 repeat operations and 4 (3.8%) had 5 repeat operations. The most common primary lesions were colorectal cancer (CRC) in 35.3% (173/489) of patients, sarcoma in 23.7% (116/489) of patients, melanoma in 16.2% (79/489) patients, renal cell carcinoma (RCC) in 7.2% (35/489) of patients and germ cell carcinoma (GCC) in 4.5% (22/489) of patients. Other cancers accounted for the remaining 13.1% (64/489) of patients. Mean follow-up was 41.2 ± 1.6 months and was complete for 91.8% of patients. Survival was 85.6% (95%CI: 81.9 – 88.9%) at 1-year, 45.2% (95%CI: 39.7 – 50.5%) at 5-years and 27.8 (95%CI: 21.2 – 34.6%) at 10-years follow-up (figure 1). On univariate Cox regression analysis CRC (p = 0.027) and GCC (p = 0.016) were associated with improved survival while melanoma (p = 0.039) was a risk factor for mortality. On multivariate Cox regression analysis CRC (p = 0.025) and GCC (p = 0.011) were associated with improved survival.



Conclusion: Pulmonary metastasis is associated with survival of less than 30% at 10 years follow-up. CRC and GCC cancers were associated with better long-term mortality while melanoma was associated with worse long-term mortality.

Keywords: metastasis, metastasectomy, Surgery

P3.15-02 CARBOPLATIN DOSE CALCULATED USING DIFFERENT FORMULA FOR EGFR AND THEIR COMPARISON WITH ACTUAL DOSE ADMINISTERED IN LUNG CANCER PATIENTS

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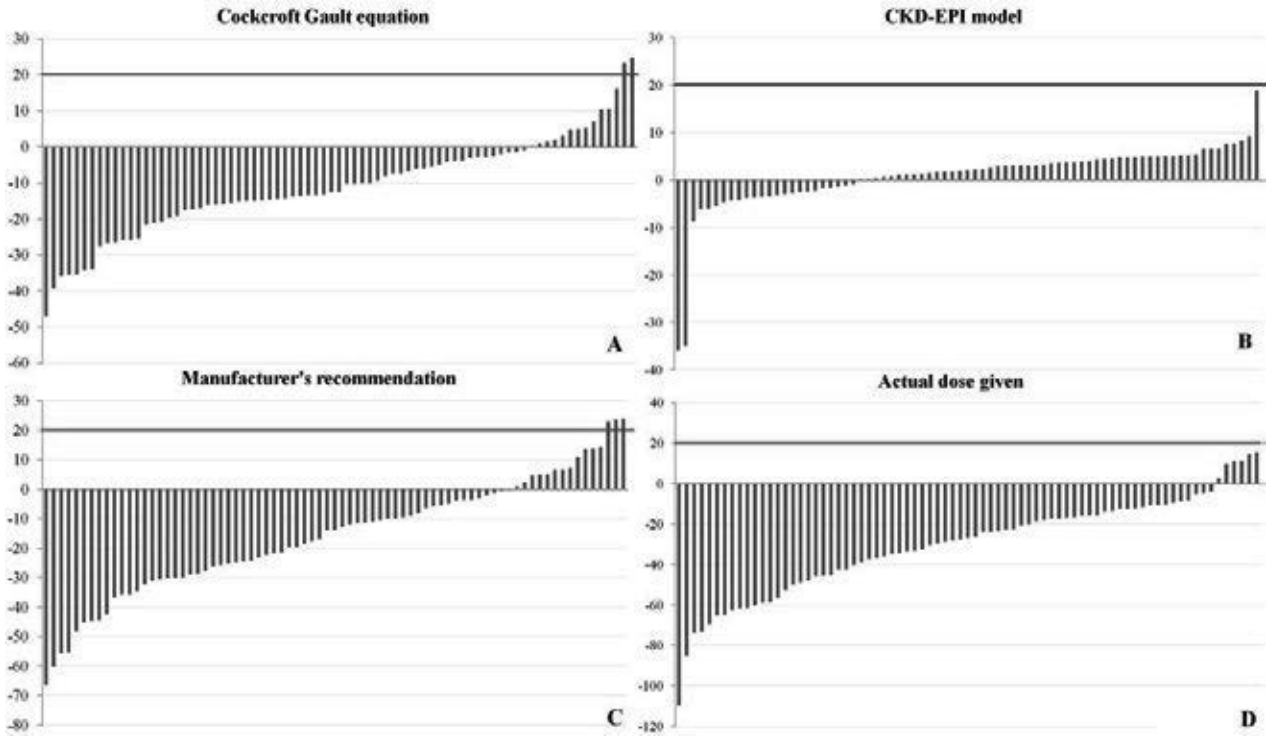
Background: Carboplatin dosage for chemotherapy is usually estimated using AUC-based dosing. Several equations are available for estimating GFR(eGFR); including Cockcroft-Gault, Chronic Kidney Disease Epidemiology Collaboration(CKD-EPI), and a recent equation(1). However, while calculating dosage of carboplatin, several factors other than estimated-GFR[including performance status(PS), vial package strengths] merit consideration. Do we require high degree of precision in eGFR and how does each of these equation perform in real-life settings**? Method:** We performed a retrospective audit of lung cancer patients undergoing first-line chemotherapy at our centre, with the aim of determining discrepancies between actual doses of carboplatin administered versus those calculated using different equations. Calvert formula was used to calculate carboplatin dose, with the eGFR being obtained from Cockcroft-Gault, CKD-EPI and the Janowitz-equation. (J Clin Onc2017;35(24):2798-805) *Dose derived from GFR estimated using latter was considered reference standard.* Carboplatin dose was also calculated using manufacturer's instructions[body surface area(BSA) in kg/m^2 x 300 for GFR>60 mL/min; BSA×250 for GFR=41-60 mL/min; BSA×200 for GFR≤40mL/min]. Absolute dosage differences and percentage errors(PE) for above equations were calculated. **Result:** 77 subjects received carboplatin-based chemotherapy(Jan-Aug 2017). Dosage calculated by Cockcroft-Gault based GFR and manufacturer's recommendation had significant variation as compared to new equation-based dose. However, the actual administered doses were lower than both Cockcroft-Gault-based and manufacturer's recommended doses. Significant proportion(n=48, 62.3%) had >20% absolutePE of carboplatin dose as compared to reference standard. Carboplatin dose PEs(actual administered, calculated as per Cockcroft-Gault, CKD-EPI equation and manufacturer's recommendation) were plotted against the reference standard as waterfall chart(Figure 1A-D). All, except six(7.8%) patients(none of them were≥20% higher than the predicted), received doses≤ that calculated from the reference. **Conclusion:** Actual carboplatin administered is lower than the predicted in majority(*irrespective* of equation used for eGFR). Hence the probability of administering a potentially toxic dose, owing to incorrect eGFR might be negligible. Thus, using more accurate equations/measuring GFR may not be required.

Keywords: Chemotherapy; carboplatin; kidney function



P3.15-03 CAPTURING THE PATIENT EXPERIENCE FOR THE TREATMENT OF EGFR EXON 20 MUTATIONS IN NON-SMALL CELL LUNG CANCER

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Background: Non-small cell lung cancer (NSCLC) accounts for 80–85% of new lung cancer cases, which presents as metastatic disease 40–50% of the time. The prevalence of NSCLC patients with a mutation in the epidermal growth factor receptor (EGFR) varies by ethnicity, ranging from 15–50%, and EGFR exon 20 insertion mutations specifically account for 7–12% of all EGFR mutations. Health-related quality of life (HRQOL) was widely used, as generic measures may lack the sensitivity required to demonstrate clinical change related to new therapies. Assessments of disease-specific patient-reported outcomes (PROs) play an important role in clinical trials to evaluate the benefits of new treatments on HRQOL and in making treatment decisions for patients. This study aimed to better understand the overall symptom experience and HRQOL impact from the perspective of NSCLC EGFR exon 20 patients to evaluate the effectiveness of new treatments. **Method:** A targeted literature review was conducted in Embase and Medline (2007–2017) to identify PROs used in previous NSCLC studies for evidence of content coverage. Interviews with expert clinicians were conducted to explore the clinical perspective on treatment and observed patient experience. Following approval from an independent review board, semi-structured qualitative interviews were conducted with NSCLC patients identified through the International Cancer Advocacy Network. **Result:** Five oncologists were interviewed, reporting a wide range of NSCLC symptoms, notably shortness of breath, chest pain, bone/other pain, and substantial emotional impacts. Ten patient interviews were conducted (median age

55 [42–83] years; 60% female, 90% EGFR exon 20 insertions, median disease duration 1.8 [<1–6] years, 60% self-reported brain metastases). The most frequently reported disease related symptoms included fatigue (90%), pain (70%), shortness of breath (70%), cough (60%), weakness (30%), phlegm/congestion (30%), and hemoptysis (20%). Symptoms indicative of brain metastases included issues with vision and headaches (both 30%), speaking (20%), and balance (10%). All patients mentioned experiencing a psychological or emotional impact, with 60% describing worry/anxiety around treatment, the future, or finances. Patients also described experiencing negative impacts on daily activities, including household chores and self-care (60%), work (50%), social activities (50%), and family life (40%). **Conclusion:** Incorporation of the patient voice provided valuable in-depth insight on the NSCLC patient experience. Symptom and HRQOL impact concepts identified will inform the iterative development of a conceptual disease model. Results show the significant social, emotional, and physical impact on patients' lives, which fill an important gap and help to inform treatment decision making.

Keywords: NSCLC, EGFR Exon 20 Insertion, patient reported outcomes

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-04 AN INTERDISCIPLINARY EDUCATIONAL PROGRAM DEDICATED TO NON-SMALL CELL LUNG CANCER PATIENTS TO IMPROVE THEIR QUALITY OF LIFE

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Background: Non-small cell lung cancer (NSCLC) guidelines require access for patients and their family to an educational program to help them managing their treatments, symptoms in order to improve their quality of life. Outpatients' treatments are now very common, giving the patient more autonomy. However, to get the best therapeutic compliance and to improve the disease control, a patient education is necessary. This study describes an educational program and assessed its impact on patients. **Method:** ETOILE is an educational program dedicated to patients with advanced NSCLC treated by oral or intravenous treatment. First an educational diagnosis is made with the patient, then a tailored program is proposed with individual or collective educational sessions (informations about lung cancer, how to manage side effect, stress management, nutrition, smoking cessation, well-being.). An interdisciplinary team is dedicated to this program including medical doctor, coordinating nurse, psychologist, sophrologist, dietitian, social worker, tobacco specialist nurse, physiotherapist and social esthetician. A weekly meeting is organised to present every patient included in the program and to discuss the need of each patients. Assessments included skills acquisition by the patients and the program evaluation. **Result:** In 2016, 94 patients (66% were men, median age : 59 years), entered the ETOILE educational program. Ninety-six percent of the patients were satisfied or very satisfied with the ETOILE program. They reported an improvement in their quality of life. For 81% it allowed to have a better knowledge of their illness, for 85% to know better their treatment, 76% to manage their symptoms and adapt the food, 86% to take care of them and to have better information about all helps that can be provided. For 72% of the patients, the educational program permits to manage their stress and help their relatives throughout the disease and treatment trajectory. **Conclusion:** Providing a tailored educational program is important for patients with advanced NSCLC throughout the disease trajectory even if the disease prognosis remain poor for many patients. Our experience shows that an educational program dedicated to NSCLC patients is feasible and useful.

Keywords: NSCLC, educational program, quality of life

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.15-05 PATIENT REPORTED OUTCOMES (PROS) AS PERFORMANCE MEASURES AFTER SURGERY FOR LUNG CANCER

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Background: In Denmark and other countries, quality in lung cancer care is measured using performance indicators from clinical registries. The registries and the indicators are based on data from professionals taking care of patients and their treatment. What is missing in this quality measurement, however, is the patients' perspective. The objective of this study was to examine if patient reported outcomes (PROs) from patients with lung cancer could be used in performance measurement after surgery. Would it be feasible to use PROs in benchmarking, comparing treatment quality in different regions of Denmark? **Method:** All patients registered in the Danish Lung Cancer Registry(DLCR) from 1 October 2013 until 30 September 2015, who received curatively intended surgical treatment, were eligible(N=1,718). They were asked to complete the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire six months after surgery. From the questionnaire we chose the *global health score* (GHS) and *role functioning* (RF) as indicators, and the threshold for good performance was set to 65 points (on a scale 0-100 where 100 is the best). Information about the patients' socioeconomic position was obtained from Statistics Denmark. Results were compared between the five regions within Denmark, using the patients' home address. Patient characteristics of the five groups were compared using t-tests and chi squared tests. **Result:** Of 1,615 patients alive six months after surgery, questionnaires were completed by 999 patients (61.9%). Patient characteristics of the five groups differed significantly in e.g. performance status, cancer stage, and income. There were difference in GHS between groups, but mean RF varied significantly (see table).

Global health score (GHS) and Role functioning (RF) for the five regions

	All patients	Region 1	Region 2	Region 3	Region 4	Region 5	p
	N = 999	N = 154	N = 207	N = 212	N = 256	N = 170	
GHS mean (SD)	66.8 (22.0)	65.9 (20.5)	65.7 (23.5)	68.2 (21.8)	67.4 (21.7)	66.5 (22.5)	0.706
% with GHS ≥ 65	63.6	62.3	61.8	67.5	64.8	60.0	0.581
RF mean (SD)	68.9 (29.5)	66.0 (29.6)	67.4 (28.1)	71.5 (28.6)	69.8 (29.8)	68.9 (31.3)	0.013
% with RF ≥ 65	69.8	62.3	71.5	73.1	69.5	70.6	0.239

Conclusion: In a population with lung cancer receiving surgery, it may be feasible to use PROs for benchmarking. The next step in our study is to examine whether differences in GHS and RF are a consequence of different outcomes, or of different patient populations.

Keywords: lung cancer surgery, patient reported outcomes, EORTC QLQ-C30

P3.15-06 CAPILLARY LEAK SYNDROME IN A PRIMARY LUNG ADENOCARCINOMA PATIENT WITH THROMBOCYTOPENIA FROM INTERLEUKIN-11 TREATMENT

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Background: Capillary leak syndrome (CLS) is an uncommon complication characterized by generalized edema and hypotension. We report a 62-year-old male patient with lung and liver metastasis who had underwent liver radiofrequency ablation. **Method:** He was treated with interleukin (IL)-11 (3 mg per day) because of chemotherapy induced thrombocytopenia. **Result:** After 9 days of therapy, the patient complained of abdominal distension and with bilateral edema of all four extemities. Chest computed tomography and B ultrasound of the abdomen showed pleural effusions and ascites. IL-11 was then discontinued, fluid resuscitation was performed, fresh frozen plasma and packed red blood cells were transfused, and methylprednisolone therapy was administered. The patient had recovered after 12 days of treatment. **Conclusion:** This case report demonstrates that patients with lung cancer can develop this rare form of CLS after treatment with IL-11. The manifestation of IL-11-induced CLS indicates that it may be a severe side effect of IL-11 treatment in cancer.

Keywords: lung cancer, capillary leak syndrome, interleukin-11

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-07 A LITERATURE REVIEW AND ASSESSMENT OF LUNG CANCER QUALITY INDICATORS

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Background: Quality indicators (QIs) are used to assess various aspects of the quality of healthcare services received by patients in the "real-world". They provide a measurement tool to be utilised in care settings to develop standards or benchmarks, identify variations in care, guide performance improvement, monitor changes over time and promote accountability. The management of lung cancer is complex and rapidly evolving. Care often involves multidisciplinary assessment and management with multimodality treatment that requires a comprehensive and co-ordinated approach. Evaluating the quality of care received in "real-world" everyday care is crucial for optimising health outcomes for lung cancer patients. We reviewed quality indicators in lung cancer and assessed their utility. **Method:** A medline search was conducted using the search terms "quality indicators" and "lung neoplasms" and grey literature using a web search of government and relevant health organisations. Full-text review was performed to include only articles that fulfilled inclusion criteria of original research that developed or applied specific QIs related to the care of lung cancer patients. Data was collected on the characteristics, frequency, use and testing for each indicator. **Result:** A total of 43 articles or reports were analysed. These included 293 distinct QIs, the most frequently reported indicators were related to surgery (n=66), then symptom assessment and management (n=43) and diagnosis and staging (n=38). There were fewer indicators related to systemic therapy (n=30), radiotherapy (n=17) or combined treatments (n=10). Analysis of the characteristics of process and structure QIs was undertaken and classified as meeting all ideal or a minimum set of desirable characteristics for QIs. Of these 60 met the minimum set and only five the ideal characteristics. These included 12 related to diagnosis and staging, four to pre-treatment assessment, five to surgery, 12 to systemic treatment, six to radiotherapy, three to combined treatment, three non-specific to treatment, three to symptom assessment, 11 to supportive care and one to palliative care. **Conclusion:** A wide range of quality indicators have been developed and used in lung cancer. The most frequent are treatment related and surgical based, which only reflects a small proportion of all lung cancer patients. In order to assess their usefulness, we classified QIs according to fulfilling accepted desirable characteristics. We present these as the most useful for implementation as quality metrics. QIs must also be feasible and relevant, which must be tailored to the health service for application.

Keywords: Quality of care, lung cancer, Quality Indicators

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-08 PATIENT-REPORTED OUTCOMES (PROS) IN PATIENTS WITH LUNG RESECTION: OPEN VERSUS MINIMAL INVASIVE SURGERY

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Background: As a novel and cutting-edge indicator to evaluate the quality of surgery, e.g. minimal invasive surgery (MIS), Patient-Reported Outcomes (PROs) has not been implemented in patients with lung resection in the real world. This study aims to profile PRO-measured symptom burden in patients with lung resection of either open surgery (OS) or MIS. **Method:** We conducted a prospective study on lung resection patients from November 22, 2017 to April 23, 2018. MD Anderson Symptom Inventory-lung cancer module (MDASI-LC) was used to assess the severity of perioperative symptoms and how they interfered with daily functioning. MDASI-LC was administered on the pre-operation day and daily after surgery up to the day of discharge. Trajectories of symptom severity and interference were compared between OS and MIS via mixed effects models. **Result:** Among 78 lung resection patients, 22 received OS and 56 received MIS. Most of the resection types were lobectomies (74.4%). All patients completed pre-operation assessment and the missing rate after surgery was less than 10%. There were no statistically significant differences between OS and MIS in pre-operation variables including age, BMI, hemoglobin, neutrophil ratio, platelets and creatinine. Within the first week after surgery, the most severe symptoms were pain, cough, fatigue, disturbed sleep and dry mouth for OS patients and pain, fatigue, cough, disturbed sleep and shortness of breath for MIS patients. MIS patients reported better physiological functioning (walking, general activity and work) than did OS patients in the first 7 days post surgery (p=0.013). Among patients with MIS, those with stage II-IV reported more severe fatigue than did stage I patients over the hospitalization (p=0.018).

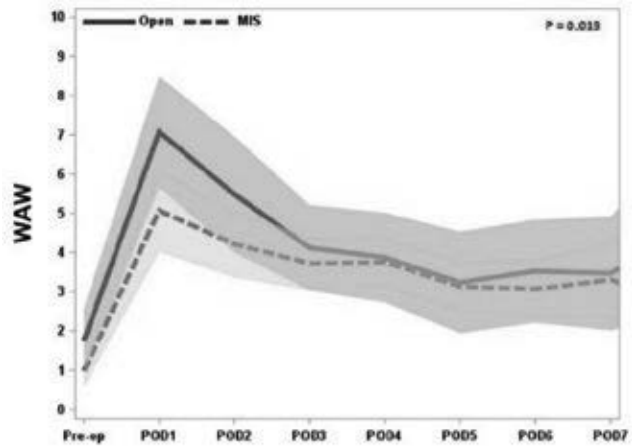

Fig 1. MIS patients had better physiological functioning than did open patients in the first 7 days post surgery.
WAW: average score of walking, activity and work.

Conclusion: This real world data preliminarily profile patients' experiences over a short period after lung resection. Compared to OS, MIS did not show a significant advantage in symptom severity, but related to better functioning on daily living. Additional recruitments and follow-up will expand patients' perceptions to the full trajectory of recovering from lung resection.

Keywords: Patient-reported outcomes, Quality indicator, lung resection

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-09 ARE LUNG CANCER PATIENTS RECEIVING EDUCATION MATERIALS? THE HEALTHCARE PROVIDER PERSPECTIVE ON DISTRIBUTION GAPS AND POSSIBLE SOLUTIONS

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Background: While new treatments for lung cancer bring new hope, they can also make understanding a lung cancer diagnosis and making treatment decisions a challenge for both patients and caregivers. Education is imperative to understanding the diagnosis and making informed treatment decisions. However, many patients and their caregivers report that they do not receive materials from their doctors. We fielded a study of healthcare providers (HCP) to understand their attitudes and practices on disseminating patient education for lung cancer. **Method:** We conducted an IRB-approved sequential mixed-method study of 216 HCPs (130 oncologists, 52 pulmonologists, and 34 nurse navigators/clinic or hospital administrators) from academic research centers, community cancer centers, and private practice to get a full and broad picture of education for lung cancer patients based on the specific role each HCP group plays in the treatment journey. The quantitative survey was followed by a qualitative interview of five HCPs to contextualize the survey findings. Questions of the study delved into perception, usage, distribution, and development of education materials. **Result:** Of the HCPs surveyed, surprisingly only 75% report that lung cancer educational materials are distributed. Nurse navigators/clinic administrators were more likely to distribute patient education materials than oncologists and pulmonologists ($p<0.05$). Notably, there is a discrepancy in who actually does the distributing: nurse navigators and community cancer center administrators say oncologists most often distribute them (80%), while oncologists and pulmonologist claim they only distribute some of the time (56%). Information format also was reported as a factor in distribution; HCPs are interested in information that can be both electronic and printable (79% of HCPs report that they distribute information via printed resources, and 59% of them still prefer printed materials, given the choice). Overall, community cancer centers report a higher rate of distribution than private practices and hospitals ($p<0.05$). However, there is typically not a point person for material review in any of these settings, and most HCPs report using information from multiple sources, such as self-created materials and materials created by other organizations. **Conclusion:** Distribution practices for educational materials are not standard and tend to be subject to the HCP's own discretion, leading to inconsistent delivery of materials. In-depth interviews with HCPs suggest possible solutions, including customization to patient/caregivers' unique type of lung cancer, availability of multiple formats of education materials for distribution, and white-labeling of materials to allow re-branding to an HCP's unique practice setting.

Keywords: Patient Education, oncologist, pulmonologist

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-10 SURVIVAL IMPACT OF PERIPHERAL BLOOD RATIOS IN LUNG CANCER ACCORDING CLINICAL STAGE

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Background: Lung cancer represents one of the most frequent and letal neoplasms in many regions, where most patients are still diagnosed as advanced disease, and many biomarkers have been studied unsuccessfully. Peripheral blood ratios as Neutrophil-to-lymphocyte ratio (NLR), Monocyte-to-lymphocyte ratio (MLR) and Platelets-to-lymphocyte ratio (PLR) have been studied as potential biomarkers of systemic inflammation but cut-off values are still difficult to stablish. We explored the survival impact of different cut-off values according clinical stages in lung cancer. **Method:** We analyzed medical records of 193 patients with lung cancer treated at ONCOSALUD–AUNA 2011-2014. Peripheral blood data was obtained retrospectively from the first medical visit and we calculated optimal cut-off values using the maximally selected rank statistics according every clinical stage (CS). Overall survival (OS) was evaluated using Kaplan-Meier method and survival curves comparison was performed using log-rank test or Breslow. **Result:** Median age was 67 years (range: 34-88), 51% were women and 71.5% had 0-1 ECOG scale. The 9.8, 11.4, 18 and 60% were CS I, II, III and IV. The most common metastatic sites were brain, bones, cervical and supraclavicular nodes. Patients with I CS underwent to lobectomy, and 59% of II and most III-IV CS received chemotherapy. The median follow-up was 4.9years, median OS was 1.4years (95%CI: 1.1-1.9) and 2 and 5years OS were 42% and 25%, respectively. The next table shows survival impact of blood ratios according CS. Optimal cut-off values were different according every CS of lung cancer, however in the IV CS group the cut-off of 2.6 and 0.31 for NLR and MLR showed significant survival impact on OS.

Clinical stage	Ratio	Cut-off value	Median OS	Prognostic value	p
I (n = 19)	NLR	<2.5	NA	Better	
		>2.5	3.2	Poor	0.001
	MLR	<0.4	5.2	Better	
		>0.4	1.7	Poor	<0.001
	PLR	<209.7	5.2	Poor	
		>209.7	1.7	Better	<0.001
II (n = 22)	NLR	<2.0	NA	Better	
		>2.0	2.5	Poor	0.133
	MLR	<0.37	NA	Better	
		>0.37	1.0	Poor	0.044
	PLR	<258.8	NA	Better	
		>258.8	0.4	Poor	<0.001
III (n = 35)	NLR	<2.3	5.4	Better	
		>2.3	1.5	Poor	0.015
	MLR	<0.53	2.6	Better	
		>0.53	0.5	Poor	<0.001
	PLR	<157.7	3.6	Better	
		>157.7	1.2	Poor	<0.001
IV(n = 117)	NLR	<2.6	1.8	Better	
		>2.6	0.7	Poor	<0.001
	MLR	<0.31	1.5	Better	
		>0.31	0.7	Poor	0.040
	PLR	<134.8	1.1	Better	
		>134.8	0.7	Poor	0.107

Conclusion: Our results suggest that exists different cut-off values for blood ratios according every clinical stage that needs to be explored among larger population data-bases to confirm it. In advanced disease, NLR and MLR show significant survival impact in this study.

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-11 ASSOCIATION BETWEEN PERIPHERAL BLOOD RATIOS AND CLINICAL STAGE DISEASE IN LUNG CANCER

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Background: Many attempts have been described to stablish peripheral blood ratios as systemic immune biomarkers in lung cancer, unfortunately they are not still considered because of lack accuracy and sensibility. In this study, we explore and correlate clinical stages to median values of peripheral blood ratios as Neutrophil-to-lymphocyte ratio (NLR), Monocyte-to-lymphocyte ratio (MLR) and Platelets-to-lymphocyte ratio (PLR) among patients with lung cancer. **Method:** Retrospectively, we review clinical and laboratory data from 193 patients with lung cancer treated at Oncosalud – AUNA from 2011 to 2014. The laboratory data (hemoglobin, leukocytes, neutrophil, lymphocyte and monocyte) were collected from blood routine test obtained from the first clinic visit. The median (range) and mean (± SD) of the ratios were determined according every clinical stage and compared using the U Mann Whitney test. **Result:** Median age was 67 years, and 63 (34-79), 64 (37-83), 69 (44-88) and 67 (38-86) years in I, II, III and IV CS, respectively. In early disease (I-II), female patients were slightly more frequent that men. Median hemoglobin was 13.6, 12.4, 13 and 12.7 gr/dl for I, II, III and IV CS, respectively. Peripheral blood levels (leukocytes, lymphocytes, monocytes and platelets) show a slightly higher level among patients with advanced disease. Median NLR, MLR and PLR are described in the following table, there was a significant difference between early and advanced disease (III and IV CS) for NLR and MLR.

(See next page)

Clinical stage	Ratio	Median (range)	Mean*	U Man Whitney test
I (n = 19)	NLR	2.1 (1.0, 8.1)	2.1	Reference
	MLR	0.24 (0.26, 0.6)	0.23	Reference
	PLR	153.7 (73.5, 253.9)	154.7	Reference
II (n = 22)	NLR	1.95 (1.1, 12.0)	2.1	0.714
	MLR	0.28 (0.2, 1.0)	0.29	0.143
	PLR	184.1 (76.1, 319.8)	186.4	0.182
III (n = 35)	NLR	3.1 (1.2, 11.3)	3.2	0.006
	MLR	0.37 (0.13, 1.4)	0.38	0.002
	PLR	165.1 (74.1, 537.2)	177.8	0.258
IV(n = 117)	NLR	3.7 (0.7, 31.6)	3.9	0.001
	MLR	0.4 (0.1, 3.6)	0.4	<0.001
	PLR	186.3 (47.5, 629.3)	187.1	0.059

Conclusion: These results suggest that there are higher levels of peripheral blood ratios related to advanced disease; but larger studies are needed to confirm it. Only NLR and MLR showed differences between early and advanced disease.

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-12 SURVIVAL IMPACT OF PATIENT ENROLLMENT IN ANTINEOPLASTIC DRUG TRIALS FOR STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Patient enrollment in antineoplastic drug trials (ADT) is essential for the development of effective therapies in stage IV NSCLC. An open question is whether NSCLC patients derive a survival benefit by enrolling in ADTs. We hypothesized that patient enrollment in ADT is associated with longer overall survival (OS) because of access to novel therapies and closer follow up, compared with no ADT enrollment. **Method:** We reviewed electronic medical records of 193 patients diagnosed with biopsy-proven, stage IV NSCLC between 01/01/2007 and 12/31/2014, who received treatments at the Seattle Cancer Care Alliance. Other inclusion criteria were age > 18 and receipt of ≥ 1 antineoplastic agent within 180 days from diagnosis. We abstracted patient clinical characteristics, tumor histology, EGFR and ALK mutation status, receipt of chemotherapy, targeted therapies, and immunotherapy up to 5 consecutive lines, participation in ADTs, and OS from diagnosis to death. We fitted multivariate Cox regression models to estimate the risk-adjusted effect of ADT participation on survival, compared with no trial participation. **Result:** Patients' mean age was 63.4; 53.9% were female; 28.5% were never smokers; 75.1% had ECOG PS of 0-1; 95.3% had non-squamous histology; 27.5% had brain metastases; 20.7% and 4.1% had EGFR+ and ALK+ NSCLC. Fifty-three (27.5%) enrolled in ≥ 1 ADT, of whom 17 (32.0%) received trial drug(s) that later became FDA approved, and 44 (83.0%) and 13 (24.5%) enrolled in phases I/II or III trials. Adjusting for ECOG PS, smoking, EGFR mutation status, type of first line therapy, and number of treatment lines, participation in ≥ 1 ADT was associated with a hazard ratio for death of 0.62 (P = 0.02; Table 1).

Trial Participation (≥ 1)	Median OS (months)	Adjusted Hazard Ratio (95% CI)	P-value
No (n=140)	12.4	reference	
Yes (n=53)	19.7	0.62 (0.42; 0.94)	0.020

Conclusion: Participation in therapeutic trials is associated with longer OS in NSCLC. Besides supporting drug development, trial enrollment may improve patient outcomes. Efforts should focus on increasing patient enrollment in drug trials.

Keywords: Trials, survival, outcomes

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-13 SURGICAL MANAGEMENT OF HUGE PULMONARY ARTERIOVENOUS MALFORMATIONS: OUR EXPERIENCE

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Background: Pulmonary arteriovenous malformations are rare lesions with significant clinical complications. These lesions are commonly seen in patients with hereditary hemorrhagic telangiectasia (formerly Osler-Weber-Rendu syndrome). Formerly called Osler-Weber-Rendu, HHT is an inherited disorder of the vasculature associated with AVMs and telangiectasias. The prevalence of HHT is 1 in 5,000 to 10,000 patients.) are present, the diagnosis is definite. If two criteria are present, the diagnosis of HHT is probable. If less than two criteria are present, the diagnosis is unlikely.Management of arteriovenous malformations (AVMs) remains challenging because of their unpredictable behavior and with high risk mortality. A multidisciplinary approach based on a new classification scheme and improved diagnostic techniques may improve their management. **Objectives:**The purpose of this study was to review our surgical experience with surgical to manage arteriovenous malformations (AVMs). **Method:** We diagnosed a 1 patient A. female birthday 02.09.1990 with pulmonary arteriovenous malformacion (PAVMs) .She has been admitted to the thoracic surgery clininic in QKUK Pristine in July 2015 with massive hemoptisis. Unknwn initially diagnose .She was presented to QKUK hospital urgently with such clinical signs, epistaxis ,cough, hemopstisi, weakness, sweat, fever, dyspnoea, thoracic malaiseand ,massive right hemothorax with clinical signs of hemorrhagic shock with massive hemoptisi, tachycardia, weak pulse, hypotension, severe anemia et hypovolemiv shock .She was treated with right pleural drainage (avarage 2000ml)and intensive therapy et hemotransfusion (8 flacons).She was treated initially with intensive therapy and hemotransfuzion and after that with hemodynamic parameters stable were treated with surgery.Pacient were completed with all the necessary of emergency examinations as thoracic radiography, biochemical examinations, CT scaner toracal, MRI ,Bronchoscopy, EKG ,cardiac echo and cateterisation ,gaseous exchange . The patient continued with the above-mentioned concerns with dyspnoea epistaxis from time to time. Cyanosis of the lips, fingers in the hands of drumsticks, petekie and ecimosis in the skin and mucous membranes, sleep disorders. After 1.5 years it is re-examined in the cardiology clinic "Nene Hospital Theresa "and is diagnosed with giant dexter pulmonary arteriovenous fistule by Pulmonary angiography.She was treated by surgical approach in 10.06.2016 .Right posterolateral thoracotomy ,segmentectomy IV-r and fistul artereovenosectomy ,pleural deainage. **Result:** Arteriovenous malformation size ranged. to 10x 8 cm located in the right lung middle lobe.She was treated by anatomical 4-th segmentectomy. Operator and post operative period is good. Clinical and imaging image of ultimate control is smooth.No mortality ,no major complication.Hospital days stay was 5 days. **Conclusion:** Diagnosis and management of AVMs by surgical therapy resection was with very good results and with limited morbidity and low mortality and no recurrence during early follow-up.

Keywords: embolotherapy, Pulmonary arteriovenous malformation(PAVMs), hemorrhage hereditare telangiectasia

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-14 USING CREATIVE CO-PRODUCTION TO DEVELOP A TREATMENT DECISION SUPPORT TOOL FOR PEOPLE WITH MALIGNANT PLEURAL EFFUSION

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Background: Malignant pleural effusion (MPE) is a common, serious problem predominantly seen in metastatic lung and breast cancer and

malignant pleural mesothelioma (MPM). Recurrence of MPE is common, and symptoms significantly impact on people's daily lives. No ideal treatment strategy for MPE currently exists. However, there are four main treatment options aimed at relieving symptoms and improving quality of life. These include aspiration, thoracoscopy with pleurodesis, bedside pleurodesis and indwelling pleural catheter Choosing which option is best depends on many factors and making decisions can be challenging in pressured clinical environments. This project aimed to develop a support tool to help this decision making process for people with MPE. **Method:** Pleural teams from three sites in the UK undertook a creative co-production (CC-P) approach led by the translating knowledge into action (TK2A) team of the NIHR Research Collaboration and Leadership in Applied Health Research and Care Yorkshire and Humber. The geographical distance between the three sites and the ill-health of service users meant a novel distributed model of CC-P was used. This comprised of three locally run workshops with clinicians, patients and carers that were designed and structured by the TK2A CC-P experts. This was followed by a joint national workshop with representatives from all stakeholder groups to consider findings and outputs from local meetings. The design team worked with participants to develop outputs including patient timelines and personas. These were used as the basis to develop and test visible and tangible prototype ideas. **Result:** Some key messages emerged that informed prototype development. Understanding and managing their pleural effusion was the priority for patients, not their overall cancer journey. Preferred methods for receiving information were varied but visual and graphic approaches were favoured. The main influences on people's decisions about their MPE treatment were personal aspects of their lives (e.g. how active they are, what support they have at home). The design team developed a first prototype (i.e. a video representing a web-based support tool) to help people identify personal priorities and guide shared treatment decisions. This requires further development before implementation into practice. **Conclusion:** The creative design methods and distributed model of co-production used in this project overcame many of the barriers to traditional co-production methods such as power, language and time. They allowed specialist pleural teams and service users to work together to create a patient-facing decision support tool owned by those who will use it.

Keywords: malignant pleural effusion, creative co-production, treatment decision support tool

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-15 ALI COULD BE A ONE OF PROGNOSTIC SURVIVAL FACTOR FOR NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Patients with terminal non-small cell lung cancer become greatly concerned about where they will die. And the Advanced Lung Cancer Inflammation Index (ALI, body mass index × albumin/neutrophil-to-lymphocyte ratio) has been demonstrated to be a prognostic factor of survival in some solid cancers. We examined the survival times of such patients according to their place of death; i.e., whether they died at home, at a hospice, or at hospital and analysis with ALI. **Method:** A retrospective cohort study of patients who were followed from their first chemotherapy session for non-small cell lung cancer until death was performed. Specifically, the study compared four groups, those that died at home, at a hospice, at hospital or alive. The study was based on mortality data from the single institute National Hospital in Japan, for the period between April 2010 and December 2015. **Result:** Among the 313 patients recruited, 214 were analyzed in this study: 90, 49, and 75 received hospital-based, home-based, and hospice-based palliative care, respectively. The patients who died at a hospice exhibited significantly longer survival than those that died at hospital (estimated median survival time, 420 days [95% confidence interval (CI), 325-612 days] vs. 252 days [95% CI, 201-316 days]; P<0.0001), and the patients that died at home also demonstrated significantly longer survival than those that died at hospital (estimated median survival time, 420 days [95% CI, 325-612 days] vs. 341 days [95% CI, 293-460 days]; P<0.0001). No significant difference in survival was detected between the patients that died at home and those that died at a hospice. At the time of data cut-off, ALI before chemotherapy in 4 groups was evaluated. There was no significant difference in BMI and NLR. However, ALI assessment showed that ALI had a higher value in the surviving patient group with a statistically significant difference from the group who died in the hospital. **Conclusion:** Patients who died at a hospice or home exhibited significantly longer survival than those that died at hospital. Social background and spiritual factors are also taken into consideration, but ALI before treatment also considered factors that contribute to prognosis.

Keywords: ALI, place of death, palliative care

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-16 MANAGEMENT OF PATIENTS WITH ALK-TRANSLOCATED NSCLC: A SIMULATION-BASED ASSESSMENT OF MEDICAL ONCOLOGISTS' PRACTICE DECISIONS

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Background: The past several years have witnessed unparalleled changes in treatment for patients with ALK-translocated NSCLC. The objective of this study was to evaluate oncologists' competence regarding the use of ALK tyrosine kinase inhibitors in the management of NSCLC and the impact of virtual patient simulation on narrowing gaps in clinical practices. **Method:** A CME certified virtual patient simulation (VPS) was made available via a website dedicated to continuous professional development. The VPS consisted of 2 cases presented in a platform that allows oncologists to assess the patients and make diagnostic and therapeutic decisions supported by an extensive database of diagnostic and treatment possibilities matching the scope and depth of actual practice. Clinical decisions were analyzed using a sophisticated decision engine, and instantaneous clinical guidance (CG) employing up-to-date evidence-base and faculty recommendations was provided after each decision. Oncologists were able to revise each decision post-CG, if desired. Rationales for clinical decisions were also collected in real time. Data were collected between 08/01/2017 and 10/31/2017. **Result:** At the time of assessment, 178 oncologists had fulfilled the participation criteria for completing the simulation. Assessment of their practice choices revealed: · In a patient with newly diagnosed NSCLC, up to 30% of oncologists did not order testing for a tumor's ALK translocation status. Moreover, only 37% ordered the appropriate therapeutic regimen. CG led to a 9% improvement in testing and 20% increase in evidence-based treatment (*P*<.001) Crizotinib remained the initial systemic treatment of choice despite data from the ALEX trial. · In a patient whose disease has progressed on crizotinib with significant disease burden, 24% of oncologists would not discontinue therapy. CG resulted in a 23% improvement in evidence-based treatment decisions (P=0.003). The primary rationales for the selected treatment differed based on the chosen regimen, disease control (26%) for continued treatment with crizotinib, better efficacy profile for the patient (24%) with use of ceritinib, andrecommended by guidelines (25%) for alectinib. · A majority of oncologists initially ordered side effect counseling in each case. CG resulted in a 18% (P=0.014) increase in the case for progression on crizotinib. **Conclusion:** This study, using an immersive VPS, provided insights into oncologists' real world practices, and the rationales behind them, in an evolving treatment landscape and uncovered a lack of clarity about identification of the most appropriate regimen for patients with ALK-translocated NSCLC. Our findings demonstrate a continued need to educate oncologists about how to select and prescribe treatment for these patients.

Keywords: NSCLC, ALK-translocated

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-17 LUNG CANCER SYMPTOM BURDEN AND QUALITY OF LIFE: FINDINGS FROM THE CANCER EXPERIENCE REGISTRY

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Background: Given earlier diagnosis and personalized treatment, lung cancer (LC) survival rates are increasing. LC can be associated with significant emotional distress, which affects health-seeking behaviors and health care utilization. This study examines LC patients' quality of life compared to other US population groups and cancer-related correlates of depression and anxiety. **Method:** 149 individuals with LC enrolled in the Cancer Support Community's online Cancer Experience Registry and completed surveys including the Patient-Reported Outcomes Measurement Information System (PROMIS-29v2.0). Using multiple regression analysis, we identify predictors of PROMIS T-scores for depression and anxiety. Independent variables included sociodemographic factors (age, gender, education, race), clinical history (time since diagnosis, relapse, LC type, line of therapy, currently receiving treatment, type of therapies received), and symptom burden (number of

comorbidities, physical functioning, fatigue, pain interference). Variables significant in bivariate analysis (p<.05) were included in multivariate models. **Result:** The sample was 66% female, 86% White; mean age 62 years (SD=9), mean time since diagnosis 3 years (SD=5). 14% had SCLC, 86% NSCLC. 76% received chemotherapy, 20% immunotherapy; 53% reported current treatment. 23% experienced a relapse, and 42% were ever metastatic. PROMIS scores for LC patients were worse than national averages (95% CI) for anxiety (54.2-57.6), fatigue (55.4-58.8), sleep disturbance (51.6-54.6), physical functioning (39.3-41.9), and social functioning (43.1-46.2). Moreover, LC patients reported worse quality of life (>1*SD*) than the national average for physical functioning (54% of respondents), fatigue (38%), social functioning (34%), anxiety (36%), pain interference (29%), depression (26%), and sleep disturbance (20%). Eight predictors explained 51% of the variance in anxiety (R^2=.51, F(8,121)=15.64 p<.001); and, greater anxiety was associated with female gender (semipartial r=.18, p<.01), lesser time since diagnosis (semipartial r=-.19, p<.01), worse self-reported health (semipartial r=-.17, p<.01), greater fatigue (semipartial r=.22, p<.01), and greater pain interference (semipartial r=.24, p<.001). Nine predictors explained 51% of the variance in depression (R^2 = .51, F(9,119)=13.74, p<.001); and, greater depression was associated with female gender (semipartial r=.17, p<.05), not being treated with immunotherapy (semipartial r=-.18, p<.01), poorer self-reported health (semipartial r=-.14, p<.05), greater fatigue (semipartial r=.25, p<.001) and greater pain interference (semipartial r=.23, p<.01). **Conclusion:** Substantial proportions of LC survivors experience worse health-related quality of life compared to the general U.S. population. Symptom burden, especially fatigue and pain interference, was associated with anxiety and depression. These results suggest the need for more comprehensive symptom management efforts throughout survivorship care, including increased access to palliative and supportive care services.

Keywords: symptom burden, distress, quality of life

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-18 COMPARISON OF PAIN CONTROL EFFECTS AND SIDE EFFECTS EARLY AFTER VATS LOBECTOMY BETWEEN IV-PCA, EPIDURAL-PCA AND ON-Q

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Background: Video-Assisted-Thoracic Surgery (VATS) is widely used as a standard surgical treatment in non-small cell lung cancer (NSCLC), the postoperative pain is reduced rather than before, but postoperative pain management is still important because the pain is a problem in itself and can cause other respiratory complications. So we compared the pain control effects and side effects of intravenous (IV) patient-controlled analgesia (PCA), epidural PCA, and continuous local anesthesia infusion (On-Q), the most commonly used pain management modalities after VATs lobectomy. **Method:** Total 94 patients who underwent VATs lobectomy in this center with NSCLC from January 2014 to August 2015 were analyzed. Of these 94 patients, 28 had epidural PCA, 36 had IV-PCA, and 30 had On-Q for postoperative pain management. The degree of pain was assessed by NPIS (numeric pain intensity scale), and we analyze NPIS from immediate postoperative period to 48 hours after operation by postoperative day. The incidence of side effects associated with pain control devices and early discontinuation due to side effects were analyzed. **Result:** The mean value of NPIS on the day of surgery was 6.04 ± 2.56 in the epidural PCA group, 4.75 ± 2.35 in the IV-PCA group, and 5.27 ± 1.87 in the On-Q group and there was no statistically significant difference. NPIS values were decreased in all three groups until 48 hours postoperatively, but there was no significant difference between groups. The incidence of side effects related to pain control devices up to 48 hours after operation was the highest in the IV-PCA group (36.1%, 13/36), in the epidural PCA group (35.7%, 10/28) and in the On-Q group (10.0%, 3/30) and there was statistically significance (p=0.032). The rate of early discontinuation of the pain control device due to side effects was 33.3% (12/36) in the IV-PCA group, 25.0% (7/28) in the epidural PCA group, and 6.7% (2/30) in the On-Q group (p = 0.032). **Conclusion:** The effects of pain control after VATs lobectomy in NSCLC patients were not significantly different in epidural-PCA, IV-PCA, and On-Q but On-Q was superior in terms of side effects and early discontinuation of pain control device. Continuous extrapleural infusion of local anesthetic via On-Q has less systemic side effects and higher procedural stability than PCA. Therefore, On-Q may be sufficient to replace PCA in pain control after VATs lobectomy in NSCLC patients.

Keywords: NSCLC, Pain control, VATS

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-19 RISK FACTORS FOR OSTEOPOROSIS IN LUNG CANCER PATIENTS

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Background: Bone related disease is increasingly a problem as lung cancer patients are usually older and the survival rate is increasing. Also cancer patients with multiple chronic comorbidities are at risk of osteoporosis (T-score of ≤ -2.5). The purpose of the study is to investigated the risk factors that attribute to osteoporosis of patients with lung cancer. **Method:** We retrospectively investigated the incidence of osteoporosis of lung cancer patients from March, 2017 to April 2018. A total of 124 patients who were diagnosed with lung cancer at one tertiary academic hospital underwent bone mineral density test. **Result:** Among the 124 patients, 40 (32.3%) showed osteoporosis. Alcohol history, smoking history, lung cancer histology, lung cancer stage, bone metastasis, and comorbidity (hypertension, diabetes, coronary artery disease, cerebrovascular accident, and chronic obstructive pulmonary disease) did not differ significantly among the osteoporosis and normal group . In univariate analysis, age (P = 0.025), BMI (P = 0.028), and female (P < 0.001) were statistically significant. In multivariate logistic regression analysis, age (OR: 1.070, 95% CI:1.016-1.126, p = 0.01), BMI (OR: 0.840, 95% CI:0.738-0.956, p = 0.008), and female (OR: 0.142, 95% CI:0.055-0.366, p < 0.001) were also statistically significant. **Conclusion: One-third of lung cancer patients were diagnosed with osteoporosis at a high rate.** Old age, low BMI and female sex were the risk factors affecting osteoporosis of lung cancer patients. Physicians should be aware to of screening bone marrow density of lung cancer patients with old age, low BMI and female group. Studies on the effect of calcium supply and bisphosphonate treatment on bone metastasis and fracture in these osteoporosis patients are underway.

Keywords: osteoporosis, Female, lung cancer

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-20 PALLIATIVE SEDATION IN LUNG CANCER PATIENTS WHOM NEEDS IMMEDIATE OR ELECTIVE INTRACTABLE SYMPTOM CONTROL

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Background: Advanced cancer patients frequently experience high-distressing symptoms which could not be relieved with standard oncological treatment even can be refractory to intensive palliative care. For these cases, palliative sedation or decrease patient's consciousness below certain level (ramsay score 4 or more) is well defined but not well standardized procedure for intractable symptoms of cancer patients. **Method:** The patients included into this study in consecutive way without any exception from November 2014 to August 2017. There were 82 patients (90.0%) and 9 patients (10.0%) with NSCLC and SCLC, respectively. Palliative sedation protocol is consisted of midazolam / morphine (30 mg/24 hr). For the effectiveness of the palliative sedation, we accept taregt RSS score of 4 for the immediate and elective patients. **Result:** There were 62 and 29 patients electively or urgently sedated. Median age of patients in elective and immediate sedation were 61.5 and 63, respectively. Additionally, main etiologies for the refractory symptoms were dyspnea, delirium and intractable pain in 44 (71.0%) vs 3 (4.8%), 15 (24.2%) vs 16 (55.2%), and 6 (20.7%) vs 7 (24.1) patients for the elective and immediate sedation groups. There was no statistically significant difference between two groups with regard to sex, age and main reasons for the palliative sedation. Duration of palliative sedation were 0.59 days in immediate group whereas this time significantly longer in elective group with 4.7 days (p<0.01). Time between last chemotherapy and start of the palliative sedation were 82.3 vs 119.0 days in elective and immediate group, respectively. In elective sedation group, target score of R4 was achieved in 32 (51.6%) patients whereas in immediate sedation group score of R4 was significantly lower than elective group and achieved in only 3 (10.3%) patients, respectively (p<0.01). Dose of 30-30 mg/24-hour IV MaM infusion was perfectly enough for the immediate sedation group , 60-60 mg and 90-90 MaM infusions were required in 10 (16.1%) and 5 (8.1%) patients for target RS. Adverse events were seen in 18 (29%) and 7 (24.1%) patients in elective and immediate group, respectively. Hypotension was the most

prominent adverse event in both groups. **Conclusion:** Palliative sedation is effective way of controlling intractable symptoms. Most common reason for palliative sedation was progressive dyspnea in lung cancer for both groups. 30-30 mg/24-hour IV MaM starting dose well tolerated and highly effective dose, 15/15 mg dose increment can be done if needed.

Keywords: lung cancer, palliative sedation, immediate or elective, intractable symptom

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-21 REAL-WORLD EXPERIENCE OF FIRST-LINE AFATINIB TREATMENT IN PATIENTS WITH EGFR MUTANT ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Published reports of first-line afatinib treatment efficacy, side-effects and resistance mechanism in the real-world setting are lacking. **Method:** A retrospective observational study of patients with *EGFR* mutant advanced non-small cell lung cancer (NSCLC) receiving first-line afatinib in University Malaya Medical Center from 1st December 2014 to 30th April 2018. **Result:** Twenty-two of 33 patients on first-line afatinib were eligible for analysis. The patients' demographic and clinical characteristics are as shown in Table 1. The mPFS was 14.3 months, overall response rate was 86.3% (19/22) and disease control rate was 95.5% (21/22). The median time-to-treatment failure was 16.2 months. The median overall survival has not been reached but 12-month survival rate was 81.8% (18/22). A patient with *exon 18 G719X* and *exon 20 S768I* mutation had received treatment for 23.3 months without disease progression (PD). The PFS of a patient with *exon 20 insertion* was 9 months and of another patient with *exon 18 G719X* and *exon 20 T790M* mutations was 4.4 months. Of patients with brain metastases, the PFS of 2 patients treated with stereotactic radiosurgery (SRS) was 15.9 months and 9 months, respectively while that of a patient who had whole brain radiotherapy (WBRT) and a patient who underwent debulking surgery only was 16.5 months and 2.6 months, respectively. The incidence of side-effects was rash 90.1% (20/22), stomatitis 63.3% (14/22), paronychia 72.7% (16/22), and diarrhea 77.3% (17/22). One (4.5%) patient each had grade 3 diarrhea and cutaneous lesions. Of 17 patients with PD, 2 (11.8%) had PD in the brain. *T790M* mutation was detected in 62.2% (8/13) patients who underwent repeat biopsy.

Demographic and clinical characteristic		First-line Afatinib (n = 22)
Age, years	Mean ± SD	59.3 ± 10.8
Gender, No. (%)	Male	9 (40.1)
	Female	13 (59.9)
Smoking status, No (%)	Never smoker	19 (86.4)
	Ex/current smoker	3 (13.6)
ECOG performance status, No. (%)	0-1	17 (77.3)
	2-4	5(22.7)
Stage, No. (%)	IIIb	1 (4.5)
	IV	21 (95.5)
Symptomatic brain metastases, No. (%)	No	16 (72.7)
	Yes	6 (27.3)
Abnormal organ function, No. (%)	No	21 (95.5)
	Yes	1 (4.5)
EGFR mutation subtype, No. (%)	Exon 19 del	17 (77.3)
	Exon 21 L858R	2 (9.1)
	Rare/complex mutation	3 (13.6)

Conclusion: Afatinib is an effective treatment of EGFR-mutant advanced NSCLC. When combined with SRS or WBRT, afatinib conferred good PFS in patients with symptomatic brain metastases. Severe side effects are uncommon and *T790M* mutation was the commonest resistance mechanism.

Keywords: Real-world data, afatinib, T790M mutation

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-22 VALIDATION OF EUROLUNG RISK MODELS IN A JAPANESE POPULATION: A RETROSPECTIVE SINGLE-CENTER ANALYSIS OF 612 CASES

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Background: The analysis of risk-adjusted outcome is beneficial for quality assessment in surgery as well as preoperative risk stratification. Eurolung risk models are recently reported, large population-based prediction tools of cardiopulmonary morbidity and mortality in patients who underwent anatomic lung resection. This study is aimed to evaluate validity of the models in a Japanese population. **Method:** From 2007 to 2014, 637 anatomic lung resections were performed in our institution. Patients who had induction therapy (n=23) and with missing data (n=2) were excluded from the analysis, and requisite variables (age, sex, body mass index, predicted postoperative forced expiratory volume in 1 s, coronary artery disease, cerebrovascular disease, chronic kidney disease, thoracotomy approach, extended resections, operation of pneumonectomy) were examined. Cardiopulmonary morbidity and 30-day mortality rates were estimated by Eurolung risk models according to the formula for computation (Brunelli A, et al. European risk models for morbidity (EuroLung1) and mortality (EuroLung2) to predict outcome following anatomic lung resections: an analysis from the European Society of Thoracic Surgeons database. Eur J Cardiothorac Surg, 2017; 51: 490-497). Aggregated Eurolung risk scores were also calculated, and patients with similar risk were classified into plural groups. These results were compared with observed outcomes. In addition, we analyzed long term outcomes of the groups using the Kaplan-Meier method. **Result:** Surgical procedures included 9 pneumonectomies, 15 bilobectomies, 483 lobectomies, and 105 segmentectomies. Cardiopulmonary complications of any grade were occurred in 137 cases; this rate was lower than predicted by Eurolung1 (22.4% vs. 28.4%). Within 30 days after operation, 4 fatal cases were experienced, which was significantly lower than expected by Eurolung2 (0.7% vs. 6.9%). Morbidity rate was clearly stratified by Eurolung1 aggregate score as 0% (n=0, score 0-1), 14.7% (n=11, score 2-4), 18.6% (n=30, score 5-7), 21.3% (n=46, score 8-11), 34.5% (n=49, score 12-16), and 33.3% (n=1, score 17-19). Stratification of mortality rate by Eurolung2 aggregate score also developed apparent trend, although the observed number of death was quite small: 0% (score 0-3), 0% (score 4-6), 1.2% (score 7-8), 1.5% (score 9-11), 4.8% (score 12-14), and 0% (score 15-17). The Higher (8-19) Eurolung1 aggregate score group showed poor 5-year overall survival compared with the lower (0-7) score group (72.3% vs. 90.4%, P<0.01). **Conclusion:** Eurolung risk models did not completely match with the morbidity and mortality in our institution. On the other hand, Eurolung1 aggregate score was useful to predict not only morbidity, but also long term outcomes.

Keywords: risk model, lung cancer, Surgery

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-23 DATA MINING THE INTERNET AND CROWDSOURCING IN GUIDING PATIENT DECISION-MAKING.

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Background: The internet, through social media, blogs and forums, has enabled patients to share experiences and outcomes. Data mining and crowdsourcing is a methodological approach to gather the individual experiences within these platforms and convert them into Real World Evidence (RWE) that can help patients make decisions, especially in the case of new treatments or treatments in trial. This abstract is a case study of how this methodology was used to inform the decision between Whole Brain Radiation (WBR) vs. osimertinb in treating brain metastasis in EGFR+, t790M, NSCLC – at a time when the results to an open label

trial were pending. **Method:** The methodology identified trusted sources and similar profiled patients. The steps: 1. Identify reputable on-line sources by referrals. 2. Crowdsource peers with same tumour group, staging, gene sequence and treatment path. 3. Analyze results and patient feedback of treatments A search identified 46 lung cancer blogs and 4 cancer forums. Inspire.com was then chosen as the crowdsourcing target as it had over 39,000 lung cancer patients registered. **Result:** The search found 470 posts on osimertinib in clinical trial; 66 discussions on brain lesions and osimertinib were accessible from the search. Conversations with patients of the same genetic profiles, metastasis and treatments were selected. The user profiles detailed clinical histories, which increased the trust factor of the data. Information was obtained from April to June 2016 with data points beginning in 2014. When reviewing the 66 self-reported cases, it was found that osimertinib was effective in patients with brain metastases in 36% of patients while 4% had no response. Quality of life and side effects were other fields that were explored. This evidence influenced the patient to choose osimertinib instead of WBR to treat her lung cancer. **Conclusion:** The Internet offers opportunities to source evidence and help patients to make informed treatment decisions. There is a risk that misinformation may lead patients in the wrong direction, which will then be a burden on the practitioner and negatively influence treatment outcomes. Datamining and crowdsourcing is a methodological system that gathers individual self-reported results from the Internet and converts it into credible RWE. For this patient, it increased the trustworthiness of the information and helped decrease anxiety about the treatment decision. Used appropriately, it has the potential to inform treatment decisions, help predict outcomes, and be a tool for post marketing surveillance that can be used to inform health technology assessment.

Keywords: support, Treatment decision, Real World Evidence

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-24 RAMATHIBODI LUNG CANCER CONSORTIUM (RLC) MODEL: MULTIDISCIPLINARY TEAM APPROACH IMPROVES LUNG CANCER PATIENTS' SURVIVAL OUTCOME

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Background: Technologies for investigation, diagnosis, and treatment for lung cancer are advance to improve patients' survival. Many investigations will be performed once the patients were suspected to have lung cancer. All processes sometime take a long time to complete investigations before starting the treatment which may affect treatment outcomes. **Method:** Ramathibodi Lung Cancer Consortium (RLC) was established in October 2014, aims to help the patients accessing all investigations and treatments faster by multidisciplinary team (MDT) approach and patient-center with one-stop service system. We conduct RLC meeting every 1st and 3rd Tuesday of the month. As of May 2017, 200 new lung cancer patients were solved all problems by RLC team. We collected and analyzed the data of lung cancer patients between 2 groups. The first group was the patient whom underwent RLC model (160 cases) and the second group was control group which was the patient whom diagnosed before establishing RLC (72 cases). Our primary endpoint was time from first visit to first treatment. Secondary endpoints were time from first visit to first interventions, number visits from first visit to first treatment, and overall survival (OS). We also did subgroups analysis for time from first visit to first biopsy, to first imaging study, to surgery, to chemotherapy, and to radiation. **Result:** Median time from first visit to first treatment was significantly decreased in RLC group (14 days) compared to 57 days in control group with HR of 2.86 (95% CI; 2.11-3.87, $P<0.001$). Median time from first visit to first intervention was also significantly decreased in RLC group (2 days) compared to 11 days in control group with HR of 2.01 (95% CI; 1.53-2.62, $P<0.001$). Median number of hospital visits was significantly lower in RLC group (1 visits) compared to control group (8 visits). All subgroup analyses showed significantly decreased duration of each investigation and each treatment in RLC group. In survival analysis, lung cancer patients whom underwent RLC model had significantly longer mOS compared to control group, especially in stage 3 and 4 disease [mOS = 2.4 vs 0.8 years, HR=0.42 (95% CI; 0.3-0.7, $P<0.001$)]. **Conclusion:** RLC model is a very useful model helping lung cancer patients to access treatment and investigations in short period of time and translate to have significantly longer survival. RLC model also provides the cooperation in lung cancer research. This model should be applied for all cancers treatment. Working as MDT is the utmost importance for cancer treatment.

Keywords: multidisciplinary team, lung cancer, patient-center system

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-25 ASSESSMENT OF DEPRESSION AMONG ADVANCED STAGE LUNG CANCER PATIENTS IN DEVELOPING COUNTRY

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Background: Lung cancer is most common cancer and leading cause of death in developing country. Among lung cancer patients, depression is common and has been associated with increased morbidity and mortality. **Method:** The study was conducted in 79 patients diagnosed with advanced stage lung cancer attending medical oncology department of B. P. Koirala Memorial Cancer Hospital, Nepal. A set of questionnaire was used to interview and collect the data. Beck's Depression Inventory (BDI-II) and its Nepali translated transcript was used to assess the depressive symptoms of patient. Based on score, depression was classified as Minimal depression, Mild Depression, Moderate Depression and Severe Depression. Verbal consent was taken before each interview to address the rights of the patient. **Result:** This study revealed lung cancer was predominant in male patients (55.7%). Patients age ranged from 42 years to 81 years with mean age 65.59 years. Among all the patients evaluated only 45/79 (57%) patients were aware of their disease status. 34 patients were unknown about their diagnosis. All the patients evaluated were found to be depressed in several degrees. 11/79 (13.9 %) of the patients had minimal, 27/70 (34.2%) had mild, 12/79(32.30%) had moderate and 29/79 (36.7%) had severe forms of depression. Depression was common in both sexes. Interestingly most of patients who were explained about their disease status had moderate to severe depression but those patients who were unknown about their disease status tend to have minimal to mild depression (table 1). The association between awareness of disease status and severity of depression were statistically significant.

Table: 1
Number of patients with different degree of depression based on awareness of disease status

	Minimal	Mild	moderate	severe
Unaware of disease status	11	21	2	0
Aware of disease status	0	6	10	29

Conclusion: The study reveals that there is high prevalence of depression among lung cancer patients in developing country. Thus all lung cancer patients need screening and appropriate management for depression also.

Keywords: Beck's Depression Inventory, lung cancer, depression

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-26 SAFETY OF NIVOLUMAB IN THORACIC MALIGNANCIES: RESULTS FROM A SINGLE INSTITUTION IN BANGLADESH

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Background: Nivolumab, an anti-PD-1 monoclonal antibody (IgG4), has emerged as a promising drug in the era of immunotherapy of today. Recent trials have demonstrated encouraging activity with favorable safety profile of nivolumab in patients with treatment-refractory lung cancer as well as esophageal cancer. However, experience of using immunotherapy is still quite new in a developing country like Bangladesh owing to its excessive cost and unavailability. **Method:** A total of 3 patients have been treated with nivolumab at a dose of 3mg/kg every

2 weeks to date at our centre. Evidence of PD-L1 expression was not present in either of the patients. All were within the ECOG performance status ≤2, and none of them were on systemic corticosteroids or immunosuppressive therapy. First case: a 48-year old male, adenocarcinoma lung with brain metastases, TTF-1 positive and EGFR negative, was treated initially with craniotomy followed by whole brain irradiation. 4 cycles of pemetrexed/carboplatin followed by 6 cycles of maintenance pemetrexed were given but the disease progressed. Then he completed 4 cycles of docetaxel which again resulted with progressive disease (PD). Now he is on nivolumab, 6 cycles completed to date. Second case: A 62-year old female, adenocarcinoma lung with contralateral lung metastases, EGFR and ALK negative, was treated initially with concurrent chemoradiation with 3 cycles of pemetrexed/cisplatin. As the disease progressed, 4 cycles of docetaxel/carboplatin were given which again showed PD. Now he is on nivolumab, cycle-6 completed to date. Third case: A 75-year old male, squamous cell esophageal cancer at lower 3rd, was non-surgical and non-chemo candidate because of uncontrolled diabetes and significant cardiac comorbidity. Nivolumab was started, and received 2 cycles. **Result:** In the first and second cases, 'stable disease' was achieved with no serious immune-mediated reactions over the period of nivolumab therapy. When evaluated with Common Terminology Criteria for Adverse Events (CTCAE version 4.03), only grade-1 elevated creatinine was seen in both patients. There was no reported toxicity of endocrinopathy, enterocolitis, intestinal perforation, hemorrhage, neuropathy, pneumonitis, hepatitis or dermatitis. In the third case, patient developed, 7 days after cycle-2, grade-3 diarrhea along with hematemesis and hematochezia. On arrival at our emergency department, he was found to be life-threatening grade-4 enterolcolitis and he died before undergoing any intervention. **Conclusion:** Nivolumab may delay disease progression with minimal toxicity but may sometimes be associated with severe immune-related events. Practice should be done with caution and prompt action is warranted once toxicity has developed in order to prevent fatality

Keywords: Nivolumab, lung cancer, esophageal cancer

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-27 INITIAL RESPONSE TO FIRST LINE TREATMENT IS THE BEST PREDICTOR OF THE PATIENT SURVIVAL IN ADVANCED NSCLC

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Background: Although most of the NSCLC patients are treated according to the standart guidelines, the patients who present in routine clinical practice usually have inferior performance status, in comparison to the patients registered in the clinical trials. Also in comparison, the frequency and thoroughness of the tests and procedures the clinical trial patients subjected are more intense as well. The oncologist practising in community needs simpler ways and means to assess patients' disease course to make timely and reliable judgement on their management. **Method:** We searched among 5130 patients treated in our clinic since 2006 to find 678 lung cancer patients of all stages and pathology. Of these, 171 advanced stage NSCLC patients that were treated primarily under our supervision are selected for the calculations. The other histologies and the patients seen once or twice for a second opinion are excluded. The common patients characteristics including age, gender, stage, date of diagnosis, the date of progression, the site and the number of metastasis etc. are all recorded. **Result:** The median age of the patients were 62, 23% were female, the median overall survival was 18 months. The majority did not receive any targeted immunotherapy because either it did not exist back then or they had access problems in more recent times. We did then univariate/moltivariate analysis of survival according to the age, gender, site of metastasis, platin vs non-platin based treatment and response to first line of chemotherapy. Of these, only the response to first line of therapy appeared as a statitically significant variable, 23 vs 14 months with p=0.0001. In over 90% of the patients, the radiological findings were in line with clinical picture. **Conclusion:** Although more complex and costly measures exist to predict the overall survival of the NSCLC patients, in our experience the clinical responsiveness to first line of chemotherapy most precisely predicted the overall survival. This simple measure may help the healthcare profesionals to understand the disease course of the patients and manage their needs in more proper fashion.

Keywords: lung cancer, survival, chemotherapy

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-28 PROGNOSTIC NUTRITIONAL INDEX FOR PREDICTING POSTOPERATIVE COMPLICATIONS AFTER SURGERY THORACIC TUMOR INVOLVING THE NEIGHBORING STRUCTURES

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Background: The prognostic nutritional index (PNI), which is scored based on laboratory data of albumin and lymphocyte count, predicts postoperative complications in various types of malignancies. This study aimed to assess the risk factors of postoperative complications, especially the preoperative immune nutritional condition as estimated with the PNI, after surgical treatment of patients for thoracic tumor involving the neighboring structures. **Method:** From July 2008 to December 2015, 159 patients with resected thoracic tumor involving the neighboring structures were retrospectively analyzed and the relationship between the preoperative PNI and postoperative complications was evaluated. There were 119 men and 40 women with a median age of 61 years (range 21–88 years). Invading neighboring structures, including chest wall, superior sulcus, diaphragm, tracheal carina, left atrium, superior vena cava, aorta, and vertebrae were performed when possible in patients with locally advanced disease. **Result:** Multivariate logistic regression analysis revealed that a preoperative PNI was a significant independent predictor of postoperative complications of Clavien-Dindo Grade ≥II (odds ratio:3.87, p=0.0489). Using receiver-operating characteristics curve analysis predicting postoperative complications, we established cutoff values 46 (Area Under the Curve; 0.61) for the PNI. Patients were divided into two groups according to the preoperative PNI: high (≥46; n=95 (59.7%)), low (<46, n=64 (40.3%)). The incidence of postoperative complications of Grade ≥ II and Grade ≥III was higher in the low PNI groups than in the high PNI groups (p=0.019 and p=0.009, respectively). The incidence of pneumonia and the length of postoperative hospital stay were significantly higher in the low PNI groups than in the high PNI groups. However, the 30 day mortality (1.88%) and 90 day mortality (4.40%) were not correlation with PNI. **Conclusion:** The preoperative PNI might be a useful marker to predict the risk of postoperative complications after surgery for thoracic tumor involving the neighboring structures. We have to intensive attention to the low PNI patients in the perioperative management.

Keywords: prognostic nutritional index (PNI), postoperative complications, Advanced surgical techniques

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-29 DEFINING THE SYMPTOM BURDEN OF NON-SMALL CELL LUNG CANCER

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Background: Symptom burden is disease and treatment symptom severity and its impact on daily functioning. Symptom monitoring has demonstrated improved cancer patient outcomes, including quality of life, resource utilization, ability to continue treatment, and survival. The use of disease-specific patient-reported outcomes (PRO) measures facilitates individualized symptom monitoring and management. The purpose of this study was to describe symptom experience from the patient perspective and identify key symptoms for a PRO measure of non-small cell lung cancer (NSCLC) symptom burden. **Method:** Patients with NSCLC described their symptom experience in single qualitative interviews. Content analysis was used to define the content for a PRO measure of NSCLC symptom burden. **Result:** Mean age of the 40 patients interviewed was 66.1 years (standard deviation = 10.9); 60.0% were male, 77.5% were white, and 56.4% had stage IV disease. Content analysis found a total of 32 symptoms, 6 reported by ≥ 20% of participants (see Table 1). Symptoms varied based on treatment modality (chemotherapy versus radiation therapy), but not stage of disease. Numbness or tingling and sore mouth were described only by patients who had received chemotherapy. Patients volunteered ways in which symptoms impacted daily activities and relationships. (See next page)

Table 1. Patient quotes from qualitative interviews describing the 6 most common symptoms (reported by ≥ 20% of participants)	
Symptom	**Participant Quote**
Shortness of breath	"The heaviness, it's like a—wow, I don't know how to explain it—like a rock and hard to breathe sometimes, just shortness of breath. Of course, the more I try to walk, or whatever, I'm more short of breath." - 67-year-old female
Cough	"I had a real bad cough. I think I actually even broke a couple of ribs coughing so much." - 52-year-old male
Distress	"Terrifying. There's no ways about it. You know, it's a terrifying experience, especially when it's dropped in your lap and you have to deal with it. You go through a lot physically and mentally." - 67-year-old male
Fatigue	"I'm more tired. I take a lot of naps where I never had been a nap person. Before I had all my energy, and I was doing lots of things, and now I'm wore out. I wake up, and I'm wore out." - 53-year-old male
Pain	"You keep trying to move it to make it feel better and no matter where you put it, it doesn't feel any better … most of the time it will bother me after I get out of bed in the morning for a while. And then if I go try to take a nap, I'll go ahead and take something for pain because I can't lay there and—I just keep moving it and moving it and nothing helps." - 68-year-old male
Constipation	"I didn't have a bowel movement. I had always taken the stool softeners because they told me to do that. And I kept thinking, "Well, it's going to work. It's going to work." Finally, I was in so much pain that I couldn't stand anymore, so I went to the hospital … and they ended up physically removing, which was horrible." - 68-year-old female

Conclusion: Patients with NSCLC experience numerous symptoms related to disease and treatment. Shortness of breath, cough, distress, fatigue, pain, and constipation were commonly reported symptoms, suggesting that clinicians should routinely and proactively monitor the presence and severity of these symptoms in NSCLC clinical care. In patients receiving chemotherapy, attention to specific treatment-related symptoms, including symptoms of neuropathy and sore mouth, is needed. While stage of disease does not produce unique symptoms, the severity of the symptoms may possibly vary by stage of disease. Clinicians should also be aware that symptoms result in interference with daily activities, relationships, life plans, treatment adherence, and mood.

Keywords: non-small cell lung cancer, symptoms, qualitative

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-30 TREATMENT PATTERNS AND SURVIVAL OF PATIENTS WITH STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC) IN THE ERA OF NOVEL THERAPIES

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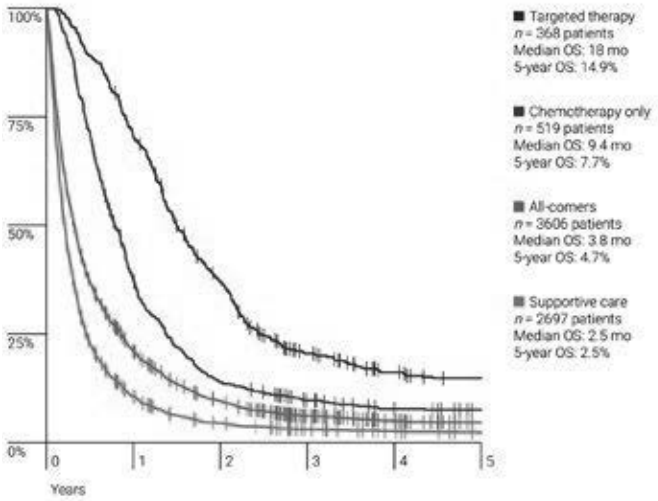
Background: Treatment strategies for metastatic non-small cell lung cancer (NSCLC) are evolving rapidly. Real–world evidence (RWE) of treatment patterns and outcomes can further our understanding of the impact of novel therapies. In this population-based study, we investigated treatments and outcomes for stage IV NSCLC in a large Canadian province. **Method:** Patients diagnosed with *de novo*stage IV NSCLC from April 1st2010 to March 31st2015 were identified. Baseline characteristics, treatments, and outcomes were analyzed. We classified treatments targeting EGFR, EML4–ALK, and ROS1 as targeted therapy and intravenous checkpoint inhibitors as immunotherapy. **Result:** A total of 6,438 patients were identified with NSCLC, of whom 3,606 (56%) had *de novo*stage IV disease. The median age of diagnosis was 69 years (range 20–100) and 52.4% were male. The median age among those who received targeted therapy and immunotherapy were 63 (27–90) and 61 (37–72) years, respectively, and 41.8% and 61.8% were male, respectively. First line treatments were: 5.7% targeted agents (n= 204), 1% immunotherapy (n = 1), 19.5% palliative chemotherapy (n= 703), 6.8% palliative radiotherapy (n= 246), and 74.8% received supportive care only (n= 2,698). Most frequent subsequent treatments in 2L included: 30.7% targeted agents (n= 125), 1.7% immunotherapies (n= 7), 67.6% palliative chemotherapy (n= 275), 32.2% palliative radiotherapy (n= 131). Median overall survival (mOS) for the whole cohort was 3.8 months (0–not reached [NR]). MOS with targeted therapies was 18 months (1.4–NR), chemotherapy was 9.4 months (1.1–NR) and supportive care only had a mOS of 2.5 months (0–NR) (Figure 1). About 1.0% of patients (n= 34) received immunotherapy at any line.



Conclusion: Survival benefit was dependent on type of treatment received, with a trend towards improved survival with newer agents.

Keywords: NSCLC, metastatic, outcomes

P3.15 TREATMENT IN THE REAL WORLD - SUPPORT, SURVIVORSHIP, SYSTEMS RESEARCH
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P3.15-31 BETTER CLINICAL OUTCOMES AND RESISTANCE MECHANISMS OF CRIZOTINIB IN ALK-POSITIVE NON-SMALL CELL LUNG CANCER

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Background: Advanced anaplastic lymphoma kinase (ALK) fusion-positive non-small cell lung cancers (NSCLCs) are effectively treated with ALK tyrosine kinase inhibitors (TKIs). However, clinical outcomes and acquired resistance were unclear. This study was to show the clinical outcomes and resistance mechanisms of crizotinib in ALK-Positive Non-Small Cell Lung Cancer (NSCLC) **Method:** From Fab 2, 2013 to Mar 10, 2018, 2360 patients in Hunan Cancer Hospital were enrolled in this project. We identified 90 ALK-positive NSCLC patients which were detected by Ventana (Roche) and Nex-generation sequencing with known ALK variants were selected for target patients. ALK resistance mutations and clinical outcomes on Crizotinib were retrospectively evaluated according to ALK variant and detection methods. Subgroups of brain metastasis, multiple gene mutation, uncommon rearrangement and concomitant mutation and dual rearrangement were also been evaluated. Nomograms for predicting survival in ALK-Positive NSCLC was also been built. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: resistance mechanisms, ALK-Positive Non-Small Cell Lung Cancer, Better Clinical Outcomes

P3.16-01 A MULTI-OMIC STUDY REVEALS BTG2 AS A RELIABLE PROGNOSTIC MARKER FOR EARLY-STAGE NON-SMALL CELL LUNG CANCER

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Background: B-cell translocation gene 2 (*BTG2*), which functions as a tumor suppress gene, has been reported to be involved in several cancers. However, no study has focused on its role in lung cancer progression or prognosis. We aimed to investigate the role of *BTG2* in early-stage non-small cell lung cancer (NSCLC) survival **Patients and Methods:** This study included 1,230 early-stage (I, II) surgically treated NSCLC patients with methylation and expression data from five international cohorts. We built a prognostic model based on BTG2 methylation. Then, we explored BTG2 expression and NSCLC survival in 3,038 cases, including the above-mentioned cohorts as well as 17 extended public datasets by meta-analysis. Further, we integrated the clinical information, expression, and methylation to build an integration model and evaluated its prediction ability using C-index. **Result:** Three risk CpG probes (cg01798157, cg06373167, cg23371584) were associated with overall survival. The prognostic model based on methylation could distinguish patient survival in the four cohorts [hazard ratio (HR) range, 1.51 to 2.21] and the independent validation set (HR = 1.85). In the expression analysis, BTG2 acted as a tumor-suppress gene in each cohort (HR range, 0.28 to 0.68). A meta-analysis showed high BTG2 expression was associated with better survival (HR = 0.61, 95%CI: 0.54-0.68). The three CpG probes were all negatively correlated with BTG2 expression. Further, the integration model based on BTG2 methylation, expression and clinical information showed a better prediction ability in the training set and validation set. **Conclusion:** The methylation and integrated prognostic signatures based on BTG2 are stable and reliable biomarkers for early-stage NSCLC. They may have new applications for appropriate clinical adjuvant trials and personalized treatments in the future.

Keywords: BTG2; non-small cell lung cancer; prognosis; methylation; expression

P3.16-02 PHASE III STUDY OF CANAKINUMAB (ACZ885) AS ADJUVANT THERAPY IN PATIENTS WITH SURGICALLY RESECTED NSCLC

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Background: Preclinical and clinical data suggest that cytokines such as interleukin (IL)-1β can promote angiogenesis and tumor growth, and are essential to tumor invasiveness. Canakinumab (ACZ885) is a high-affinity human IgGκ anti-IL-1β monoclonal antibody approved for patients with various IL-1–driven auto-inflammatory diseases. In the Phase III Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) in patients with atherosclerosis, canakinumab was associated with a significant reduction in the incidence of fatal and non-fatal lung cancer in patients with increased high-sensitivity C-reactive protein levels. ACZ885T2301 (NCT03447769) is evaluating the efficacy and safety of adjuvant canakinumab versus placebo in patients with surgically resected non-small cell lung cancer (NSCLC). **Method:** This Phase III, randomized, double-blind, placebo-controlled study is enrolling patients (≥18 years, Eastern Cooperative Oncology Group Performance Status ≤1) with completely resected (R0) American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) v.8 stages II–IIIA and IIIB (T >5 cm and N2) NSCLC, who have completed standard-of-care adjuvant treatments, including cisplatin-based chemotherapy and mediastinal radiation therapy (if applicable). Prior treatment with neoadjuvant chemotherapy or radiotherapy is not permitted. Approximately 1500 patients will be randomized 1:1 to receive canakinumab (200 mg every 3 weeks [Q3W], subcutaneous [s.c.]) or placebo (Q3W, s.c.) on Day 1 of 21-day cycles for 18 cycles or until disease recurrence, unacceptable toxicity, treatment discontinuation at the discretion of the investigator or patient, death, or loss to follow-up. Following baseline screening, imaging assessment will be performed every 12 weeks for the first year (treatment phase) following Cycle 1 Day 1, then every 26 weeks during Years 2 and 3, and annually during Years 4 and 5 (post-treatment surveillance phase). Randomization will be stratified by AJCC/UICC v.8 stage, tumor histology, and region. The primary objective is to compare disease-free survival (DFS) in the canakinumab versus placebo arms, as determined by local investigator assessment. Secondary objectives include a comparison of the two treatment groups with respect to overall survival (key secondary objective), lung cancer-specific survival, safety, pharmacokinetics and immunogenicity of canakinumab, and patient-reported outcomes. Exploratory objectives include assessment of the relationship between pharmacokinetics, pharmacodynamics, safety, and efficacy, and evaluation of correlation between cytokines/soluble markers and efficacy endpoints. Enrollment is ongoing. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Canakinumab, ADJUVANT, NSCLC

P3.16-03 UNCOMMON EGFR MUTATIONS AS A WORSE PROGNOSTIC FACTOR FOR SURGICALLY RESECTED LUNG ADENOCARCINOMA

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Background: The characteristics and prognosis of patients with lung adenocarcinoma harboring uncommon epidermal growth factor receptor (*EGFR*) mutations have not been clarified. Here, we examined whether the presence of uncommon *EGFR* mutations is a prognostic factor for patients treated surgically. **Method:** In this multi-institutional retrospective cohort study, clinicopathological data were collected from 1,463 patients who underwent complete surgical resection for lung adenocarcinoma between 2005 and 2012 at five institutions and were examined for *EGFR* mutation status. Differences in postoperative overall survival (OS) and recurrence-free survival (RFS) according to *EGFR* mutation status were evaluated. **Result:** Of 1,031 eligible patients, 500 (48.5%), 497 (48.2%), and 34 (3.3%) had wild-type *EGFR* (WT), common *EGFR* mutations (CMs), and uncommon *EGFR* mutations (UCMs), respectively. In the UCM group, 19 patients had a single mutation, including exon 18 G719X (n = 7), exon 20 T790M (n = 6), or exon 21 L861Q (n = 5), and 15 patients had compound mutations. The clinicopathological characteristics were not significantly different between the CM and UCM groups. The 5-year OS rates in the WT, CM, and UCM groups were 76.3%, 88.6%, and 68.4%, respectively. OS was significantly shorter in the UCM than CM group (p = 0.011), although no significant difference was observed between the UCM and WT groups (p = 0.83). The 5-year RFS rates in the WT, CM, and UCM groups were 63.7%, 75.4%, and 58.1%, respectively. RFS was significantly shorter in the UCM than CM group (p = 0.006), although no significant difference was observed between the UCM and WT groups (p = 0.41). The use of *EGFR*–tyrosine kinase inhibitors after recurrence did not affect the prognosis with respect to *EGFR* mutation type. Among those with single mutations in the UCM group, patients harboring T790M were younger, more likely to be males and smokers, and more likely to have a larger tumor size, lymph node metastasis, pleural invasion, and lymphovascular invasion, compared with those harboring G719X or L861Q. T790M was also associated with shorter OS and RFS; the 3-year OS rates were 50.0%, 83.3%, and 100% and the 3-year RFS rates were 16.7%, 71.4%, and 80.0% for patients harboring T790M, G719X, and L861Q, respectively. **Conclusion:** Among patients with surgically resected lung adenocarcinoma, OS and RFS were significantly shorter in those with UCMs compared with CMs, implying that UCMs may be a worse prognostic factor.

Keywords: Surgery, Prognosis, uncommon EGFR mutation

P3.16-04 COMPARISON OF 2D AND 3D CONSOLIDATION TO TUMOR RATIOS TO PREDICT LESS INVASIVE LUNG ADENOCARCINOMA

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Background: Increases in lung cancer screening with computed tomography have led to more frequent detection of lesions like early stage lung adenocarcinomas. Patients with a ground-glass nodules(GGN) dominant small lesion have an excellent prognosis after complete resection. The consolidation to tumor diameter ratio(d-CTR) is a widely utilized 2D radiological parameter, and lesions with d-CTR<0.5 are candidates for segmentectomy instead of lobectomy. However, the radiological and pathological features of an adenocarcinoma can be contradictory. Some lesions diagnosed as a pure GGN may actually be invasive adenocarcinomas. The purpose of this study was to compare 2D and 3D parameters of lesions to identify less invasive pathological Stage I adenocarcinoma. **Method:** We retrospectively evaluated 42 lesions from 41 patients who underwent curative resection for pathological Stage I adenocarcinoma from May 2016 to December 2017 at Sakaide citizen hospital. We defined Adenocarcinoma in situ and minimally invasive adenocarcinoma as less invasive histological subtypes. Besides, we defined lesions exhibiting lymphatic or vascular invasion as invasive lesions. The 2D parameter was the d-CTR. The 3D parameter was the volume ratio of the solid part to the whole tumor(v-CTR). We used a cut-off value of 0.5 for the 2D parameter, and then cubed that value to obtain a cut-off of 0.125 for the 3D parameter. **Result:** There were 29(69.1%) invasive histological subtypes lesions, 8(19.0%) lymphatic invasion lesions and 11(26.2%) vascular invasion lesions. There were 20(47.6%) lesions d-CTR<0.5, and 12(28.6%) lesions v-CTR<0.125. The 20 lesions with d-CTR<0.5, compared to the 22 with d-CTR>0.5, were significantly more likely to be less invasive histological subtypes(p<0.0001), exhibit no lymphatic invasion(p=0.0009), or exhibit no vascular invasion(p=0.0005). In multivariate analysis, having a d-CTR<0.5 was a significant predictive factor for less invasive lesions. Similarly, the 12 lesions with v-CTR<0.125, compared to the 30 with v-CTR>0.125, were more likely to be less invasive histological subtypes(p<0.0001), exhibit no lymphatic invasion(p<0.0001), or exhibit no vascular invasion(p=0.0014). However, the 8 lesions with v-CTR>0.125, despite having d-CTR<0.5, all had invasive histological subtypes(p=0.0009). **Conclusion:** The values d-CTR<0.5 and v-CTR<0.125 could be predicted factor of less invasive lesions in early-stage lung adenocarcinomas. Furthermore, the study suggested that the 3D CTR parameter is more accurate than the 2D CTR parameter for making these predictions.

Keywords: lung cancer, Consolidation to tumor ratio, Limited pulmonary resection

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.16-05 A NANOTECHNOLOGY-ENABLED STRATEGY FOR IMAGE-GUIDED TRANSBRONCHIAL AND TRANSPLEURAL PHOTOTHERMAL THERAPY OF PERIPHERAL LUNG CANCER

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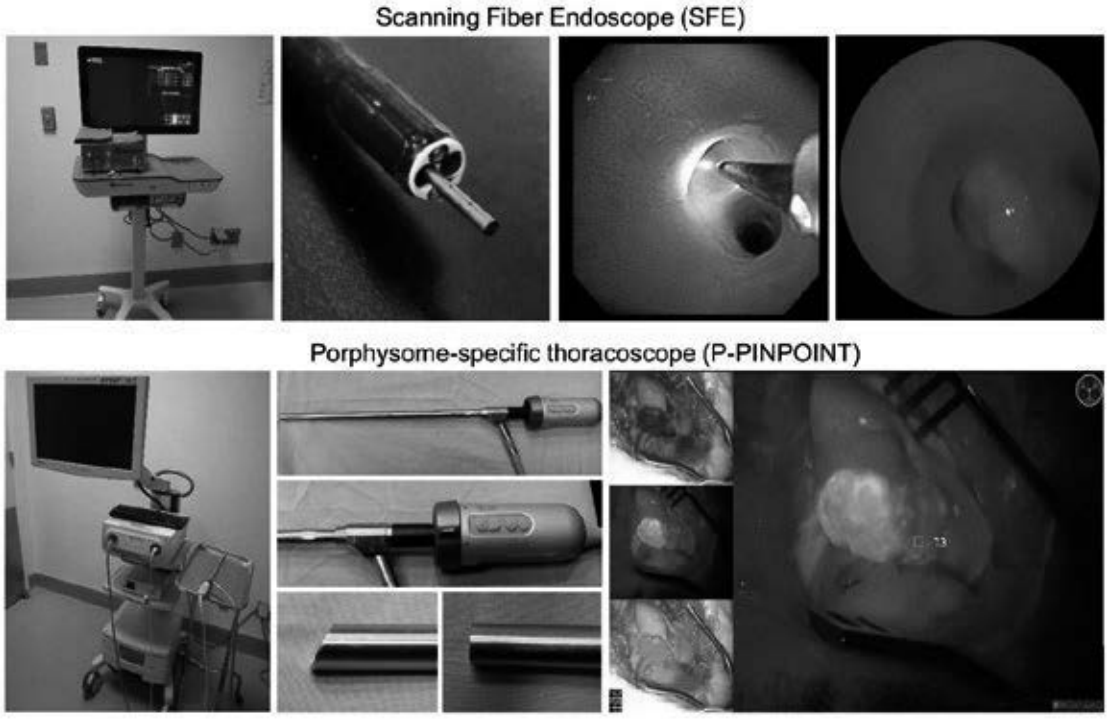
Background: Surgical resection has been established as standard of care for early-stage peripheral non-small cell lung cancer (NSCLC). However, the development of non-surgical treatment and minimally invasive therapeutics is urgently needed due to the known morbidity of surgery, particularly in high-risk patients. We have previously demonstrated the potential of porphysome nanoparticle-enabled fluorescence-guided photothermal therapy (PTT) of peripheral lung cancer in preclinical animal models. In an effort to prepare this technology for clinical application, we developed a porphysome-specific fiberscope (scanning fiber endoscope [SFE]) and porphysome-specific thoracoscope (P-PINPOINT), both capable of operating in fluorescence mode, for image-guided transbronchial and transpleural PTT to treat endo-/peribronchial and subpleural tumors respectively. **Method:** In our study, we used three animal models: an *in vivo* human lung cancer xenograft (A549) in mice, another *in vivo* orthotopic VX2 tumor in rabbits, and an *ex vivo* pig lung into which A549 tumor tissue was transplanted. Forty-eight hours after intravenous injection of the porphysomes, the animals were used for imaging evaluation by SFE and P-PINPOINT, followed by photothermal ablation. **Result:** The SFE, whose 1.2mm diameter is small enough to pass through the working channel of a conventional bronchoscope, could visualize porphysome-laden tumors located inside or close to the peripheral bronchial wall. The P-PINPOINT system had high sensitivity for porphysome fluorescence and enabled image-guided thoracoscopic resection of porphysome-accumulated tumors close to pleural. Porphysomes also enhanced the efficacy of SFE-guided transbronchial PTT and P-PINPOINT-guided transpleural PTT, resulting in selective and efficient tumor tissue ablation in the rabbit and pig models. **Conclusion:** These promising results suggest potential in the clinical translation of this novel platform to impact non-surgical and minimally invasive treatment options for early-stage peripheral lung cancer. This could offer new strategies for the treatment of non-small cell lung cancer.

Keywords: Image-guided therapy, PTT, Nanoparticle



P3.16-06 DOES COMPREHENSIVE MUTATION ANALYSIS ADD PROGNOSTIC VALUE IN RESECTED EARLY STAGE LUNG ADENOCARCINOMA?

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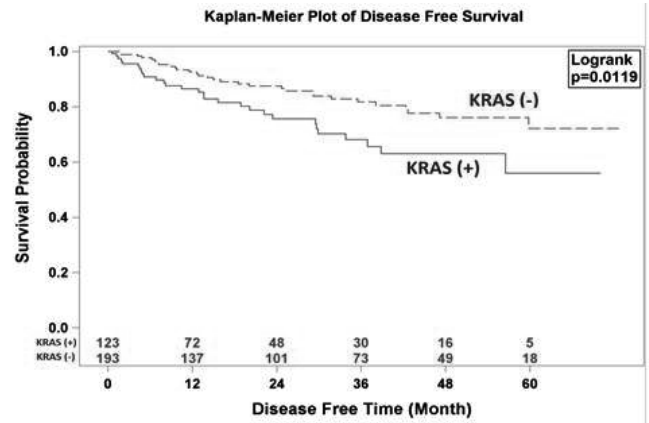
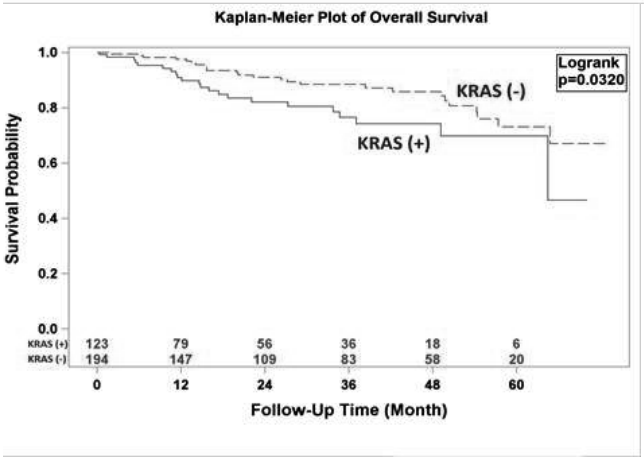
Background: Recent efforts have been directed to enhance staging of non-small cell lung cancer by including common or targetable mutations. However, the predictive value of isolated mutations has been inconsistent between studies, possibly related to mutation interactions, confounding, and heterogeneous patient cohorts. We sought to determine the prognostic role of common mutations in resected early stage lung adenocarcinoma patients. **Method:** Lung cancer mutation panel (PULMOL) using next generation sequencing was routinely obtained on tumors of 317 patients who underwent lobectomy and mediastinal lymphadenectomy for stage I-II adenocarcinoma from 2011-2017. Frequency of mutations was determined, and association with disease-free survival (DFS) and overall survival (OS) following complete resection was tested using Cox regression analysis. **Result:** At total of 248 (78%) patients had at least one mutation, 20% had two or more detected mutations. KRAS and EGFR genes were most frequently affected, in 39% and 24% of patients. EGFR mutations were almost exclusively seen in KRAS-negative patients, except for nine KRAS+/EGFR+ patients. TP53 mutation was the most common co-existing mutation in 59% of cases. Other frequent mutations were MET (6%), BRAF (5%), HRAS (4%), and ALK rearrangement (3%). KRAS mutation, and presence of two or more mutations were the only molecular predictors of decreased DFS and OS on univariate analysis (Figure). In a multivariate model, adjusting for pathologic stage, smoking status, histologic subtype, tumor factors and adjuvant therapy, KRAS and EGFR mutations were independently associated with decreased DFS (KRAS, HR 2.84 [95%CI:1.28-6.30]; EGFR, HR 3.24 [95%CI:1.40-7.48]) and OS (KRAS, HR 2.95 [95%CI:1.35-6.42]; EGFR, HR 2.87 [95%CI:1.25-6.61]).





Conclusion: Routine mutation analysis may yield important prognostic information in patients with completely resected early stage lung adenocarcinoma and may enhance staging when accounting for other known prognostic factors. KRAS mutation was the strongest predictor of worse survival. The prognostic value of EGFR should be further explored in KRAS-negative tumors.

Keywords: Adenocarcinoma, Mutation Analysis, Prognosis

P3.16-07 THE IMPACT OF CLINICAL AND MOLECULAR PROFILE OF RESECTED EGFR-MUTANT NON-SMALL CELL LUNG CANCER ON THE RISK OF DEVELOPING BRAIN METASTASES

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Background: Brain metastases are common in non-small cell lung cancers (NSCLC) with activating *EGFR* mutations (EGFRm), occurring in 44%-63% of patients. To date, there are no known clinical or molecular factors to predict the risk of brain metastases in these patients. **Method:** In this retrospective single-institution study, we identified 106 patients with *EGFR*m NSCLC who underwent surgery for primary lung tumor. Clinical and demographic data was collected from electronic records. Whole Exome Sequencing (WES) of the primary tumor was performed utilizing the Agilent SureSelect Exome v6+COSMIC baits followed by sequencing on the Illumina HiSeq2500 platform. Development of brain metastases was correlated with clinical/pathologic features, *EGFR* mutation type, co-mutation of EGFR and other frequently mutated genes; and non-synonymous tumor mutation burden (TMB). Statistical analysis used Fisher exact test for categorical variables, Mann-Whitney test for continuous variables of association with the risk of developing brain metastases, and Gray's test for the probability of brain metastases over time. **Result:** Of 106 patients who underwent surgical resection of primary *EGFR*m NSCLC, WES was successful for 73: 51 (70%) females, 52 (71%) never smokers, 38 (52%) stage I, 14 (19%) stage II and 21 (28%) stage III; 42 (57%) *EGFR* exon 19 mutation, 30 (41%) exon 21, 1(1%) Exon 20 insertion mutation. Twenty-five patients (34%) developed brain metastases. Patients with brain metastases were younger (median age 61 vs. 65 years, p=0.021), had more advanced stages (p=0.012), with a trend towards higher rates in females (p=0.066). One patient with brain metastases had de-novo EGFR T790M mutation in the primary tumor. No difference was seen regarding smoking history, *EGFR* mutation type, *TP53* co-mutation, and median TMB. The 5-year probability of brain metastases increased with increasing stage (14% stage I; 43% stage II, [HR=3.00], 44% stage III, [HR=3.13], p=0.03), and a trend towards higher probability among females (33% vs. 19%; HR=0.39 for males, p=0.074), and younger patients (37% ≤65 years vs. 15% >65, HR=0.37 in older patients, p=0.042). There was no difference in probability of brain metastases based on smoking history, ethnicity, *EGFR* type (33% exon 19 vs. 22% exon 21, p=0.28), *TP53* co-mutation (31% vs. 27% without TP53, p=0.59), or TMB (24% TMB≤2.87 vs. 32% TMB>2.87non-synonymous mutations/Mb, p>0.99). **Conclusion:** While our findings suggest that younger age, advanced stage, and female sex may be associated with the development of BM in EGFRm NSCLC, we could identify no molecular predictor of BM based on *EGFR* subtype, *TP53* co-mutation or TMB.

Keywords: Whole exome sequencing, brain metastases, EGFR mutation

P3.16-08 BASELINE QUALITY OF LIFE IS INFLUENCED BY THE DURATION OF ABSTINENCE FROM SMOKING IN CANDIDATES TO LUNG CANCER SURGERY

C. Pompili[1], G. Velikova[1], K. Franks[2], J. Robson[3], S. Dixon[4], M. Callister[3], A. Brunelli[5]

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Background: The optimal interval of smoking cessation before Non-Small Cell Lung Cancer (NSCLC) surgery is still unknown. The objective of this study is to evaluate the influence of smoking cessation on the preoperative quality of life (QoL) of surgical NSCLC patients. **Method:** 266 consecutive ever smokers (133 females) with a pack year history >=20 undergoing lung resections for NSCLC and with complete preoperative QoL data were analysed. The EORTC QoL summary score was calculated (SumS) as the average of the individual functional and reversed symptom scales (excluding Global-Health and Financial-Impact scales). The following smoking-related variables were tested for a possible association with SumS: age when the patient quit smoking and months elapsed from smoking cessation (for current smokers a value of 0 was used). These variables were entered as independent predictors in a stepwise multivariable regression analysis along with several patient-related baseline factors. **Result:** 108 patients were current smokers, 158 were ex smokers (quit at least 1month before surgery). We found no difference of preoperative QoL SumS between current smokers and ex smokers (81.5 vs. 83.0, p=0.66). Amongst the 158 ex-smokers, 69 quit smoking before the age of 60. Their SumS was similar to the one of those who quit older (84.2 vs. 82.0, p=0.30). A linear regression showed a significant association between the duration of abstinence from smoke and their QoL SumS (coefficient 0.02, SE 0.009, p=0.03). When the analysis was adjusted for other confounders using a multivariable regression analysis, the duration of abstinence from smoking (p<0.0001-longer time better QoL)(Fig1) and the age at which the patient quit smoking (p=0.001-older age better QoL)remained independently associated with SumS along with performance score. Figure 1: Lowess Curve plotting SumS against the months elapsed from the time quit smoking. **Conclusion:** Patients should be counselled to stop smoking prior surgery independently as the QoL has expected to increase.

Keywords: quality of life, lung resection, Smoking Cessation

P3.16-09 HIGH PREOPERATIVE D-DIMER LEVEL PREDICTS EARLY RECURRENCE AFTER SURGERY FOR NON-SMALL CELL LUNG CANCER

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Background: Carcinoma cells often affect the coagulation and fibrinolysis among cancer patients. Plasma dimerized plasmin fragment D (D-dimer) has been reported as the prognostic marker of various type of malignancies. For non-small cell lung cancer (NSCLC) patients, significance of D-dimer levels still remains unclear. **Method:** Two hundreds and thirty five patients with NSCLC who underwent radical surgery between April 2015 and March 2017 were retrospectively reviewed. We divided two groups including 1) high D-dimer (over 1.0ug/mL) group (hDD group, n=47), and 2) normal D-dimer group (nDD group, n=188). The clinical characteristics, tumor CT findings, pathological findings, and clinical outcomes were analyzed. **Result:** The mean D-dimer level was 2.49±2.58 among hDD group. The hDD group had the character of 1) male gender, 2) elder patients, 3) larger tumor size (p=0.0011), 4) pure solid appearance (p=0.0203). The hDD group showed worse overall survival (OS), disease free survival (DFS), and disease specific survival (DSS) than nDD group (Figure 1-A, B, C; log-rank test, p<0.0001, =0.0007, =0.0003, retrospectively) and these findings were also observed only for the p-Stage IA cases. Interestingly patients with grand glass attenuation-dominant nodule were not affected by D-dimer level with favor prognosis. Pathology showed more frequent vessel involvement (v+) in hDD group (p=0.033), but there was no significant difference for histology or histological subtypes of adenocarcinoma.

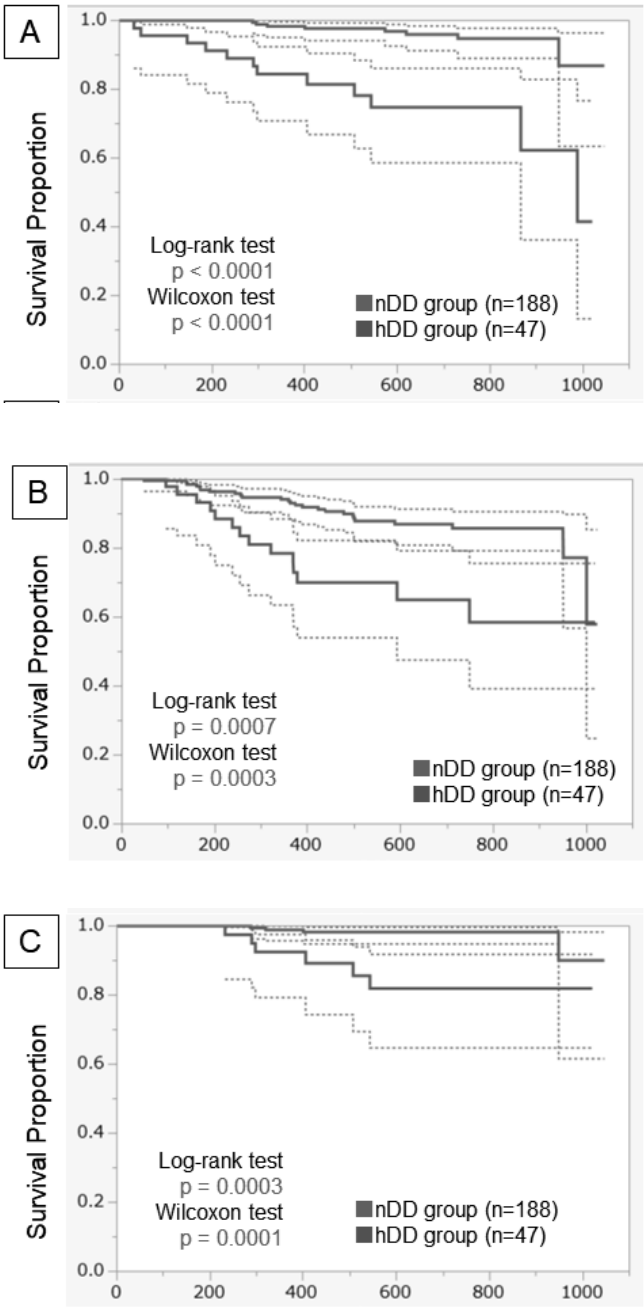

Figure1: Kaplan-Meier survival curves of postoperative overall survival (A), disease free survival (B), and disease specific survival (C) by preoperative D-dimer level. **Conclusion:** The preoperative D-dimer level predicts the postoperative early recurrence and poor prognosis in the patients with NSCLC with pure solid appearance on chest CT.

Keywords: D-dimer, NSCLC, Prognosis

P3.16-10 RADIOMIC FEATURES ON CT ARE PROGNOSTIC OF RECURRENCE AS WELL AS PREDICTIVE OF ADDED BENEFIT OF ADJUVANT CHEMOTHERAPY IN ES-NSCLC

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Background: Early-Stage non-small cell lung cancer (ES-NSCLC) accounts for approximately 40% of NSCLC cases, with 5-year survival rates varying between 31-49%. The decision to offer adjuvant chemotherapy for these patients is primarily dependent on several clinical and visual radiographic factors as there is a lack of biomarkers which can accurately stratify and predict disease risk **Method:** Retrospective chart review between 2005-14 yielded 315 ES-NSCLC patients who underwent surgery with the primary tumor having relapsed in 75 cases. From the entire cohort, 74 underwent adjuvant chemotherapy. This cohort was randomly divided into a training(N=60) and validation(N=255). A total of 248 intratumoral(IT) and peritumoral(PT) radiomic textural features were extracted for every patient. The most stable, significant and uncorrelated features were selected from training cohort using LASSO Cox-regression model. Performance of imaging features was evaluated using hazard ratio(HR) and concordance index(CI). Linear Discriminant Classifier(LDA) was trained using top imaging features and performance of predicted labels was assessed using Kaplan-Meier survival curves and log-rank test. **Result:** Top nine radiomic textural features (from the Haralick, Collage, Laws, Gabor texture families) included a combination of four IT and five PT from 0-12mm distance outside the nodule. The features were prognostic of recurrence (N=255, CI=0.66, HR =1.8, p<0.05). To evaluate the predictive model, subset analysis was performed on the test set. The imaging feature based classifier was able to identify low and high risk groups in the surgery alone setting (N=181, CI=0.73, HR=4.4, p<0.005), potentially identifying patients who might have benefitted from adjuvant chemotherapy. Meanwhile, in the group of patients who received adjuvant chemotherapy following surgery, the classifier did not identify any difference between high and low risk groups (N=74, CI=0.69, HR=1, p>0.05). **Conclusion:** We identified radiomic features from within and outside lung nodule that were prognostic of recurrence and also predictive of added benefit of adjuvant chemotherapy in ES-NSCLC.

Keywords: NSCLC, adjuvant-chemotherapy, Radiomics

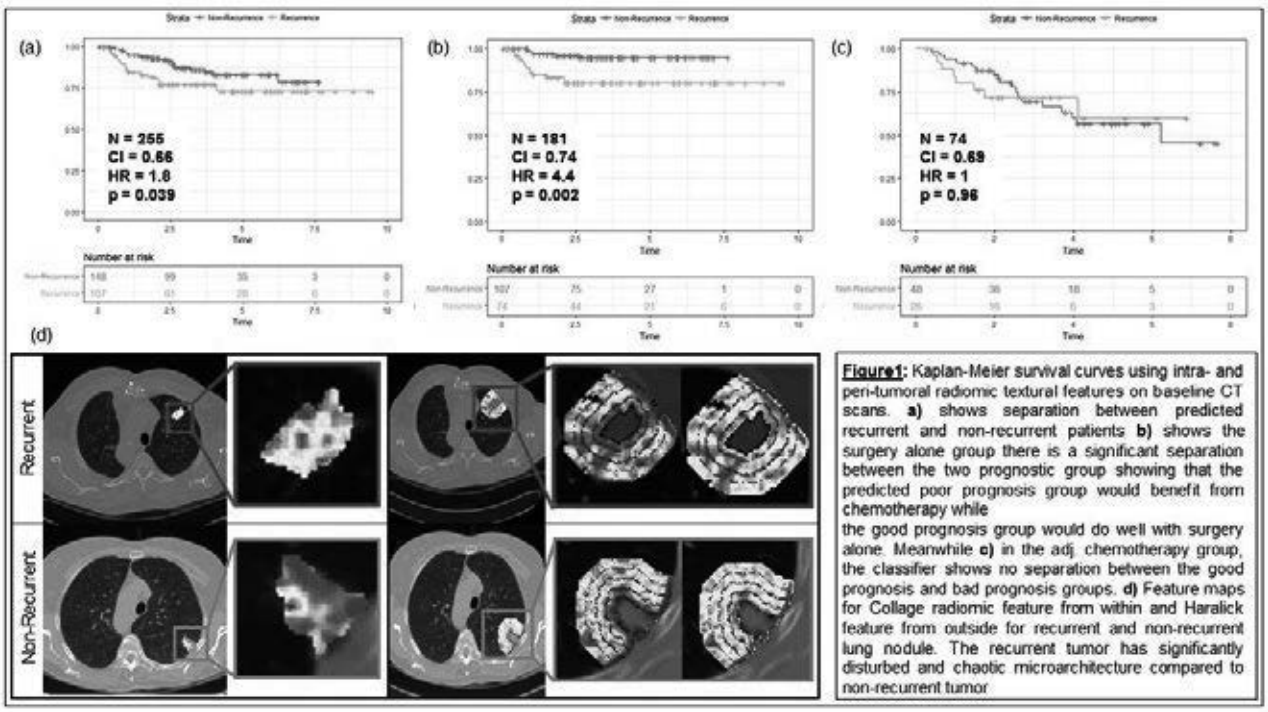

Figure1: Kaplan-Meier survival curves using intra- and peri-tumoral radiomic textural features on baseline CT scans. **a)** shows separation between predicted recurrent and non-recurrent patients **b)** shows the surgery alone group there is a significant separation between the two prognostic group showing that the predicted poor prognosis group would benefit from chemotherapy while the good prognosis group would do well with surgery alone. Meanwhile **c)** in the adj chemotherapy group, the classifier shows no separation between the good prognosis and bad prognosis groups. **d)** Feature maps for Collage radiomic feature from within and Haralick feature from outside for recurrent and non-recurrent lung nodule. The recurrent tumor has significantly disturbed and chaotic microarchitecture compared to non-recurrent tumor

P3.16-11 PATTERN OF RECURRENCE OF COMPLETELY RESECTED LUNG ADENOCARCINOMA VARIES ACCORDING TO EGFR MUTATION STATUS

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Background: The prognostic significance of epidermal growth factor receptor (EGFR) mutations in resectable lung adenocarcinoma is not well defined. We evaluated the influence of EGFR mutation status on postoperative recurrence timing with the use of event dynamics. **Method:** A total of 644 patients with lung adenocarcinoma who underwent complete resection and examined for EGFR mutation status between 2008 and 2015 were studied. Disease-free survival (DFS) were calculated using the Kaplan-Meier method and compared between EGFR mutation-positive patients (n=322) and EGFR wild-type patients (n=322). Event dynamics, based on the hazard rate, were evaluated and only first events (distant metastases or local recurrence) were considered. **Result:** There was no statistical significance in recurrence rate (9.9% versus 14.6%; p=0.09) between EGFR mutation-positive patients and EGFR wild-type patients. In patients with pathological stage I, DFS was significantly better in the EGFR mutant group than the wild-type group (p=0.009), whereas the EGFR mutant group had an inferior DFS compared with the wild-type group among patients with pathological stage II or higher (p=0.110). The resulting hazard rate curves indicated that the recurrence risk pattern was definitely correlated with EGFR mutation status, with an early highest peak during the first year for EGFR wild-type patients and a late maximum peak in the fifth year for EGFR mutation-positive patients.

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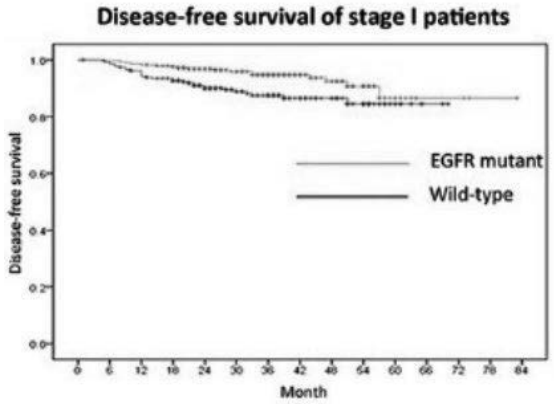

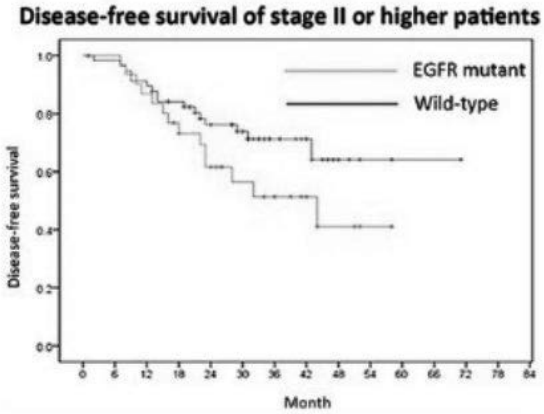

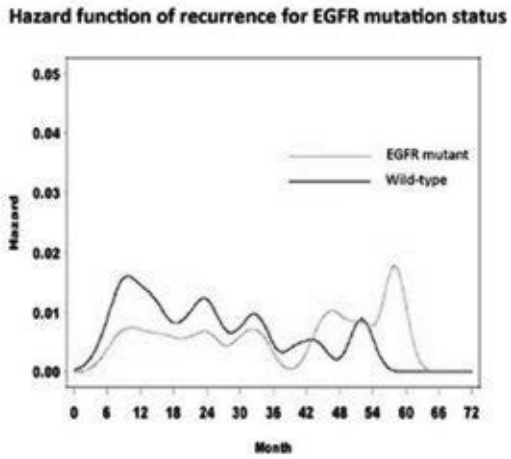

Conclusion: The prognostic value of EGFR mutations appears to be different according to pathological stage in completely resected adenocarcinoma. The hazard and the peak times of recurrence differ considerably between EGFR-mutant and wild-type patients.

Keywords: EGFR, Surgery, recurrence dynamics

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-12 STANDARD CONVENTIONAL LOBECTOMY VS STEREOTACTIC BODY RADIOTHERAPY IN PATIENTS WITH EARLY STAGE NON-SMALL CELL LUNG CANCER (NSCLC) – A REVIEW

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Background: Lobectomy is the standard of care surgical treatment for all operable NSCLC . In most patients who are not operable surgical candidates , lesser minimal invasive pulmonary resections or nonoperative options may be indicated , Stereotactic ablative radiotherapy (SABR) offers a promising alternative to these groups of unhealthy patients . In this review , we look into various published studies & articles in various databases , to evaluate the survival outcomes , cost-effectiveness , complications & evidence-based conceptualizations behind both treatment modalities in these studies via a summarized review . **Method:** A extensive literature search was performed using MEDLINE ,OVID & PUBMED search databases in the last 10 years . A retrospective review & meta- analysis of these papers were conducted using matched-pair analyses & propensity matched scoring & standard statistical analysis . A total of 21 papers were reviewed & a meta-analysis of these survival outcomes were compared between the standard conventional Lobectomy with the newer SABR treatment arm in early lung cancer patients . **Result:** Pending - applying for late-breaking abstract **Conclusion:** Pending -applying for late breaking abstract

Keywords: NSCLC , lobectomy , SABR

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P3.16-13 LONG-TERM OUTCOMES OF STEREOTACTIC BODY RADIATION THERAPY FOR STAGE I NON-SMALL CELL LUNG CANCER IN PATIENTS LESS THAN 70 YEARS OF AGE

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Background: We retrospectively analyzed the treatment outcome of stereotactic body radiotherapy (SBRT) for stage I non-small cell lung cancer (NSCLC) in patients less than 70 years of age. **Method:** We retrospectively analyzed patients with stage I (cT1-2aN0M0) NSCLC, treated with SBRT between 2000 and 2014. 43 consecutively treated patients less than 70 years of age were identified. Staging was reassessed by UICC 7th. Both biopsy-proven and clinically diagnosed stage I NSCLC were included. Overall survival (OS), cause-specific survival (CSS), local control rate (LCR), regional lymph node control rate (RLNCR), and distant control rate (DCR) were calculated and compared between subsets of patients. Kaplan-Meier estimates were utilized for survival analyses, and evaluated by the log-rank test. Common Terminology Criteria for Adverse Events (CTCAE) v4.0 scales were recorded during follow-ups and utilized for toxicity assessments. **Result:** For the 43 patients included, median age was 65 years (Range: 50-69 years), median Karnofsky performance status was 100 (Range: 80-100), and median follow-up time was 58 months (Range: 7-193 months). Median prescription dose was 48 Gy in 4 fractions (Range: 48-70Gy in 4-10 fractions). The rates for OS and CSS at 5 years were 63.8% and 91.5%, respectively. The 5-year LCR, RLNCR, and DCR were 92.4%, 91.7%, 78.7%, respectively. In the subsets analysis, patients were subcategorized into Group Ia and Group Ib, according to the T-stage, or subcategorized into Operable group and Inoperable group. Although there was no significant between the groups, Group Ia, and Operable group showed a better result in OS, but not in others. Regarding treatment toxicity, severe (grade 3 or above) radiation pneumonitis occurred in 6.8% of the cases, and no other toxicities of Grade 2 or above were observed. **Conclusion:** SBRT for stage I NSCLC in patients less than 70 years of age yielded good long-term survival outcomes with acceptable toxicity.

Keywords: lung cancer, SBRT, Younger patient

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-14 SBRT IN EARLY STAGES OF LUNG CANCER

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Background: We present the experience in our department with SBRT in early stages of lung cancer. **Method:** Between April 2012 and January 2018, 59 patients with 65 different locations underwent to SBRT in early stages of lung cancer (51 men and 8 woman, with a median age of 76 years). 44 patients had histological confirmation (22 adenocarcinomas, 13 squamous cell carcinomas, 1 adenosquamous and 1 typical carcinoid). There was not histological confirmation in 15 patients. In all patients, PET-CT was used for the diagnosis. The T-stage classification (8th Edition of the TNM Classification), was the following: T1a (6), T1b (24), T1c (16), T2a (10), T2b (6), T3 (3). The treatment planning was made using vacuum body fixation and abdominal compression to reduce intrafractional organ motion. We made five CTs planning in all patients: 3 free breathing, inhalation and exhalation. The internal target volume (ITV) was delineated based on the fusion of five CTs. The planning target volume

(PTV) was determined an adding additional setup margin to ITV. We made different fraction schemes, and the most used were 5x1200 cGy and 8x750 cGy. **Result:** The assessment of response was performed with CT and/or PET-CT. With a median follow up of 24 months, the local control was 88%, with an overall survival of 76%. The tolerance to treatment was excellent, appearing as acute toxicity, rib pain (G1-G2) in 4 patients, asthenia (G1) in 3 patients, and as chronic toxicity, costal fracture in one patient. **Conclusion:** The local control obtained in early stages of lung cancer treated with SBRT in our series is high, with an excellent clinical tolerance.

Keywords: SBRT, Early stages

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P3.16-15 KINETIC ENERGY DISTRIBUTION FOR GATED TECHNIQUE AT LUNG ABLATIVE BODY RADIOTHERAPY (SABR)

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Background: Gated technique could be applied for lowering the dose spillage of motion target stereotactic body radiotherapy. There are three clinical steps in gated therapy. The first is the target delineation with 4DCT, the second is the localization for region of interested based on selected gated window and CBCT images, and the third is the gated delivery. At current clinical scale, radiation and target formed six combinations, which were determined by motion and static state of both radiation and target at the condition of with and without gated approach. In this study, the kinetic energy distribution for phased targets were evaluated based on gated radiotherapy procedure. **Method:** A Patient with tumor adjoined to the heart was selected to simulate a gated lung SBRT case with 9 co-plane beams. The prescription was 50Gy in 5 fractions. The internal target volume (ITV) based on window size was selected to be 20% to 60% of breathing cycle phase. And this fixed radiation beam aperture was determined by the sum of target from phases at 20%, 30%, 40%, 50% and 60%. The dosimetric characteristics of these individual targets, their sum, and overlap region were described with coverage level, conformity index, homogeneity index, and kinetic energy distribution was defined to be the product of mean dose and prescribed target volumes (PTVs) at different phase window sizes. The ranges of these energy distributions were compared with static target with static radiation beam. **Result:** For image sets at phase 20%, 30%, 40%, 50%, 60%, sum of these phase and overlap region, the ITVs were 12.8cc, 14.2cc, 14.4cc, 16.2cc, 13.7cc, 25cc and 6.5cc; their corresponding prescription dose coverage were 96.6%, 98.2%, 96.1%, 96.3%, 97.9%, 95% and 99.3%; their corresponding conformity indexes were 1.88, 1.55, 1.67, 1.56, 1.73, 1.11, and 2.94; their homogeneity indices were equal to 1.64; and the integral energy were 4.69KGycc, 5.69KGycc, 5.31KGycc, 5.59KGycc, 4.97KGycc, 7.77KGycc and 3.04KGycc. **Conclusion:** In this static beam with motion target simulation, the overlap region received about 1.9 times of kinetic energy density to that of single phase target. The spillage level to adjoined critical structure could be lower with smaller gated window. The relationship between kinetic energy distribution and clinical dosimetry sufficiency could be further investigated in different physical scale levels.

Keywords: Stereotactic ablative body radiotherapy (SABR), lung, Kinetic Energy Distibution

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-16 LONG TERM OUTCOMES OF BODY GAMMA-RAY STEREOTACTIC ABLATIVE RADIOTHERAPY FOR PATIENTS WITH STAGE I/II NON-SMALL CELL LUNG CANCER

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Background: The authors evaluated the efficacy, patterns of failure, toxicity and cost of body gamma-ray stereotactic ablative radiotherapy (Body Gamma-ray SABR) for patients with medically inoperable, clinical stage I/II non-small cell lung cancer (NSCLC) with 8 years of follow-up. Clinical staging was performed according to the sixth edition of the American Joint Committee on Cancer TNM staging system. **Method:** Eligible patients who had no previous treatments, with histologically confirmed NSCLC, determined as clinical stage I /II, underwent OUR-QGD type of the body gamma-ray SABR (70 grays in 10 fractions for gross target volume) at the Radiation Oncology Department, People's Liberation Army Airforce General Hospital, Beijing, China from January 2007 to July 2010. All patients were immobilized by vacuum bag, and then a slow CT scan was performed without any respiration gating. The total radiation dose of 50%, 60%, and 70% isodose line were prescribed in 50, 60, and 70 Grey (Gy) correspondingly, covering 100% of the planning target volume (PTV), 90% of the clinical target volume (CTV), and 80% of the gross target volume (GTV) in 10 fractions. The CT scan and/or positron emission tomography/computed tomography were every 3 months for the first 2 years, every 6 months for the next 3 years, and then annually thereafter to evaluate the efficacy of the treatment. The primary endpoint was overall survival. **Result:** A total of 29 patients were eligible for analysis. The median age of the patients was 71 years (55-87), and the median follow-up was 8.1 years (6.8-10.3). The 1-year, 3-year, 5-year and 8-year overall survival rates were 93.1%, 72.1%, 59.4% and 44.8%, and the local, regional and distant disease recurrence were 10.3%, 13.8% and 13.8% at 5 years and 10.3%, 17.2% and 20.7% at 8 years. Two patients (6.9%) experienced grade 3 treatment-related adverse events. No patients developed grade 4 or 5 adverse events. The median cost of body gamma-ray SABR is 4838 dollars (4615-4923 dollars). **Conclusion:** With long-term follow-up, the results of the current study demonstrated outstanding local control and low toxicity after body gamma-ray SABR in patients with clinical stage I/II NSCLC. The dominant failure included regional and distant disease recurrence. And the body Gamma-ray SABR is pretty cost-effective.

Keywords: Patterns of failure, non-small cell lung cancer, Body gamma-ray stereotactic ablative radiotherapy

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-17 CARDIAC SPARING IN STEREOTACTIC BODY RADIOTHERAPY OF EARLY STAGE NSCLC PATIENTS

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Background: In NSCLC patients who receive radiotherapy, cardiac toxicity was not well established as a possible factor until the results of the RTOG 0617 showed associations between cardiac dose and survival. These associations have been confirmed both in early and in locally advanced stage NSCLC patients. Cardiac sparing is not yet systematically pursued, and there is currently no agreement on cardiac constraints to be used. We investigated the feasibility of cardiac sparing in early stage NSCLC patients who receive SBRT. **Method:** Ten patients with early stage NSCLC in a middle or lower lobe, treated to 3x18 Gy between 2015 and 2017 using a dual arc VMAT technique were randomly selected. Retrospectively, clinical plans were adapted to minimize the maximum heart dose, while clinical constraints were respected. Mean Lung Dose (MLD) and cardiac doses Dmax, Dmean and V_{5Gy} were compared between clinical and cardiac spared plans using a paired t-test. **Result:** Median GTV was 3.05cc (range 0.54-23.2cc), 7 left sided tumors, 3 right sided. All cardiac spared plans fulfilled the clinical constraints on tumor coverage, conformity and organs at risk. All cardiac parameters were significantly decreased; a reduction in max heart dose of 8.2 Gy, reduction in mean heart dose of 1.0 Gy, and reduction in heart V_{5Gy} of 10.3%, with p-values <0.001, 0.008 and 0.014 respectively. MLD was increased by a mean of 0.51 Gy (p-value 0.002). Results are shown in table 1.

Difference in cardiac and lung doses between clinical plans and cardiac spared plans.

Patient	Difference Heart_ Dmax (Gy)	Difference Heart_Dmean (Gy)	Difference Heart_V5 (%)	Difference MLD (Gy)
1	-6.1	-0.2	-2.5	0.2
2	-6.6	-0.9	-6.8	0.5
3	-2.8	0	-0.1	0.1
4	-8	-0.5	-3.7	0.8
5	-8	-0.2	-1.9	0.7
6	-8.6	-1.8	-13.4	0.2
7	-12.8	-2.9	-34.9	1.3
8	-12.4	-0.4	-5.6	0.2
9	-7.4	-1.4	-14.8	0.6
10	-9.4	-1.9	-19.5	1

Difference in cardiac and lung doses between clinical plans and cardiac spared plans.				
Patient	Difference Heart_ Dmax (Gy)	Difference Heart_Dmean (Gy)	Difference Heart_V5 (%)	Difference MLD (Gy)
Average	-8.21	-1.02	-10.32	0.56

Conclusion: Cardiac sparing is feasible for early stage NSCLC patients treated with SBRT, without compromising target coverage, and with minimal increase in mean lung dose. As cardiac exposure is associated with increased mortality, cardiac sparing has the potential to increase survival, and should be considered for all early stage NSCLC patients treated with radiotherapy. These data will need to be confirmed in a larger, prospective cohort.

Keywords: SBRT, Cardiac sparing, Cardiac toxicity

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-18 MODERN RADIOTHERAPY INCREASES PATIENT ACCESS TO CURATIVE INTENT RADIOTHERAPY IN NON-SMALL CELL LUNG CANCER

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Background: Technical developments in the delivery of radiotherapy such as image-guided radiotherapy (IGRT) and intensity modulated radiotherapy (IMRT) have permitted the introduction of advanced radiation techniques such stereotactic ablative radiotherapy (SABR). These new techniques have the advantage of more accurate localisation of the tumour and reduced irradiation of normal tissues. In our centre, we have implemented a range of new techniques to deliver IGRT (such as PET/CT and 4-dimensional CT planning, and cone beam CT during treatment delivery). We postulate that using the advanced techniques increases the access to curative intent radiotherapy treatment of lung cancer. We seek to assess the access rates to curative intent thoracic radiotherapy. **Method:** Using our institutional lung radiotherapy database we analysed the data recording intent of treatment with reference to the stage and performance status (PS) of all patients with stage 1-3 non-small cell lung cancer (NSCLC) in 2007 and compared this to the same population receiving radiotherapy during 2017 and up to April 2018. **Result:** In 2007, 217 patients with stages 1-3 NSCLC received any radiotherapy compared to 218 patients for the 2017/2018 cohort. Within the 2017/2018 cohort 96% of patients (n=94) received radical radiotherapy compared to 28% of patients in 2007 (n=26). Of the 94 patients receiving radical treatment in 2017/2018, 61% received SABR. This increase was largely due to in the introduction of SABR. In those patients with stage 3 disease, overall fewer patients received any radiotherapy in 2017/2018 compared to 2007, however the number of patients receiving curative intent radiotherapy increased from 20 (13% of all stage 3 patients) to 44 (37%). Of note in those patients receiving curative intent radiotherapy there was an increase in access for patients with poorer PS, with only 7% of patients with a PS ≥2 in 2007 receiving curative intent radiotherapy compared with 42% of patients in 2017/2018. **Conclusion:** In our series, we report an increase in the proportion of patients with NSCLC receiving curative intent radiotherapy. Furthermore, more patients with a poorer performance status received curative intent radiotherapy. We suggest that the introduction of advanced radiotherapy techniques has permitted the curative intent treatment of patients who were previously treated with a palliative approach to management.

Keywords: curative intent, Radiotherapy, Non-small cell

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P3.16-19 CLINICAL OUTCOMES OF STEREOTACTIC BODY RADIATION THERAPY FOR T2N0M0 NON-SMALL CELL LUNG CANCER

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Background: For patients with inoperable stage I non-small cell lung cancer (NSCLC), stereotactic body radiation therapy (SBRT) is considered standard. However, the effectiveness and safety of SBRT specifically for T2N0M0 NSCLC remains controversial. This retrospective study investigated the safety and efficacy of SBRT in T2N0M0 NSCLC. **Method:** The medical records of 29 patients with T2N0M0 NSCLC treated by SBRT were reviewed. The overall, progression-free, and cause-specific survival rates were determined. **Result:** The mean follow-up was 20.1 months. At years 1, 2, and 3, the overall survival rates were 93.1, 93.1, and 89.7%, respectively; the corresponding cause-specific survivals were 96.6, 96.6, and 93.1%; the progression-free survivals were 75.9, 65.5, and 62.1%; the local control rates were 100, 96.6, and 96.6%; the regional control was 86.2, 79.3, and 75.9%; and distant control was 89.7, 82.8, and 79.3%. Twenty patients (69.0%) developed symptoms of grade 1 toxicity: dyspnea, chest pain, fatigue, cough, esophagitis, or pneumonia. Among these, 5 patients suffered grade ≥2 therapy-associated pneumonitis, and one patient experienced grade 4 adverse pulmonary effects. **Conclusion:** SBRT was efficient and safe for patients with inoperable T2N0M0 NSCLC, imposing tolerable toxicities. These results warrant a prospective study to develop the multidisciplinary criteria for SBRT in T2N0M0 NSCLC.

Keywords: Stereotactic body radiation therapy, non-small cell lung cancer, Prognosis

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-20 FEASIBILITY OF LIMITED RESECTION FOR PERIPHERAL SMALL-SIZED NON-SMALL CELL LUNG CANCER ACCORDING TO FDG ACCUMULATION AND IMAGING FINDINGS

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Background: With the progress of diagnostic imaging modalities, such as CT and FDG-PET, the number of resectable lung cancer, particularly small peripheral lung cancer, is increasing. We focused on the SUVmax of FDG-PET as a prognostic factor for lung cancer and established criteria for limited resection on the basis of CT findings and SUVmax. Since 2007, we continuously monitored the recurrence and prognosis of non-small cell lung cancers (NSCLCs) resected using our criteria. Here, we report the results of this study. **Method:** Between December 2007 and December 2015, 611 consecutive patients underwent surgery for NSCLC at our institution. Of these, 73patients with cT1aN0M0 who underwent limited resection (partial resection or segmentectomy) were enrolled. The criteria for undergoing limited resection were as follows: ①tumor GGO ratio of ≥0.75and ② tumor SUVmax of ≤1.5. GGO ratio was calculated using the following equation: GGO ratio=[(maximum diameter of the tumor) – (maximum diameter of tumor consolidation)] / (maximum diameter of the tumor). The group that met our criteria and underwent limited resection was designated as intended limited resection group (ILR group), and the group subjected to limited surgery without meeting the criteria treated as control group. **Result:** The study included 35 men and 38 women with a median age of 65 (range, 36–84) years. In total, 51 patients who met our criteria were included in the ILR group, and 21 patients who did not meet the criteria were included in the control group. The control group was selected for limited resection in terms of complications, pulmonary hypofunction, and heart failure. Regarding surgical approach, in the ILR group, 19 patients underwent partial resection and 32 underwent segmentectomy; in the control group, 13 patients underwent partial resection and 8 underwent segmentectomy. According to our criteria, no relapsed cases were reported in the ILR group. Moreover, the 5-year overall survival rates of the ILR and control groups were 100% and 60.5%, respectively, and the disease-free survival rates were 100% and 56.0%, respectively, indicating a significant difference (P < 0.0001). In the control group, 6 patients showed the recurrence of lung cancer. **Conclusion:** In this study, we analyzed the feasibility of our criteria for performing limited resection on the basis of CT findings and SUVmax. In the ILR group, no relapsed cases were reported, suggesting that our criteria may be useful in determining patient's eligibility for undergoing reduction surgery.

Keywords: NSCLC, limited resection, GGO

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-21 ROBOTIC THORACIC SURGERY IN LUNG CANCER RESECTION – A COMPREHENSIVE REVIEW

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Background: Minimally invasive VATS thoracic surgery is currently the gold standard approach for most thoracic procedures . It has come along way since major maximally invasive thoracotomy approaches .

Minimally invasive thoracic procedures indefinitely has its distinctive positive outcomes & other secondary benefits to patients & surgeons . Introduction of robotic technique into thoracic surgery has brought huge advantage to patients & surgeons as well as maximised treatment modalities more efficiently . In the review , we will look into the state of art robotic thoracic surgeries available , feasibility , outcomes , accessibility & costs and the pitfalls . **Method:** A extensive literature search was performed using MEDLINE ,OVID & PUBMED search databases in the last 10 years . A retrospective review & meta- analysis of these papers were conducted using matched-pair analyses & propensity matched scoring & standard statistical analysis . A total of 43 papers were reviewed & a meta-analysis of these studies in terms of feasibility , outcomes , accessibility & costs and the pitfalls were looked into . A summary review into the current state of robotic thoracic surgery , with the its current limitations and future adaptations were also looked into **Result:** pending data collection & interpretation . Applied late-breaking abstract **Conclusion:** pending -applied late-breaking abstract

Keywords: robotic thoracic surgery , NSCLC , advances in Lung resection

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-22 WEDGE RESECTION FOR SMALL PULMONARY LESIONS WITH PREOPERATIVE BRONCHOSCOPIC BARIUM MARKING

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Background: Barium marking is one of the various types of preoperative marking used with minimal pulmonary lesions. We evaluated the safety and efficacy of wedge resection for small pulmonary lesions after using preoperative bronchoscopic barium marking. **Method:** A retrospective study was conducted for patients who underwent barium marking before surgery between January 2009 and January 2018. Lesions were localized in advance by chest computed tomography (CT); then, a catheter was inserted into a bronchus close to the lesion under bronchoscopic guidance. Small amounts of barium sulfate (0.1–2 ml) was injected under fluoroscopic guidance. During surgery, the lung surface was observed with a thoracoscope to check color change by barium. In case of the absence of clear identification by visual inspection, the lung was palpated to search for the barium marker. Once barium was detected, A grasping forcep was used to hold the lesion and barium en bloc, and a wedge resection was performed with stapling devices. **Result:** We retrospectively investigated 29 lesions in 29 patients who underwent barium marking before surgery. Five lesions were solid nodules with a longest diameter of 0.5–1.4 cm (mean, 0.9 cm). Eight lesions were partially solid nodules with an overall longest diameter of 0.8–2.2 cm (mean, 1.3 cm) and solid longest diameter of 0.3–0.8 cm (mean, 0.5 cm). Sixteen lesions were pure ground-glass nodules (GGNs) with an overall longest diameter of 0.7–1.7 cm (mean, 1.0 cm). The only complication of marking was mild pneumothorax that did not require drainage in 1 patient. On performing CT after barium marking, the distance between marked barium and the lesion was 0.0–3.7 cm (mean, 0.9 cm). The period between marking and surgery was 5–33 days (median, 15 days). We performed wedge resection in all cases, and all lesions were resected completely. Pathological results showed adenocarcinoma in situ in 20 patients, primary lung adenocarcinoma in 4, metastatic pulmonary tumor in 3, an inflammatory pulmonary nodule in 1, and an intrapulmonary lymph nodule in 1. All margins were pathologically negative. The only postoperative complication was arrhythmia that required an anti-arrhythmic drug in 1 patient. **Conclusion:** Wedge resection for small pulmonary nodules after using preoperative bronchoscopic barium marking was safely conducted with satisfactory outcomes.

Keywords: wedge resection, Small pulmonary lesions, bronchoscopic barium marking

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.16-23 SOFT-TISSUE SARCOMA OF THE CHEST WALL, SURGICAL RESECTION: ANALYSIS OUR CASES PERIOD OF TIME DECEMBRE 2004-JULY 2017

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Background: Soft tissues include muscle, fat, blood vessels, nerves, tendons and joint linings (synovial tissue). Cancerous tumors (sarcomas) of the soft tissue are rare, but there are many types. Because soft tissue sarcomas arise from a number of different kinds of tissue, they can occur anywhere in the body. Outcomes for people with soft tissue sarcomas depend on the type, size, grade, stage and location of the tumor, as well as a person's age and general health. Clasification from grade are :low ,midle ,high diferenciations.Aim of Study: Our objective was to introduce a patient diagnosed with neglectetd giant soft tissue chest wall liposarcoma . **Method:** Records of 32 patients admitted to our institution from January 2004 to July 2017 were treated in our clinic' A patient with the initials K.B bored 17/06/1950 .He was admitted to our hospital in thoracal surgery at 19.09.2012 with diagnosis : soft tissue tumor left chest wall .Pacienti without other diseases . We did all necessary examinations , CT , MRI and determined the extent of tissue tumor. **Result:** Ages ranged from 13 to 86 years (median, 38 years); the ratio of male to female patients was 3:1. The initial complaint was mass or pain in 98% of the cases. Histologic types were as follows: desmoid tumor (n = 5), 15 %; liposarcoma (n = 7), 21%; rhabdomyosarcoma (n = 6), 18%); fibrosarcoma (n =4 , 12%); malignant peripheral nerve tumor (n = 3, 9%); malignant fibrous histiocytoma (n = 1, 3%); tenosynovial sarcoma (n = 1),3 %; hemangiopericytoma (n = 2) ,6%%); alveolar soft part sarcoma (n = 2),6%); and other types(lymphoma) (n = 2),6%). Resection was the primary treatment in 28 cases (87%).All patients were treated by multimodal treatment ,chemoradition therapy and surgery. Local recurrence developed in 25%. Metastases occurred in 15 (46%) of the cases (metachronous in 12, synchronous in 3) and were more common in patients with high-grade disease than in those with low-grade disease Overall 5-year survival was 60%. Five-year survival rate for those with high-grade sarcomas was significantly lower than that for low-grade sarcomas .Tumor size and age of patient were not prognostic. **Conclusion:** Surgery is important in the treatment of most sarcomas. [l]Additional treatments, including chemotherapy and radiation therapy, may be administered before and/or after surgery. Thoracic wall soft-tissue sarcomas are best controlled by wide surgical resection.

Keywords: sarcoma, Soft tissue, chest wall resection

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.16-24 PROGNOSTIC VALUE OF POSITIVE LYMPH NODE RATIO IN NON-SMALL CELL LUNG CANCER

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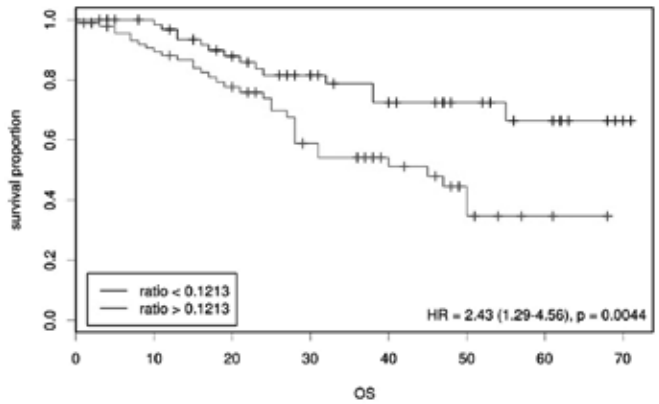
Background: Previous studies had shown the importance of lymph node (LN) resection in T1 NSCLC and recommended no less than 16 LN examination. Few of them reported the role of positive lymph node ratio (PLR). This study was performed to elucidate the prognostic value of PLR in T1 LN positive NSCLC. **Method:** Patients with T1N1-2M0 NSCLC who underwent complete tumor and LN resection in the SEER database from 2009 to 2014 were identified. PLR was defined as positive LN/examined LN. The cut-off value wad determined by ROC. The overall survival of patients was evaluated using Kaplan-Meier and Cox regression analysis. Those whose LN examination number was less than 16 were excluded. **Result:** A total of 362 cases were included in the primary cohort. Among them, female accounted for 51.7%. The median number of examined and positive LN were 21 and 2, respectively. Patients with lower PLR had better OS in N2 but no significant result was observed in N1. **Conclusion:** PLR has significant prognostic value in N2 group. Greater PLR predicts worse prognosis. More cases and clinical data are warranted to verify the effect of PLR in the contemporary staging system.

(See next page)

Charactersitcs	N1 stage (n=198)	N2 Stage (n=164)	*p* value
Age(years)			0.165
mean	66.2	64.8	
Standard deviation	9.4	9.2	
Gender, male (%)	99 (50)	76 (46.3)	0.488
Tumor size(mm)			0.080
mean	21.7	20.6	
Standard deviation	5.8	5.7	
Nodes examination			0.089
Median	21	22	
Quartile	18-27	19-29	
Nodes positive			<0.001
Median	1	4	
Quartile	1-3	2-8	



Keywords: lymph node, NSCLC, SEER

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-25 IMPACT OF DIABETES MELLITUS ON SURVIVAL OUTCOME IN PATIENTS WITH PATHOLOGICAL STAGE IA NON-SMALL CELL LUNG CANCER

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Background: The aim of this study was to investigate the impact of diabetes mellitus (DM) on prognosis of non-small cell lung cancer (NSCLC) patients with pathological stage IA. **Method:** A retrospective study was performed on 506 patients with pathological stage IA in NSCLC, who underwent complete resection between 2008 and 2012. We investigated the clinicopathological features and prognosis of patients with DM (DM group; N = 62) and those without (non-DM group; N = 444) retrospectively. Median follow-up period was 5.2 years. **Result:** *The DM group consisted of more males, high serum CEA level, history of smoking and heart disease, vascular invasion and lymphatic permeation than the non-DM group. 5-year overall survival (OS), recurrence free survival (RFS) and disease specific survival (DSS) rate in the DM group (5-year OS rate, 80.6%; 5-year RFS rate, 77.4%; 5-year DSS rate, 91.6%) were significantly worse than those in the non-DM group (5-year OS rate, 92.0%; 5-year RFS rate, 90.6%; 5-year DSS rate 97.6%) (p = 0.001, p = 0.001 and p = 0.014; respectively). The univariate and multivariate analyses revealed that DM was an independent prognostic factor for RFS and OS (P = 0.027 and P = 0.020, respectively). Relapse in the DM group was higher than that in the non-DM group (p = 0.036). Distant metastases in the DM group (10%) were significantly more common than in the non-DM group (3%) (p = 0.015).* **Conclusion:** Pathological stage IA in NSCLC patients having diabetes mellitus have a decreased survival compared with those without.

Keywords: lung cancer, Diabetes Mellitus, Prognosis

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.16-26 ANATOMIC SEGMENTECTOMY IN STAGE I NON-SMALL-CELL LUNG CANCER REVEALS EQUIVALENT LONG-TERM OUTCOMES COMPARED TO LOBECTOMY

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Background: Lobectomy represents the prefered surgical procedure for patients with early stage non-small cell lung cancer (NSCLC). The choice for the right surgical procedure for stage I patients remains controversial. Aim of our study is to analyze short term and long term outcome of patients undergoing anatomic segmentectomy compared to lobectomy. **Method:** In this retrospective cohort study we included all patients with stage I NSCLC undergoing anatomic segmentectomy or lobectomy from 2006 until 2013 at your institution. A Propensity Score analysis was carried out with respect to age, gender, cardiovascular comorbidities, lung function (FEV1 >60%) and histology (adenocarcinoma vs squamous cell carcinoma). Overall survival and disease free survival as well as morbidity were endpoints of the study **Result:** In total, 385 patients with peripheral located stage I NSCLC who neither underwent neoadjuvant nor adjuvant treatment were identified in our database. After applying propensity core matching, 47 patients underwent anatomic segmentectomy and lobectomy was performed in 47 patients. Of these 94 patients, 76 (81%), were in stage IA and 18 (19%) in stage IB. Adenocarcinoma was the histology in 67 (71%) patients and 27 (29%) patients had squamous cell lung cancer. 25 (27%) patients were operated by VATS and 69 (73%) patients underwent thoracotomy. In all patients, the postoperative complication rate was 11,7% and mean hospital stay was 9 days. There were no significant differences with regard to postopertative morbidity, 30- and 90-day mortality between the anatomic segmentectomy group and lobectomy group. 3- and 5-year overall survival (OS) were 79% vs. 84% and 69% vs. 76%., respectively. There was no significant difference between both groups regarding overall survival (p=0.302) and disease free survival (p=0.603). Interestingly , there was no significant difference in OS und disease free survival in both groups when tumor size was bigger than 2 cm(p=0.728 and p=0.432). **Conclusion:** The benefit of lobectomy over anatomic segmentectomy in patients with stage I NSCLC is still not clear. In our cohort, oncologic short- and long-term outcome of anatomic segmentectomy was comparable to outcome after lobectomy. However, the results of prospective randomized studies are warranted to clarify the value of sublobar resections for stage I NSCLC.

Keywords: Surgery, sublobar resection, lobectomy

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-27 CLINICAL OUTCOME OF PREOPERATIVE INTERVENTION BRONCHOSCOPY FOLLOWED BY SURGERY

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Background: The report of patients with respiratory disease who could receive surgery after bronchial intervention (IVB) is relatively rare. We still experience patients with advanced lung cancer that develops with severe dysplasia and bleeding. To assess the usefulness intervention bronchoscopy combined with surgery. **Method:** We experienced a total of 5 lung cancer patients treated by surgery after IVB at Tokyo Medical University Ibaraki Medical Center. Chief complain were severe dysplasia in 4 cases and bronchial bleeding in one case. The lesions were located at central bronchus in 4 cases. Histological types were 2 squamous cell carcinomas, 1 adenocarcinoma, 1 large cell carcinoma, and 1 pleomorphic carcinoma. Endobronchial snare & argon plasma coagulation (APC) were firstly performed in 2 cases, airway stentings using Dumon stent or Dumon-Y stent in 2 cases, and endobronchial Watanabe spigot (EWS) in 1 case. We evaluated the clinical outcome retrospectively. **Result:** *4 cases with obstructive lesions were treated by endobronchial snare and APC, and the other 2 cases were used bronchial stent. EWS was used to occlude the bronchi in the purpose of stopping blood aspiration in advanced adenocarcinoma case. After reducing the massive bleeding using EWS, we could perform salvage surgery. Performance status improved from 2 and 3 to 1 in all patients. All cases showed their symptom improvements after IVB, and were examined full staging (cT4N0M0) and checked operative risk. Thereafter, we could undergo*

salvage surgery (lobectomy: 2, bi-lobectomy: 1, pneumonectomy: 1, tracheoplasty: 1, carinoplasty: 1). Mean time of IVB followed by surgery was 115.7 days. Overall survival was 22.5 months (1-107.2 months), 5 years survival was 50%, and recurrent rate was 40% (2/5), respectively. . **Conclusion:** IVB followed by surgery is useful modality, and we should realize that there are some patients who can be treated by surgery after IVB because of improvements of their conditions. Also, IVB can be effective for reducing performance status.

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-28 SURGERY OF STAGE I NON-SMALL CELL LUNG CANCER IN PATIENTS AGED 70 YEARS OR OLDER

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Background: Non-small cell lung cancer (NSCLC) is a typical disease of the elderly patients, and is becoming increasingly. Surgical resection is standard treatment for early-stage NSCLC. The strong predictor of long-term survival for lung cancer is reported to be age. We evaluate the influence of age for stage I non- small cell lung cancer in elderly patients 70 years or older. **Method:** 156 cases with stage I (UICC 8th) non-small cell lung cancer aged 70 years or more who underwent surgery at our hospital between 2007 and 2016 were studied. The patients' medical records were reviewed with age, gender, type of operation, postoperative morbidity, postoperative mortality and survival results. **Result:** There were 89 male and 67 female. The average ages were 78.2years (range, 70-90 years). The 5-year survival of all patients was 75.7%. Two groups were compared: patients aged 70 to 79 years, patients aged 80 years or more. At pathologic analysis, 74.5% and 70.7% were stage IA, 25.5% and 29.3% were stage IB. Procedure performed was lobectomy in 52.1% and 39.7%, segmentectomy in 40.8% and 39.7%, and wedge resection in 7.1% and 20.7%. Postoperative complications were documented in 12 patients (12.2%) and 11patients (19.0%) without any difference in two groups. The 30-day mortality was 0.6% , and the 90-day mortality was 0.6% . No case died for lung cancer and 14 cases (male 11) died for other disease within 5 years after lung resection in 70-79 years. The 5-year survival was 81.3%. 3 cases died for lung cancer and 12 cases (male 8) died for other disease within 5 years after lung resection in 80 years or more. The 5-year survival was 66.3%. Comparing the 5-year survival by male and female at 5 year interval were 90.0% and 90.2% in 70-74 years, 68.5% and 90.5% in 75-79 years, 61.1% and 88.9% in 80-84 years, and 82.5% and 25.0% in 85 years or more. The reason for the poor prognosis of patients in 75-79 years, 80-84 years male and 85 years or more female was that many deaths by other disease occur. **Conclusion:** Lung resection for stage I NSCLC patients in 70 years or more expected long-term survival. However, the cause of death was found to be more death from other disease than lung cancer after lung resection. We thought that the management of other disease improved the prognosis after lung resection for stage I NSCLC in elderly patients aged 70 years or older.

Keywords: non-small cell lung cancer, elderly, Prognosis

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-29 PREDICTION OF LYMPH NODE METASTASES IN CLINICAL T1AN0M0 NON-SMALL CELL LUNG CANCER

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Background: Lung cancer with smaller tumor size is now frequently being detected because of prevalent use of computed tomography (CT) as a screening tool for pulmonary lesions. A small group of cT1N0M0 NSCLC have a worse prognosis than what they are expected to be, and nodal upstaging after surgery is a main reason. Prediction of the pathologic nodal upstaging is important. In our study, we aim to reappraise the prediction factors of lymph node metastases in cT1aN0M0 (AJCC 7th edition for lung cancer) NSCLC. **Method:** Cases of cT1aN0M0 NSCLC after surgical resections in National Taiwan University Hospital from 2011 to 2015 were retrospectively reviewed. The prediction factors of interest are tumor size, tumor ground glass opacity (GGO) percentage in chest CT, and preoperative serum carcinoembryonic antigen (CEA) level. Logistic regression model was done to find predictive factors for nodal upstaging. **Result:** A total of 770 patients were included for study, 14 (1.8%) were found to have pN_+ (nodal upstaging) after pulmonary resection. Larger tumor size, less tumor GGO percentage, and higher preoperative serum CEA level are significant predictors for nodal upstaging. In patholoy, less lepidic component of tumor, presence of visceral pleural invasion, and presence of lymphovascular invasion were also significantly correlated with nodal upstaging. With preoperative variables grouped into categorical data, tumor size ≥ 1.5 cm, CEA ≥ 3 ng/mL, and GGO< 25% have a strong predictive value for lymph node metastases.

Table 3. Preoperative variables for prediction of pN_+ in cT1N0M0 NSCLC

Variables	pN_+	
	Odd ratio (CI)	*p*
Tumor size ≧ 1.5 cm	10.961 (3.026-39.709)	< 0.001
CEA ≧ 3 ng/mL	4.997 (1.169-21.36)	0.030
GGO < 25%	19.901 (2.589-152.94)	0.004

pN_+= pathologic $N_{1,2}$ disease, NSCLC= non-small cell lung cancer, CEA= carcinoembryonic antigen, GGO= ground glass opacity

Conclusion: For patients with clinical stage T1aN0M0 NSCLC, tumor size, serum CEA level, and GGO percentage in CT are significant predictive factors for lymph node metastases after surgery. For patients with tumor size less than 1.5 cm, serum CEA level less than 3 ng/mL, and GGO predominant tumor, avoiding lymph node dissection can be justified. Sublobar resection, instead of standard lobectomy, may be a good alternative for this group of patients.

Keywords: lung cancer, nodal upstaging, lymph node metastases

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-30 THE IMPACT OF THE SURGICAL APPROACH ON LYMPH NODE UPSTAGING IN CURATIVE INTENT LUNG CANCER SURGERY

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Background: Radical mediastinal lymphadenectomy is an essential part of lung cancer surgery. The purpose of preoperative mediastinal staging is to identify patients who benefit from induction treatment. However, even in early stage lung cancer some patients present with N1 or N2 disease only intra- or even post-operatively. Accordingly, this study aims to evaluate the impact of different surgical approaches and tumor size on the rate of nodal upstaging. **Method:** We performed an analysis of our prospectively collected database from January 2016 (for robotic assisted surgery January 2015) to March 2018 and nodal upstaging with regard to surgical approach and T status in all patients with early stage T1/T2 NSCLC undergoing primary resection with curative intent. **Result:** A total of 452 T1 or T2 stage NSCLC patients were operated with curative intention. Upstaging occurred in 65 cases (14.4%), from which 43 (9.5%) patients had pN1 and 22 (4.9%) had pN2 disease. Staging was performed according to ESTS guidelines. 366 patients (81%) were preoperatively evaluated by PET/CT and/or EBUS. 293 patients received PET/CT and 169 of them had an additional EBUS. 73 patients received EBUS based on conventional staging without PET/CT. There was a significant difference (p=0.01) in upstaging between T1 and T2 tumors (10.5% (7%N1/3.5%N2) and 19.4% (12.8%N1/6.6%N2), respectively). A stratification based on the surgical approach is shown in Table 1.

(See next page)

	N	T1 All	T1 N1	T1 N2	T2 All	T2 N1	T2 N2
Uniportal VATS	69	10.6%	6.4%	4.2%	13.6%	9.1%	4.5%
Multiportal VATS	145	8.7%	4.35%	4.35%	18.2%	7.3%	10.9%
RATS	65	6.3%	6.3%	0%	12.1%	9.1%	3%
Thoracotomy	173	14.9%	10.3%	4.6%	24.4%	18.6%	5.8%

Conclusion: Irrespective of the surgical approach the rate of N1 upstaging is significantly higher in patients with T2 tumors compared to T1 tumors. The rate of mediastinal upstaging is comparable in both groups. The distribution between T1 and T2 tumors needs to be taken into account when analyzing upstaging rates in primary lung cancer surgery.

Keywords: upstaging, lung cancer surgery, radical mediastinal lymphadenectomy

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-31 YOUNGER PATIENTS OPERATED FOR LUNG CANCER HAVE BETTER OVERALL SURVIVAL

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Background: Median age of patients diagnosed with lung cancer is 63 years. Incidence of lung cancer in population of patients younger than 50 years of age is relatively low. The aim of this study was to compare the clinical outcomes of patients with early lung cancer onset (ELCO, onset before the age of 50) and late lung cancer onset (LLCO, onset after the age of 50). **Method:** We have retrospectively analyzed the prospectively collected data of 1517 patients with Lung cancer treated in a Thoracic Surgery Department in the years 2007-2015. Patients were divided into two groups, group I - 78 patients with ELCO and group II - 1439 patients with LLCO. We have compared overall survival in unmatched and matched population. In order to reduce potential selection bias being a result of different histology and different rate of concomitant diseases we performed a propensity-score matched analysis (based on exact matching – by sex, pTNM, type of operation, pathological diagnosis and Charlson Comorbidity Index). The latter analysis was performed in 65 ELCO patients with 453 LLCO patients. **Result:** In the unmatched population we found no differences in gender, pTNM and type of surgery performed. Younger patients were also more likely to have typical carcinoid (23.1% vs 2.6%, p<0.05, OR 11.06 95%CI 5.695-21.360) and mucoepidermoid tumours (2.6% vs 0.3%, p<0.05, OR 7.547 95%CI 0.997-44.708), whereas the older patients were more likely to have squamous cell lung carcinoma (39.7% vs 23.1%, p<0.05, OR 0.455 95%CI 0.256-0.799). Older patients were more likely to be smokers (82% vs 59%, p<0.05 OR 0.316, 95%CI 0.192-0.519). Median Charlson Comorbidity Index in younger population was 0 and in the older population was 1 (p<0.05). Five-year survival in EOLC group was 71.9% vs. 58.7% in LLCO (p=0.008). The propensity score-matched analysis with exact method, comparing sex, pTNM, type of operation, pathological diagnosis and Charlson Comorbidity Index, showed that younger patients had better survival rates compared to older patients (p<0.001 HR=0.559, 95%CI 0.360-0.865). Five-year survival in patients with ELCO was 77.6% comparing to 61.5% in LLCO patients (p=0.011). **Conclusion:** Patients with early lung cancer onset have higher five-year survival after surgical treatment compared to patients with late lung cancer onset irrespectively of histology.

Keywords: lung cancer, Surgery, Early onset

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-32 A STUDY OF POSTOPERATIVE RECURRENCE IN PATHOLOGICAL STAGE 1 NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Even in pathological stage 1 non-small cell lung cancer, there are some cases in which recurrence occurs after surgical treatment. The prognosis of the recurrent cases is poor despite the early stage of their disease. An analysis of the clinicopathological factors of these recurrent cases may help improve the prognosis. **Method:** A total of 199 patients underwent surgical treatment for primary lung cancer from July 2010 to December 2017 in our hospital. We retrospectively analyzed the clinicopathological factors of 131 patients (65.8%) with pathological stage 1 disease. To compare the clinical data, we divided the 131 patients into 2 groups depending on the presence of recurrence. Group A was recurrent cases and group B nonrecurrent cases. For the statistical analysis, the T-test, F-test, and chi-squared test were used. **Result:** Group A included 19 cases and group B 112 cases. The mean age was 71.3±5.4 years in group A and 70.7 ± 8.0 years in group B (p = 0.75). The procedures performed in group A were lobectomy in 14, segmentectomy in 2, and wedge resection in 3, while those performed in group B were lobectomy in 83, segmentectomy in 18, and wedge resection in 11 (p=0.13). The mean tumor size was 2.5±0.9 cm in group A and 2.0±0.9 cm in group B (p<0.05). In group A, pathologic T factor 1a was found in 0 patients, 1b in 3, 1c in 6, and 2a in 10. In group B, 1a was found in 17 patients, 1b in 48, 1c in 23, and 2a in 24 (p <0.05). Pleural invasion (pl) in group A was 0 in 13 patients, 1 in 6, and 2 in 0, while that in group B was 0 in 99 patients, 1 in 11, and 2 in 2 (p=0.56). Positive lymphatic invasion (ly+) and venous invasion (v+) were found in 6 and 10 patients in group A and 14 and 17 patients in group B, respectively (p <0.05, p <0.01). The mean survival time after the operation was 1185.8±557.0 days in group A and 1034.3±736.0 days in group B (p=0.39). **Conclusion:** The mean tumor size and pT outcomes showed significant differences between the two groups. Furthermore, ly and v were positive significantly more frequently in the postoperative recurrence group. In conclusion, the tumor size, ly+, and v+ indicate a high malignant potential and may be considered predictors of a poor prognosis in patients with early-stage lung carcinoma.

Keywords: recurrence, pathological stage 1 non-small cell lung cancer, postoperative adjuvant therapy

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-33 CHARACTERISTICS AND RISK FACTORS OF RECURRENCE AFTER SEGMENTECTOMY IN PATIENTS WITH CLINICAL STAGE I NON-SMALL CELL LUNG CANCER

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Background: Although lobectomy is the standard surgical procedure for operable non–small cell lung cancer (NSCLC), sometimes we performed segmentectomy for compromised patients, and patients with small-sized NSCLC and adequate pulmonary function for curative intent. The aim of this study was to investigate first recurrence sites and risk factors of recurrence in NSCLC patients who underwent segmentectomy. **Method:** We retrospectively reviewed 136 patients with clinical stage I NSCLC (the 7th edition of the TNM classification) who underwent segmentectomy at Niigata University Medical and Dental Hospital between 2000 and 2016. We investigated first recurrence site to classify as intrathoracic or extrathoracic recurrence. The significant demographic, clinical, and pathologic factors identified with the log rank test in univariate analyses were analyzed with the Cox proportional hazards regression model to examine independent predictors for recurrence in multivariate analysis. For the significant predictor, we determined optimal cutoff points by receiver operating characteristic (ROC) analysis and Youden's Index **Result:** Of the 136 patients in this study, 81 were male and 55 were

female, and the median age was 71 years (range, 41 to 86 years). During the median follow-up period of 1568 days (range, 15 to 6584 days), recurrence was developed in 11 patients. Intrathoracic recurrence was developed only in 4 patients, including 2 patients with surgical resection margin recurrence. The 5- and 10-year recurrence-free probabilities were 89.7% and 89.7%, respectively. Solid tumor component size on computed tomography (CT) was identified as an independent significant predictor (hazard ratio [HR], 3.459). To illustrate ROC curve and use Youden's Index, the optimal cutoff points were determined as 1.5 cm for solid component size on CT. **Conclusion:** In the study, the NSCLC patients with solid component of larger than 1.5 cm on CT had a higher risk for postoperative recurrence after segmentectomy. However it is still unknown whether these patients could be cured by lobectomy, because many of the patients with postoperative recurrence had extrathoracic recurrence.

Keywords: segmentectomy, recurrence

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-34 THE IMPACT OF PREOPERATIVE EXERCISE THERAPY ON THE SURGICAL OUTCOMES OF PATIENTS WITH LUNG CANCER AND COPD: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Although isolated studies have looked at the impact of preoperative exercise on patients with lung cancer and chronic obstructive pulmonary disease (COPD), a comprehensive meta-analysis of the available data has hitherto been lacking. **Method:** Articles were searched from PubMed, Embase, and Cochrane library, with the following criteria: lung cancer patients with or without COPD; undergoing resection; receiving preoperative exercise training. Key outcomes were analyzed using meta-analysis. **Result:** Seven studies containing 404 participants were included. Patients receiving preoperative exercise training had a lower incidence of postoperative pulmonary complications (PPCs) (Odds Ratio (OR) 0.35, 95% Confidence Interval (CI) 0.21 to 0.59) and shorter length of hospital stay (Standard Mean Difference −1.02 days, 95% CI −1.31 to −0.74 days). Exceptionally, incidence of pneumonia remained unchanged. Patients with COPD could not obviously benefit from exercise training to reduce PPCs(OR 0.44, 95% CI 0.18 to 1.08)but still might achieve faster recovery. No significant difference in pulmonary function was observed between the two groups. However, 6-minutes walking distance and VO_2 peak were significantly improved after exercise training. **Conclusion:** Preoperative exercise training might not reduce PPCs for COPD patients undergoing lung cancer resection, but still facilitate faster recovery. Muscle capacity was strengthened after rehabilitation, which emphasized the possible mechanism of the protocol design.

Keywords: Preoperative exercise, lung cancer, copd

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-35 STAIR CLIMBING EXERCISE MAY AMELIORATE PULMONARY FUNCTION IMPAIRMENT IN PATIENTS AT ONE MONTH AFTER LUNG CANCER RESECTION

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Background: Surgical resection remains the primary treatment for patients with localized non-small cell lung cancer (NSCLC). Despite the possibility of a cure, lung resection is associated with an immediate pulmonary function impairment. Stair-climbing test as a reliable indicator of pulmonary function, is often performed preoperatively to select patients. It also has been reported that stair-climbing yielding greater values of VO2 is a more stressful exercise than cycle ergometry. The benefits of this intervention in postoperative patients remain unclear. Thus, this study aimed to evaluate the effects of performance at the postoperative symptom-limited stair climbing exercise on pulmonary function. **Method:** We retrospectively analyzed 36 consecutive NSCLC patients undergoing video-assisted thoracoscopic surgery lobectomy and systematic mediastinal lymphadenectomy from November 2017 to January 2018. In the postoperative pulmonary rehabilitation program, all patients were suggested to perform symptom-limited stair climbing exercise in addition to routine physiotherapy (walking, incentive spirometry, breathing) from the first day after surgery. Patients were encouraged to climb gradually to the maximum number of floors at a pace of their own choice, and to stop in case of exhaustion, insufferable pain, limiting dyspnea or leg fatigue. A nursing professional was indispensable for the management of chest drains and supervision of any symptoms. Heart rate, pulse oxygen saturation were continuously measured using a portable pulse oximeter. Stair climbing exercise was performed at least twice a day during and after hospital stay. According to their performance of the exercise, patients could be divided into two groups. Stair climbing group completed the exercise training as planned, while routine physiotherapy group was reluctant to stair climbing exercise except for routine physiotherapy. Pulmonary functions were performed on all patients preoperatively and at one month postoperatively. **Result:** Totally, 25 patients (15 in stair climbing group and 10 in routine physiotherapy group) were included in the final analysis. The average preoperative and postoperative FEV1 for patients in two groups were 2.69±0.83 L vs. 3.08±0.72 L (p=0.244) and 2.08±0.72 L vs. 2.23±0.60 L (p=0.592), respectively. The difference in FEV1 decline between stair climbing group and routine physiotherapy group was significant (0.61±0.26 L vs. 0.84 ± 0.23 L, p=0.032). **Conclusion:** This study suggested that symptom-limited stair climbing as a more stressful exercise performed postoperatively in patients may ameliorate pulmonary function impairment at one month after lung resection. Prospective randomized controlled trials are therefore warranted.

Keywords: lung cancer, Pulmonary Function, stair climbing

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-36 ADJUVANT CHEMOTHERAPY MAY IMPROVE THE OUTCOME OF PATIENTS WITH NON-SMALL-CELL LUNG CANCER WITH METASTASIS OF INTRAPULMONARY LYMPH NODES.

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Background: Survival benefit of adjuvant chemotherapy (AC) of patients with intrapulmonary lymph node (IPLN) metastasis (level 12–14) needs investigation. We evaluated the impact of AC on patients whose metastatic nodes were limited to intrapulmonary levels after systematic dissection of N1 nodes. **Method:** First, 155 consective cases of lung cancer confirmed as pathologic N1 were collected and evaluated. Patients received systematic dissection of N2 and N1 nodes. For patients with IPLN metastasis, survival outcomes were compared between those receiving AC and those not receiving AC. **Result:** In this group, 112 cases (72.3%) had IPLN metastasis and 55 cases (35.5%) had N1 involvement limited to level 13–14 without further disease spread to higher levels. Patients with IPLN involvement had a better prognosis than that of patients with hilar–interlobar involvement. For the intrapulmonary N1 group (level 12–14-positive, level 10–11-negative or unknown, n = 112), no survival benefit was found between the AC group and non-AC group (5-year overall survival (54.6±1.6 vs. 50.4±2.4 months, p = 0.177, Figure 1A). However, 76 of 112 cases for whom harvesting of level-10 and level-11 nodes was done did not show cancer involvement in pathology reports (level 12–14-positive, level 10–11 both negative), oncologic outcome in this group was better for patients receiving AC than those not receiving AC (5-year OS: 57.3±1.5 vs. 47.1±3.2 months, p = 0.002, Figure 1B). Similarly, survival benefit of AC didn't exist in patients with lymph node metastasis to level 13–14 (level 13–14-positive, 10-12-negative or unknown, n=55, Figure 1C), but was found in 38 patients with complete examination of N1 nodes (58.3±1.7 vs. 51.0±4.2 months, p = 0.048, Figure 1D).

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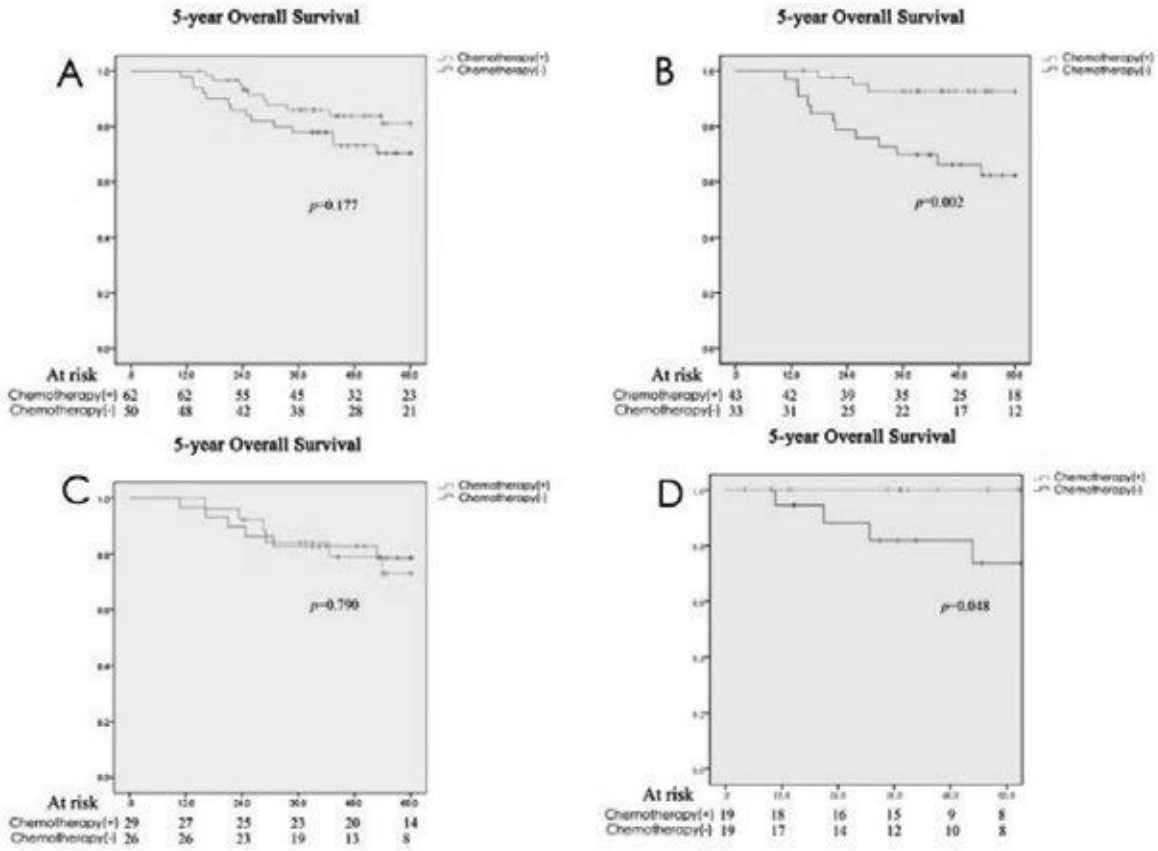

Conclusion: Oncologic outcome may be improved by AC for patients with involvement of N1 nodes limited to intrapulmonary levels after complete examination of N1 nodes.

Keywords: adjuvant chemotherapy, outcome, intrapulmonary lymph node metastasis

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-37 COMPARISON OF LONG-TERM OUTCOMES BETWEEN VATS AND OPEN LOBECTOMIES FOR STAGE I NSCLC: PROPENSITY SCORE-MATCHING ANALYSIS

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Background: *Video-assisted thoracoscopic surgery (VATS) lobectomy is widely spread for patients with clinical stage I non-small cell lung cancer (NSCLC). The postoperative survival and safety of VATS lobectomy are reported equal or better than those of open lobectomy.* **Method:** We retrospectively reviewed the clinical data of 186 patients underwent lobectomy with clinical and pathological stage IA NSCLC from January 2008 to December 2013. Perioperative clinical factors and outcomes of patients with clinical and pathological stage IA NSCLC who underwent lobectomy were compared between VATS (n=63) and thoracotomy (n=123) using a propensity score-matching analysis. **Result:** In the analysis of 61 matched cases, the VATS group showed decreased blood loss and lower value of the C-reactive protein (CRP) at the peak, despite longer operative time. The VATS group demonstrated a significant longer survival, despite greater number of preoperative comorbidities than the thoracotomy group. The 5-year overall survival (OS) of VATS and thoracotomy were 100% and 89% each (log-rank p=0.02). The 5-year disease-free survival (DFS) of VATS and thoracotomy were 100% and 81% in each (log-rank p<0.01). **Conclusion:** The results of this study indicate that VATS has some advantages compared with thoracotomy in early stage lung cancer patients.

Keywords: non-small cell lung cancer (NSCLC), Video-assisted thoracoscopic surgery (VATS), lobectomy

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-38 SYSTEMATIC REVIEW AND META-ANALYSIS OF METHODS TO PREDICT POSTOPERATIVE LUNG FUNCTION FOLLOWING LUNG CANCER RESECTION

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Background: Prediction of postoperative lung function is a critical part of assessment of fitness for lung cancer resection. Multiple techniques of prediction have been reported but formal assessment of the comparative accuracy of these methods has not been performed. **Method:** A systematic review and meta-analysis using the generic inverse variance method was performed according to a prospectively registered strategy (PROSPERO ID:[CRD42017058955]). Extraction of accuracy measures to predict postoperative FEV_1, FVC and TLCO was planned; assessment of bias was performed using a preliminary version of the PROBAST tool. **Result:** Searches retrieved 3817 studies, of these 17 met inclusion criteria and passed risk of bias assessment for inclusion in meta-analysis. Most studies measured FEV_1. Only 1 study which passed risk of bias assessment reported absolute TLCO values. All techniques had a Standard Error range of more than the minimum clinically important difference in FEV_1 of 100ml, CT measures of lobar volume and lung tissue density had the lowest range at 207ml. **Conclusion:** Prediction based on the commonly used methods of segment or subsegment counting gives imprecise estimates of postoperative lung function and may lead to patients being turned down for curative resection. More precise methods using CT density and volume are preferable. There is inadequate evidence to justify any prediction technique for postoperative TLCO over another.

Keywords: Prediction, Surgery, lung function

P3.16-39 WHICH SURGERY FOR GROUND GLASS OPACITY LUNG NODULES?

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Background: Pulmonary ground glass opacity (GGO) nodules represent a significant dilemma in oncology since its diagnosis in clinical practice has increased because of growing application of low dose computed tomography and screening programme. The aim of this study is to analyse the clinical and pathological features, the overall survival (OS) and Disease Free Interval (DFI) in surgically resected solitary ground glass nodules in order to assess the surgical treatment of choice. **Method:** We retrospectively analysed 49 patients (M/F=25/24) with a mean age of 67,7 years (range 40-81) who underwent lung resection for solitary GGO nodules among 570 reviewed CT of patients treated for lung neoplasms between 2010 and 2016. The cohort included 22 pure GGO nodules and 27 part-solid GGOs (also called mixed GGOs). **Result:** Median maximum diameter of GGOs, defined as the largest axial diameter of the lesion on the lung-window setting, was 17 mm (range,5–30). GGO nodules were removed by wedge resection, segmentectomy, or lobectomy in 17 (35%), 9 (18%), and 23 (47%) cases, respectively. Pathology showed minimally invasive adenocarcinoma (MIA), invasive adenocarcinoma (IA) or multifocal adenocarcinoma (MAC) in 9 (18%), 37 (76%) and 3 (6%) cases, respectively. With a median follow up of 47 months the OS and DFI of the entire cohort was 46,3 and 43 months respectively. The histotype (p=0,008), the size of GGO (p=0,014) and the PET-SUV max (p=0,001) were independent prognostic factors of worse survival. Sex, age, previous lung surgery, type of surgical resection and the mediastinal lymph-node evaluation did not impact on OS and DFI. Analysing the 22 pure GGO nodules, we found a 3-year OS and DFI of 98% and 100% respectively, significantly different from 80% and 75% respectively of part-solid GGOs (log-rank p=0,043 and p=0,011). **Conclusion:** Our data suggest an indolent behaviour of tumours presenting as solitary GGO nodules, especially in case of pure GGOs. In our series wedge resections guarantee the same results in terms of OS and DFI when compared to lobectomies. Sublobar resections without mediastinal lymph-nodes evaluation represent the treatment of choice for pure-GGO. More studies are needed to assess its role for part–solid GGO nodules.

Keywords: GGO, Surgery, Adenocarcinoma

P3.16-40 DELAYED CUT-END RECURRENCE AFTER WEDGE RESECTION FOR PULMONARY GROUND-GLASS OPACITY ADENOCARCINOMA

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Background: Most pulmonary ground-glass opacity (GGO) nodules indicated by high resolution computed tomography (HRCT) are pathologically well differentiated adenocarcinomas. **Method:** We performed a limited resection trial of GGO lesions 2cm or smaller from 2003 to 2009, in which accumulated 95 patients were included. The lesion had to be a pure or mixed GGO nodule with a tumor disappearance ratio of 0.5 or greater on HRCT. We confirmed negative surgical cut-end during surgery by margin lavage cytology. **Case:** In the trial, a 51-year-old man underwent right lower lobe wedge resection for a 1.7 cm mixed GGO lesion. The tumor was papillary predominant adenocarcinoma, pT1NxM0. The resection scar started to become thicker 8 years after the initial surgery. When the lesion grew larger at 10 years, it was diagnosed as adenocarcinoma by needle biopsy. We performed a right lower lobectomy and lymph node dissection. **Result:** Pathologically, the second tumor was adenocarcinoma similar to the initial one, papillary predominant with lepidic and acinar components. No pleural or vessel invasion was identified, and there were no nodal metastases. Cut-end staples and sutures used during the initial surgery to control air leakage were identified within the tumor. Genetically, 2 specimens from the initially resected GGO adenocarcinoma were studied and showed no epidermal growth factor receptor (EGFR) gene mutation or echinoderm microtubule-associated protein-like 4 (EML4) - anaplastic lymphoma kinase (ALK) fusion gene. A needle biopsy specimen from the second adenocarcinoma also had no EGFR mutation or EML4-ALK fusion gene, however, the lobectomy specimen had EGFR mutation (L858R in exon21). **Conclusion:** Small papillary-predominant adenocarcinoma might develop delayed cut-end recurrence more than 5 years after limited resection. Careful follow-up with special attention to the cut-end[S1] is necessary ideally for 10 years.

Keywords: minimally invasive, lung cancer, wedge resection

P3.16-41 POSTOPERATIVE PEMBROLIZUMAB FOR THE PATIENTS WITH PATHOLOGIC STAGE I ADENOCARCINOMA WITH SOLID OR MICROPAPILLARY PATTERN

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Background: Prognosis of surgically resected stage I adenocarcinoma was relatively fair with up to 75% of 5 year disease free survival rate. However, in some cases, in spite of the very small-sized tumor, recurrence as systemic metastasis is found. Solid or micropapillary subtype adenocarcinoma are reported as poor prognostic subtypes, additional treatment after surgical resection for those subgroup was required to improve survival. We reported that incidence of PD-L1 strong positivity is significantly higher in solid-predominant subtype of adenocarcinoma, PD-L1 inhibitor can be more effective adjuvant treatment modality in those subtype. **Method:** Design: Open-label, single arm, single center, phase 2 trial. (NCT03254004) Eligibility: The subject must have primary lung adenocarcinoma with stage I and less than 4 centimeter, whose tumor should be solid-predominant or micropapillary (>5%) by postsurgical pathological examination. Objective: The primary objective of this study is to assess the improvement of disease-free survival rate by adjuvant therapy with pembrolizumab for solid or micropapillary adenocarcinoma with pathologic stage I and tumor size less than 4 cm. The secondary objective is to assess the safety profile of adjuvant pembrolizumab in adjuvant setting. Treatment: Pembrolizumab 20mg IV infusion every 3 weeks for 12 months until disease progression or prohibitive toxicity. The treatment should be started within 8 weeks after surgery. Statistics: The hypothesis is that adjuvant pembrolizumab will improve 3-year disease-free survival from 65% to 80% in pathologic stage Ia lung adenocarcinoma patients with solid/micropapillary subtypes. Assuming that the subject enrollment period is 1.5 years, follow-up of last registered subject period is 4 years, and the disease free survival period follows the exponential distribution, a significance level 5% (one side) and 63 peoples are required 85% at the power of test. At this time, assuming that the dropout rate is 10%, it is necessary to register 70 subjects Assessment : Chest CT (covering up to both adrenals) will be done every 3 months till 1 year since the study treatment, and then every 4 months afterward till 2 years and thereafter every 6 months till 3 years. Brain MRI and bone scan will be done at 1 year and 2 years since the study treatment. This study is an investigator-initiated trial with support from MSD. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: adjvuant therapy, lung cancer, Immunotherapy

P3.16-42 EARLY STAGE NON-SMALL CELL LUNG CANCER SURVIVAL IN A CHILEAN PRIVATE TEACHING HOSPITAL

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Background: Lung cancer is the leading cause of cancer death worldwide. The long-term survival is one the most important outcome for therapies in oncology. In early stages, it permits to adequatly evaluate the quality

of the oncological resections of thoracic surgery teams, and in advanced stages it evaluates the quality of the multidisciplinary teams. Screening programs and early diagnosis are the most efficient way to improve survival in lung cancer patients. The results of the surgical treatment in early-stage non-small cell lung cancer of our center is presented. **Method:** All patients treated by our thoracic surgery team for early-stage non-small cell lung cancer, between june 2010 and december 2017, were entered prospectively and consecutively to a web database. Demographic, clinical and pathological data, as well as every adverse event were recorded. All our patients underwent to an exhaustive staging process. Statistical descriptive analysis of clinical and demographic variables and 5 year overall survival by stage are shown. **Result:** 174 patients were included with median age of 67.7 years old (range 38-86 years), 51.7% female. Adenocarcinoma was the most frequent histology (60.9%). 81% were treated in Stage I and 29% in Stage II. For Stage I patients, the median follow-up time was 50 months (IQR: 23.6 - 70.3), and 5-year overall survival 89.79% (95% CI 82.11-94.29). For Stage II patients, the median follow-up time was 33.6 months (IQR: 16.9 - 56.1), and 5-year OS 63.47% (95% CI 33.2-82.91) Stage Ia and Ib patients had similar 5y OS: Ia 89.26% (95% CI 80.09-94,35) and Ib 91.3% (95% CI 68.98-97.82) **Conclusion:** The epidemiological profile of our patients is similar to that published in most of the series, and adenocarcinoma is the main histology in early stage NSCLC in our center. 5-year overall survival in stage I patients are good compared to other international publications, which we believe is directly related to the exhaustive preoperative and intraoperative study. Correctly assessing the cardiopulmonary capacity of patients allows us to reduce postoperative morbidity and mortality. Accurate staging (imaging, systematic lymph node dissection) allows our group to ensure that stage I patients are actually in stage I, avoiding sub-treating patients who might otherwise require adjuvant therapy.

Keywords: NSCLC, Thoracic Surgery, Early-Stage Non-Small Cell Lung Cancer

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-43 IS SUBLOBAR RESECTION FOR STAGE I INVASIVE ADENOCARCINOMA (≤2-CM) FEASIBLE?

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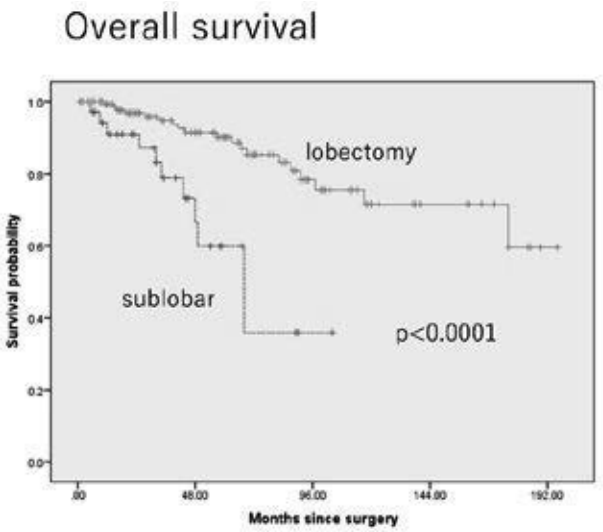
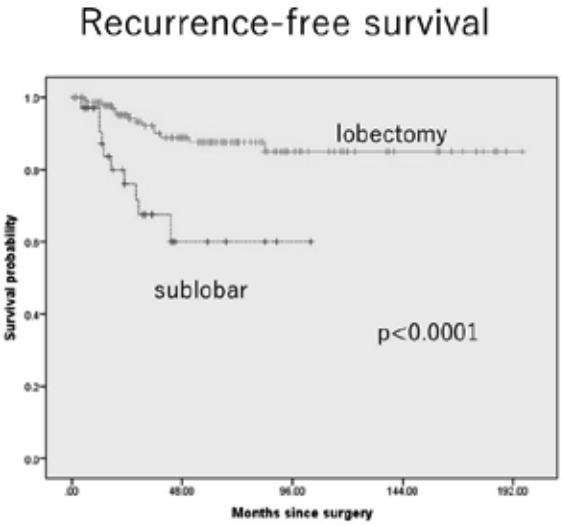
Background: Recent studies have reported that sublobar resection is not inferior to lobectomy for small-sized non-invasive adenocarcinoma (ADC); however, the adequacy for small-sized invasive ADC (IAD) remains unclear. The objective of this study was to identify prognostic factors and validate sublobar resection for small-sized IAD. **Method:** We retrospectively reviewed patients with therapy-naïve, pathological stage I (≤2-cm) IAD, who had undergone complete resection from 1998-2015. Each tumor was evaluated by comprehensive histologic subtyping according to the 2015 World Health Organization classification. Overall survival (OS) and recurrence-free survival (RFS) was estimated using the Kaplan-Meier method. **Result:** 179 patients met inclusion criteria. 104 (58%) were male and 75 (42%) were female, with a median age of 68 years; sublobar resection was performed in 35 (20%), and lobectomy or pneumonectomy in 144 (80%). Median pathological tumor size was 1.5 cm, with a median invasive component size of 0.9 cm, and pleural, lymphatic, or vascular invasion in 27 (15%), 25 (14%), and 49 (23%) patients, respectively. In IAD, the elderly patients and ever smokers were likely to undergo sublobar resection (p=0.015, 0.011, respectively). Patients undergoing sublobar resection for IAD had significantly worse prognosis (5-year OS: 59.9%, 90.2%, p<0.0001) and increased risk of local recurrence (5-year RFS: 60.0%, 87.6%, p<0.0001). Multivariable analysis revealed that sublobar resection, age, and sex was an independent risk factor of overall survival and sublobar resection and vascular invasion was an independent risk factor of recurrence for IAD ≤2-cm.





Conclusion: Sublobar resection in patients with IAD ≤2-cm was significantly associated with increased risk of recurrence and worse prognosis.

Keywords: Adenocarcinoma, sublobar resection

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
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P3.16-44 ROBOTIC-ASSISTED THORACIC SURGERY FOR EARLY-STAGE NON-SMALL-CELL LUNG CANCER: INITIAL EXPERIENCE IN BRAZIL

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Background: Robotic approach for anatomic lung resection has brought an innovative development in minimally invasive thoracic surgery. The aim of this was to assess the safety and effectiveness of robot-assisted resection in patients with stage I-II non-small-cell lung cancer (NSCLC) in Brazil. **Method:** Retrospective analysis of prospectively maintained databases of 2 groups of surgeons from São Paulo and Rio de Janeiro,

respectively. We retrieved data regarding demography, diagnosis, operative time, lymphadenectomy, and morbidity of patients undergoing robotic surgery from March-2015 to April-2018. Continuous variables are presented as means and standard deviation. The Shapiro-Wilk test was used for the assessment of normality. Non-parametric data is represented as medians. Categorical variables are presented as absolute numbers and percentage. Alpha error was defined as 5%. **Result:** 140 consecutive patients were included (80 Males/60 Females). Mean age was 66 ± 9 years old (range:30-85). The majority of patients had adenocarcinoma (n=101;72%), followed by epidermoid (n=29;21%) and carcinoid tumors (n=10;7%). Lobectomy was the most common operation (n=119;85%), followed by anatomic segmentectomies (n=21;15%). Mean overall operative time was 209 ± 80 minutes (214 ± 80 for lobectomies and 167 ± 51 for segmentectomies; p=0.01). Mean number of lymph nodes resected was 12 ± 6, and the mean number of lymph nodes stations sampled was 6 ± 1. There was no conversion to either VATS or thoracotomy in our series; neither major intraoperative bleeding. Postoperative complications occurred in 30 patients (21%). Prolonged air leak was the most common (n=13;9%) and 7 patients were discharged with a chest tube. Chylothorax occurred in 4 patients (2.8%), but all were treated with dietetic measures. Median length-of-stay was 3 days (IQR:2-6). The overall 30-day mortality was 0.5% (n=1). One patient had a procedure-related death, 25 days after a lobectomy. He developed pneumonia, sepsis and multiple organ failure. 138 patients (98.5%) are still under follow-up. Disease recurrence occurred in 7.8% of patients (n=11). **Conclusion:** Robot-assisted pulmonary resection is safe, effective and provides good outcomes, even within the context of an initial experience. Further follow-up should provide insight regarding long-term oncologic disease control.

Keywords: Robotic surgery, lung cancer, Early-stage

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.16-45 THE RATES AND SURVIVAL OF SURGICALLY-RESECTED SECOND PRIMARY LUNG CANCERS IN PATIENTS UNDERGOING RESECTION OF AN INITIAL PRIMARY LUNG CANCER.

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Background: The Lung Cancer Screening Trial demonstrated improved overall survival (OS) and lung cancer specific survival (LCSS), likely due to finding early-stage non-small cell lung cancer(NSCLC). Patients with a past history of lung cancer were excluded from this trial. The purpose of our investigation is to suggest whether long-term surveillance strategies (4 years after surgical resection of the initial lung cancer(1LC)) would be beneficial in NSCLC patients by assessing the rates of second lung cancers(2LC) and the OS/LCSS in 1LC as compared to 2LCs when treated surgically. **Method:** The SEER13/18 database was retrospectively reviewed for years 1998-2013. The 1LC population(N=58,758) consisted of all patients with Stage I-III (AJCC 6th) NSCLC undergoing a definitive resection, while the 2LC population (N= 384) consisted of 1LC patients who developed a 2LC > 48 months after 1LC. Log-rank tests were used to determine the OS/LCSS differences between the 1LC and 2LC in the entire surgical group(EG) and in those having an early-stage tumors (ESR, tumors <4cm with no node involvement). Joinpoint analysis was used to assess changes in rates of 2LCs in comparison to all other second cancers after resection of a 1LC. **Result:** Median follow-up in the 1LC and SLC populations was 76 and 46 months. The rate of 2LCs was significantly less than all other second cancers until 2001 when the incidence of 2LCs increased sharply and became significantly greater than all other second cancers in females starting in year 2005 and in men starting in year 2010. OS/LCSS, adjusted for propensity score by using inverse probability weighting, demonstrated similar OS, but worse LCSS for 2LCs in the EG, but similar OS/LCSSs in the ESR group. Unlike the 1LC group, OS in the 2LC group was not dependent upon T/N stage, age, resection type, and race. OS in the 1LC and 2LC decreased with divorce, positive nodes, and poor differentiation. **Conclusion:** Because the rate of 2LCs are increasing and because the OS/LCSS of the 1LC and 2LC are similar in early-stage lesions, we feel that continued surveillance of patients in order to find early-stage disease may be beneficial.

Keywords: lung cancer; survivorship; second cancers

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.16-46 THE COMPARISON BETWEEN NON-INTUBATED AND INTUBATED THORACOSCOPIC RESECTION FOR PULMONARY NODULE: A META-ANALYSIS

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Background: General anesthesia with single-lung ventilation is considered mandatory for thoracoscopic anatomical resection for non–small cell lung cancer (NSCLC). Few studies have demonstrated non-intubated thoracoscopic surgery offers several advantages over the procedure with tracheal intubation. Thus, we performed a meta-analysis with the aim of evaluating whether non-intubated thoracoscopic anatomical resection offers better perioperative outcomes over intubated thoracoscopic anatomical resection to pulmonary nodule. **Method:** A comprehensive search of online databases was performed. Intraoperative and postoperative variables were compared between subgroups. The odds ratio (OR) or SMD and its 95% CI was calculated using a random effects model. Heterogeneity across studies was examined by the Cochran Q chi-square test and the I^2 statistic. **Result:** A total of 4 eligible studies including 556 patients were recruited. All included studies had comparable baseline characteristics and surgical procedures. Non-intubated anesthesia thoracoscopic surgery was performed on 250 patients, whereas the other 306 patients underwent intubated surgery. Patients who underwent non-intubated surgery correlated with significant shorter postoperative hospital stays (SMD=-0.36, p<0.001) (Figure A) and postoperative fasting time (SMD=-2.80, p<0.001) (Figure B). Patients underwent non-intubated surgery also exhibited a trend toward lower cardiovascular complication rates (1.45% vs 2.69%, OR=0.59, p=0.551) and respiratory complication rates (8.23% vs 11.18%, OR=0.78, p=0.454), shorter anesthesia duration (SMD=-0.48, p= 0.056) and operative time (SMD=-0.07, p=0.521) with no statistical significance. **Conclusion:** Non-intubated thoracoscopic anatomical resection showed significantly shorter postoperative fasting time and hospital stay compared with intubated thoracoscopic anatomical resection, indicating a more rapid recovery after surgery. Further large scale study should focus on prospective validation of feasibility and safety for non-intubated thoracoscopic approach.

Keywords: Nonintubated thoracoscopic anatomical resection, Intubated thoracoscopic anatomical resection, lung cancer

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.16-47 ANALYSIS OF THE NOVEL CHEST TUBE (COAXIAL DRAIN) FOR LUNG CANCER SURGERY

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Background: The chest tube following a thoracic surgery must immediately read a sign of the postoperative abnormal findings and should be safe and effective in draining both air and fluid. The purpose here is to elucidate the efficacy of the novel chest tube (Coaxial Drain) after anatomical pulmonary resection in patients with lung malignant tumor. **Method:** At first, we analyzed the evacuation of air of various chest tubes (TC: Thoracic Catheter, BD: Blake drain, CD: COAXIAL DRAIN). We measured the maximum pressure and the time required for pressure to reduce under 0.2hPa. Additionally, we verified fluid emission amount and evacuation site of various chest tubes. Next, a clinical trial was performed. This study included patients who underwent anatomical pulmonary resection and mediastinal lymph node dissection for lung malignant tumor between September 2017 and April 2018. One chest tube (2 4Fr.TC or 2 4Fr.CD) was positioned apically and posteriorly after surgery. We reviewed the postoperative pain, the amount of chest tube drainage and the presence of subcutaneous emphysema. Pain intensity was evaluated by using The Prince Henry Hospital pain scale (PHPS), and satisfaction scores were evaluated by numeric rating scores (NRS). **Result:** The decompression time of TC was the shortest and its time of CD was shorter than BD (BD>CD>TC). The fluid emission amount increased in proportion to the cross-section area of a drain (CD >TC >BD). All cases found no severe pain in this clinical study. There were no significant differences of pain scale between the TC group and the CD group (PHPS; p=0.83, NSR; p=0.78). No significant difference was observed in total drainage and duration of drainage both the groups. Subcutaneous emphysema occurred in 4 of 8 TC patients and 4 of 20 CD patients, indicating no significant difference between the two groups (p=0.172). There were no complications in any patient. All patients recovered and were discharged home. Moreover, all the cases in which Coaxial Drains

were used obtained good wound healing at the drain insertion site. **Conclusion:** When air leakage occurs, air evacuation with the only BD or TC tends to be insufficient, irrespective of suction conditions. Coaxial Drains have both air inner lumen and liquid duct channels for drainage capability. Therefore, we think Coaxial Drains provide proper drainage of both airs and fluid after pulmonary resection.

Keywords: Coaxial Drain, lung cancer surgery

P3.16 TREATMENT OF EARLY STAGE/LOCALIZED DISEASE
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.16-48 IS PREOPERATIVE SUV(MAX) OF PRIMARY TUMOR A PREDICTOR OF RELAPSE FOR OPERABLE NON-SMALL CELL LUNG CANCER?

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Background: Positron emission tomography-computed tomography (PET / CT) is currently recommended to rule out metastatic disease in non-small cell lung cancer (NSCLC), even in early stage patients. In this study, our aim is to evaluate the effect of maximum value of standardized uptake values (SUVmax) of primary tumor in PET/CT before surgery on relapse in operable NSCLC. **Method:** Data from 191 operable stage I-III NSCLC patients who had preoperative PET/CT was retrospectively analyzed between 2006-2018. Demografic and clinicopathologic findings were analyzed.Patients were staged according to TNM 8th edition. ROC curve analysis was performed to determine the ideal cut-off value of preoperative SUV max to predict relapse. The findings were analyzed using SPSS. **Result:** At the time of diagnosis, median age was 62 years (39-82) and 84% of patients were male. Eighty-nine percent of our patients were smokers and smoking rate in males was 98%. Most common pathologic subtype was adenocarcinoma **(Table 1).** Mean follow-up duration was 35 months (1-128 months). Fourty-seven percent recurred and median progression free survival time (PFS) was 45 months (29-60 months). Median overall survival (OS) was 80 months.The ideal cut-off value of preoperative SUVmax that predicted relapse was 10.75 in the ROC analysis [AUC: 0,58 (0,50-0,66) p<0,05 with a sensitivity of 65%, and specificity of 57%*].* Median PFS was 89 months in patients with preoperative SUVmax ≤ 10.75, and 34 months in patients with SUVmax > 10.75 (HR= 1.69; 95% CI 1.09-2.61; P =0.01). **Table 1 Demographic and clinicopathological findings**

Gender	Male		160 (%84)
	Female		31 (%16)
Smoking	Yes		171(%89)
	No		20 (%11)
Stage	Stage 1 (n=51)	Stage 1A1-A3	33 (%17)
		Stage 1B	18 (%10)
	Stage 2 (n=78)	Stage 2A	17 (%8)
		Stage 2B	61(%32)
	Stage 3 (n=62)	Stage 3A	53(%28)
		Stage 3B	9 (%5)
Pathology Subtype	Adenocarcinoma		98 (%51)
	Squamous cell carcinoma		81 (%42)
	Others		12 (%7)
Adjuvant treatment (n=123)	Stage 1		5 (%4)
	Stage 2		65(%53)
	Stage 3		53 (%43)
Recurrences	Yes		90 (%47)
	No		101 (%53)
Recurrence patterns	Local		15 (16 %)
	Systemic		75 (84 %)
Status	Alive		131 (%69)
	Ex		60 (%31)

Conclusion: Approximately 30% of NSCLC patients are diagnosed at early stage. Although surgery is curative treatment in early stage, recurrences are common. Preoperative SUV(max) of primary tumor in PET/CT might be a predictor of postoperative relapse for operated NSCLC.

Keywords: PET/CT,Suv-max of primary tumor,Early stage lung cancer

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.17-01 PD-L1 EXPRESSION, EGFR MUTATIONS AND ALK EXPRESSION IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS FROM BRAZIL

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Background: Despite the importance of the mutational profile to outcomes in non-small cell lung cancer (NSCLC), there is limited data describing the prevalence of molecular alterations such as ALK translocations, EGFR mutational status and programmed death-ligant 1 (PD-L1) expression in tumors from Brazil. The aim of this study was to investigate the mutational profile of lung adenocarcinoma of specimens from Brazil and correlation between high PD-L1 expression in NSCLCs with known driver oncogenes ALK and EGFR **Method:** We retrospectively evaluated PD-L1 expression in 132 surgically resected primary lung adenocarcinoma including 57 with EGFR status mutation and 121 with ALK expression. PD-L1 and ALK expression were evaluated by immunohistochemical analysis with the SP263 and D5F3 assays, respectively. EGFR mutation status was assessed by sequencing. **Result:** Of the 132 samples analyzed, 2 (1.5%) had a PD-L1 tumor proportion score (TPS) of 1%–4%, 31 (23,5%) had a PD-L1 TPS of 5%–49% and 20 (15.2%) ≥50%. ALK expression was detected in 18 (14.9%) of the 121 tumor samples and 3 (16.7%) of them had a PD-L1 TPS of ≥50%. Forty-two (73.7%) patients had wild-type EGFR, and 15 (26.3%) had mutant EGFR being exon 21 L858R and exon 19 deletion the most frequent mutation. Of the 15 tumors with EGFR mutations, 11 (73.3%) did not express PD-L1 and 4 (26.7%) had a PD-L1 TPS of 1%–49% **Conclusion:** Considering that a subset of patients with ALK expression had a PD-L1 TPS of ≥50%, further studies will be required to examine the efficacy of PD-1/PD-L1 inhibitors in such patients.

Keywords: lung adenocarcinoma, PD-L1, EGFR

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.17-02 INCREASING RADIATION DOSE TO CENTRAL STRUCTURES IS ASSOCIATED WITH WORSE SURVIVALFOLLOWING THORACIC PROTON REIRRADIATION

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Background: Historically, thoracic reirradiation has been associated with high rates of toxicity from cumulative doses delivered to organs at risk (OARs). Conformal treatment in the form of proton therapy (PT) offers the opportunity to deliver definitive doses of radiotherapy with limited dose to surrounding OARs. We performed dosimetric analyses of patients undergoing thoracic re-irradiation with PT to identify parameters associated survival outcomes. **Method:** We identified patients with complete clinical and dosimetric information who received thoracic re-irradiation with PT on an IRB-approved prospective patient registry. Prior radiation courses were fused with PT plans to create composite plans, which were recalculated to an equivalent dose of 200 cGy per fraction (EQD2) using an α/β of 3. Toxicity was retrospectively assessed using CTCAE v4.0. Toxicity, disease control, and survival were estimated with the Kaplan-Meier method. The Cox proportional hazards model was used to estimate hazard ratios for univariate analysis (UVA), and significant dosimetric parameters were further assessed using cutpoint analysis. Patients were dichotomized based on these cutpoints, and survival differences were assessed using the log-rank test. **Result:** A total of 25 patients were included with a median age of 64 years (range 26-89). The majority of patients had non-small cell lung cancer (84%). Median PT re-irradiation dose was 6000 CGE (range 4000-6250) in 30 fractions (range 5-30 fractions). At a median follow-up of 17.5 months (range 1-34), one-year rates of local control, distant control, and overall survival,

were 70.9%, 55.6%, and 71.2% respectively. No grade 4/5 toxicities were observed, and there were 5 late grade 3 events (2 non-malignant pleural effusions, 2 episodes of hemoptysis, 1 one esophageal stricture) with an estimated rate of 21% at 1 year. UVA revealed worse survival in patients with increasing maximum dose to the esophagus, carina, heart, pulmonary artery, and spinal cord, and increasing mean dose to the esophagus ($p<0.05$ for each). Patients who received a cumulative point max dose of ≥ 7500 cGy to the esophagus, ≥11620 cGy to the heart, ≥ 12000 cGy to the pulmonary artery, or ≥ 3250 mean dose to the esophagus had significantly worse survival than those who did not (all $p<0.05$). **Conclusion:** PT re-irradiation is a viable treatment option for patients with thoracic recurrences and offers excellent outcomes with limited toxicity. In this study, we identified dosimetric parameters associated with worse survival that can be used in treatment planning for recurrent disease.

Keywords: Proton Therapy, Thoracic Reirradiation

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.17-03 SURVIVAL AND SIDE EFFECTS IN NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH COMBINATION OF CHEMOTHERAPY AND CONFORMAL RADIOTHERAPY

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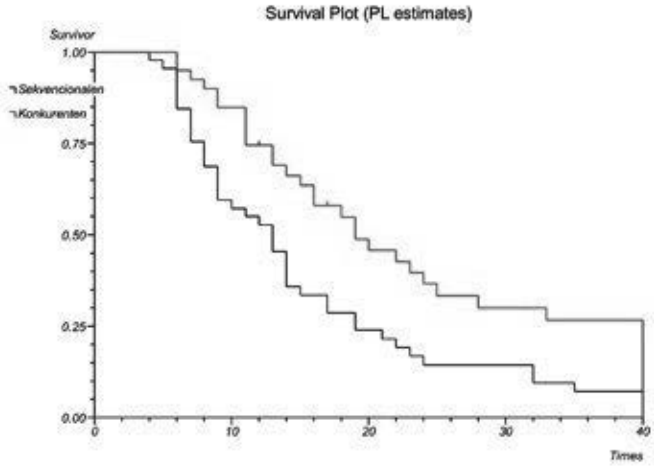
Background: Combined modality therapy is standard of care for patients with unrespectable locally advanced non-small cell, however, insufficient data are available regarding what is the best combination of chemotherapy and radiotherapy. **Method:** s: To evaluate the treatment results, study of 85 patients was randomly assigned to one of the two treatment arms. In the sequential arm, 45 patients had previously received sequential chemotherapy with 4 cycles of carboplatin and etoposide followed by conformal radiotherapy (RT). In the second concurrent arm, 40 patients received concomitant chemotherapy of cisplatine and etoposide and conformal RT, followed by two cycles of consolidation chemotherapy of carboplatine and etoposide. We described all phases of the conformal RT. **Result:** s: From October 2005 to April 2008, 85 patients were enrolled. The median survival was 13 months for the patients in the sequential arm and 19 months for those in the concurrent treatment arm. The differences were statistically significant (log-rank test p=0.0039) Figure 1. The disease-free survival was 9 months in the sequential arm and 16 months in the concurrent treatment group. The differences were statistically significant (log-rank test p=0.0023). Treatment-related toxicities were assessed according RTOG/EORTC criteria. Acute esophagitis and incidence of neutropenia were higher in the concurrent arm. Grade 3 esophagitis was characteristic only for concurrent treatment and it was reason for radiotherapy interruption, but no longer than 7 days.



Conclusion: s: Given the higher toxicity in the concurrent-consolidation schedule, it should be reserved for patients younger than 70 years, having good performance status and minimal weight loss.

Keywords: conformal thoracic radiotherapy, sequential arm, concurrent consolidation arm

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.17-04 DEALING WITH THE N2 DISESASE IN NON- SMALL CELL LUNG CANCER- ON THE EDGE.

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Background: The current guidelines for the evaluation of mediastinal lymph nodes in the setting of lung cancer include EBUS with fine-needle aspiration and cytological evaluation to be enlarged on computed tomography (CT; short axis ≥1 cm). Optimal management of clinical stage IIIA (N2) NSCLC is controversial. This study is a systematic review and meta-analysis of published randomized control trials of multimodality management strategies for NSCLC. **Method:** We conducted a comprehensive literature search of the Pubmed databases for relevant studies comparing patients with stage IIIA (N2) NSCLC undergoing surgery alone, chemotherapy and/or radiotherapy alone, or surgical resection after neoadjuvant treatment with chemotherapy and/or radiotherapy. We estimated hazard ratios, odds ratios (ORs), and 95% confidence intervals (CIs) for survival data. **Result:**

Author	treat	No	Median OS	3 ys surv	p	Medi-an DFS	p
Albain et al	S	202	23.6	37.9	0.24	12.8	0.017
	CRT	194	22.2	33.9		10.5	
Van Meerbeek et al	S	167	16.4	24.9	0.596	17.2	0.605
	CRT	165	17.5	27.8		15.8	
Katakami et al	CRT	29	39.6	51.7	>0.05	12.4	0.187
	Cht	29	29.9	39.3		9.7	
Girad et al	CRT	32	-	51.8	-	17.2	-
	Cht	14	24.2	25.4		12.5	

There was no significant difference in overall survival (OS) or progression-free survival (PFS) in stage IIIA (N2) NSCLC patients who received neoadjuvant chemotherapy or chemoradiotherapy prior to surgical resection compared to those who received neoadjuvant chemotherapy or chemoradiotherapy prior to radical radiotherapy. There was a significant increase in pathological complete remission in the mediastinal lymph nodes in stage IIIA (N2) NSCLC patients who received neoadjuvant chemoradiotherapy prior to surgical resection compared to those who received neoadjuvant chemotherapy. **Conclusion:** In general, North American surgeons are more likely to surgically stage the mediastinum before operation,

are less likely to offer surgical treatment when N2 disease is identified preoperatively and are more likely to use induction therapy

before resection. In contrast, European surgeons may offer operation as the initial treatment followed by adjuvant therapy in

selected cases of N2 disease, and they may perform a more aggressive intraoperative nodal dissection. Neoadjuvant chemotherapy and/or radiotherapy prior to surgical resection do not appear to be clinically superior to neoadjuvant chemotherapy and/or radiotherapy prior to definitive radiotherapy in IIIA (N2) NSCLC patients

Keywords: Non-smal cell lung cancer, N2 disease, Treatment

P3.17-05 MULTIMODALITY TREATMENT FOR SUPERIOR SULCUS NON-SMALL-CELL LUNG CARCINOMAS

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Background: Superior sulcus tumor (SST), to this day remain a complex and challenging condition. The SWOG9416 (Intergroup0160) and the JCOG9806 trial culminated in showing that trimodality therapy with chemotherapy, radiation and surgery provided optimal outcomes. Since that time, the treatment of SST is evolving and preoperative chemoradiotherapy is increasingly used. Dramatic survival benefit, however, has not been reported recently. We reviewed our experience with patients undergoing thoracotomy for lung cancers invading the superior sulcus. **Method:** Analysis of all consecutive patients in our retrospective database, who had potentially resectable SST (cT3-T4) and were treated with multimodality treatment. In the induction chemoradiotherapy cases, surgery with attempted complete resection was performed in patients showing response or stable disease on computed tomography after multidisciplinary discussion. **Result:** From 2009 to 2017, 10 patients, included 9(90%) men and 1(10%) women with a median age of 63 years, underwent thoracotomy. Pathology revealed Ad.5(50%), Sq.4(40%) and La.1(10%) patient(s). The majority (80%) underwent preoperative therapy; chemoradiation in 7(70%) (i.e. CDDP+S-1+concurrent RT 66Gy in 5, CDDP+VNR+concurrent RT 45Gy in 2) and radiation alone in 1(10%) patient(s). Two cases(20%) did not have any preoperative treatment although they received adjuvant chemotherapy using platinum doublet (CDDP+VNR in 1(10%) and CDDP+DTX in 1(10%) patient). Clinical stages were IIB(T3N0) in 5(50%), IIIA(T3N1 or T4N0) in 4(40%), and IIIB(T3N2) in 1(10%) patient(s). Of 8 patients with induction therapy, down stage was obtained in 2(20%); c-T3N1 to yc-T3N0 in 1 and c-T3N2 to yc-T3N0 in 1 patient. Complete resection was achieved in all patients (100%) and pathologic therapeutic response was Ef3,Ef2,Ef1b in 4,3,1 patient(s), respectively. Operative mortality was 0%. With a mean observation time of 20 M, 8(80%) were alive and 2(20%) were dead. Of these one died from cancer relapse in small intestine and the other from diabetes mellitus. Actuarial 5-year overall survival (OS) was 43.8% and cancer specific survival (CSS) was 87.5%. In patients with induction chemoradiotherapy, 5-year OS and CSS were both 83.3%. **Conclusion:** In selected patients with SST, multimodrity treatment was feasible with acceptable morbidity and mortality. The complete resectability was high, and long-term survival was promising especially in whom underwent induction chemoradiotherapy followed by surgery. Our results may provide a benchmark against which new treatment regimens can be evaluated. The potential benefit of preoperative chemoradiotherapy must be assessed by whether it leads to higher rates of complete resection and a lower risk of local relapse. Further evaluation and long term follow up would be necessary.

Keywords: Chemoradiotherapy, Surgery, superior sulcus tumor

P3.17-06 IMPACT OF INTEGRATING PET-CT IN RADIOTHERAPY PLANNING OF NON SMALL CELL CARCINOMA LUNG: DOSIMETRIC AND RADIOBIOLOGICAL COMPARISON

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Background: For conformal radiotherapy planning of NSCLC ,CT scan has been the commonly used imaging modality.The integration of PET and CT scans allows the simultaneous use of biologic and anatomic imaging data for better delineating tumor and sparing normal critical structures. The impact of this integration of two modalities in conformal radiotherapy planning has been studied in this article.The aim is to assess the impact on target volume delineation using CTvs PETCT based plans, and to determine the radiobiological effect on tumor & normal tissue by comparing Tumor control probability & normal tissue complication probability of CT & PET-CT based plans. **Method:** 15 patients of inoperable NSCLC planned for radical radiotherapy, underwent a planning CT scan of the thorax. Target volumes were contoured ICRU 50 recommendations. Later a planning PET-CT scan was taken and the PETCT images with the auto contoured MTV (Metabolic target volume) images, were then fused with the planning CT images using rigid bony registration. Margins were given to PETMTV for the generation of PET CTV and PET PTV. Organ at risk were contoured. 3 Dimensional conformal radiotherapy (3DCRT) plans were initially made on the planning CT images keeping in mind the tolerance of various organs, mainly the normal lungs and spinal cord. Following which similar treatment plans were made on the planning PETCT images. These PETCT plans were then compared with the 3D-CRT plans generated using CT images both dosimetrically from data obtained from Dose volume histograms (DVH) and radiobiologically from mathematical models like TCP and NTCP. **Result:** PET-CT resulted in a statistical significant (p = 0.01) decrease in PETCT generated MTV (103cc) versus GTV delineated on CT (157cc,statistically significant (p=0.05) higher lymph nodal volume detection (26cc) than that detected using CT scan (15cc). The PETCT CTV (334cc) and PTV (800cc) were significantly less than the CT CTV (432cc) and PTV (949cc). PETCT resulted in a statistical significant decrease in the volume of the normal lung irradiated in terms of V40 (p=0.027) and the MLD (p=0.017) but the decrease in other parameters like the V5, V10, V20 did not reach statistical significance. TCP for PETCT based plans was slightly higher than that with CT based plans, PETCT planning showed statistically significant decrease in the NTCP for lung and spinal cord. **Conclusion:** Incorporation of PETCT into radiotherapy planning of NSCLC is technically feasible and dosimetrically appealing but requires matched clinical correlation in terms of local tumor control and normal tissue complications.

Keywords: Non small cell lung cancer, PET, Computed tomography, Radiotherapy planing

P3.17-07 THE BENEFICIAL EFFECT OF THE HIGH DOSE IRRADIATION DURING CONCURRENT CHEMORADIOTHERAPY IN LOCOREGIONAL ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Purpose: To investigate the effectiveness of high dose irradiation in locoregional advanced non-small cell lung cancer (NSCLC) after concurrent chemoradiotherapy (CCRT). **Method:** s: We retrospectively analyzed 36 patients with stage III NSCLC treated with CCRT between January 2011 and March 2016. CCRT was consisted of weekly chemotherapy using paclitaxel/cisplatin, docetaxel/cisplatin, etoposide/cisplatin or cisplatin alone and median dose of 66 Gy (range 50.0 ~ 73.5 Gy) involved field irradiation during 7-8 weeks. The primary and secondary endpoints were overall survival (OS) and locoregional progression free survival (LRPFS), respectively. The OS and LRPFS were calculated from the start of CCRT using the Kaplan-Meier method. Univariate analysis was done using log-rank test. Significant variables on univariate analysis were included into multivariate analysis using Cox proportional harzard model. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. **Result:** s: The median follow up duration was 8 months (range 1 ~ 64 month). Among 36 patients, 22 (61.1%) patients showed partial response, 8 (22.2%) patients had stable disease. The 1- and 2-year OS rates were 54.0% and 46.8%. The median OS was 4.2 months in the low dose group (< 64.8 Gy) and 35.4 months in the high dose group (≥ 64.8 Gy) (p < 0.001). The median LRPFS was 4 months in the low dose group and 16.1 months in the high dose group (p < 0.001). The high dose group was shown a significantly better OS and LRPFS. Radiation dose was significantly associated with OS (HR 0.18, p=0.001) and LRPFS (HR 0.24, p=0.013) on multivariate analysis. Grade ≥3 pneumonitis, esophagitis, and hematologic toxicity were shown in 5.6%, 8.3%, and 22.2% of patients. **Conclusion:** s: High dose irradiation may improve treatment outcomes for patients with locoregional advanced NSCLC after CCRT. However, further investigation should be required to confirm our results.

Keywords: non small cell lung ca, high dose radiotherapy, concurrent chemoradiotherapy

P3.17-08 ASSESSING PRIMARY LUNG CANCER LESION USING RATIO METRICS OF T1 AND T2-WEIGHTED IMAGES IN MAGNETIC RESONANCE IMAGING

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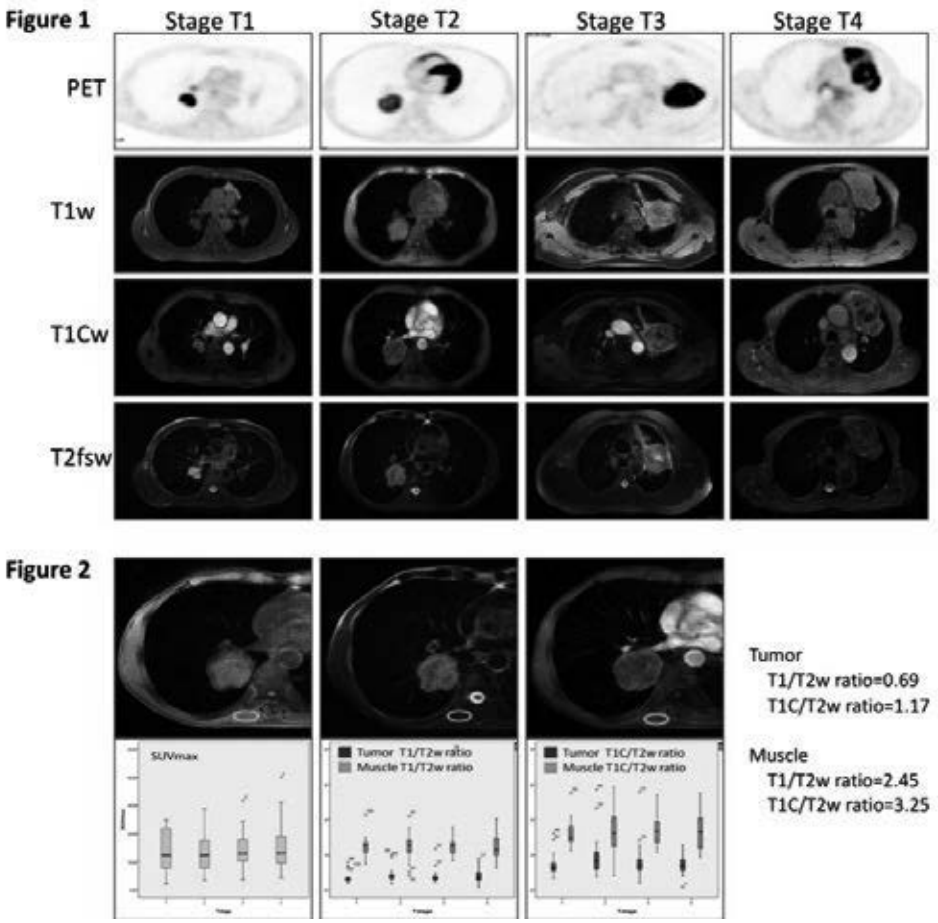
Background: To assess if ratio metrics of T1-weighted (T1w) and T2-weighted (T2w) images in magnetic resonance imaging (MRI) could serve as a sensitive marker to improve the diagnostic efficacies of primary pulmonary lesions with reference to T stages in lung cancer patients. **Method:** Based on the ratio of T1- and T2-weighted signal intensities, we studied a large cohort of NSCLC patients with different T stages using a novel magnetic resonance imaging analysis technique. A total of 101 patients with PET/CT scan and biopsy-proven primary lung lesions were investigated. Gross pulmonary lesions were manually contoured, and corresponding tumor SUVmax, tumor T1-weighted (T1w)/T2-weighted (T2w) intensity ratio, tumor T1-enhanced (T1C)/T2w intensity ratio, muscle T1w/T2w intensity ratio and muscleT1C/T2w intensity ratio had been measured and correlated with T stages. **Result:** There were 25 patients with T1 disease, 29 with T2 disease, 27 with T3 disease and 20 with T4 disease. All the 101 lung lesions were SUV avid, MRI imaging and (18)F-FDG PET/CT agreed on T stages in all patients (100%). Median SUVmax were 12.4 in T1, 12.4 in T2, 12.9 in T3 and 13.0 in T4 patients, respectively. Patients showed lower T1/T2w ratio values in tumor while higher T1/T2w ratio in muscle area (median tumorT1/T2w ratio: 0.69, median muscleT1/T2w ratio: 2.45, P=0.000). In contrast enhanced MRI, a higher T1C/T2w ratio was observed in tumor as compared to T1/T2w ratio (median tumorT1/T2w ratio: 0.69, median tumorT1C/T2w ratio: 2.45, P=0.000). However, tumor T1Cw/T2w ratio was still lower than muscle T1C/T2w ratio (median tumorT1C/T2w ratio: 2.45, median muscleT1C/T2w ratio: 3.25, P=0.000). **Conclusion:** The T1/T2-weighted ratio can improve diagnostic efficacies of primary pulmonary lesions that match hypermetabolic tissues in PET/CT and enables more detailed tissue characterization of lung cancers.

Keywords: magnetic resonance imaging, Primary lung cancer leision, T1/T2-weighted ratio



P3.17-09 RETROSPECTIVE ANALYSIS OF THE EFFICACY AND SAFETY OF MULTIMODAL TREATMENT FOR LOCALLY-ADVANCED NSCLC IN ELDERLY PATIENTS

F. Mazzoni[1], S. Bongiolatti[2], G. Di Pierro[1], L. Paglialunga[1], V. Scotti[3], K. Ferrari[4], B. Fantechi[1], L. Voltolini[2]

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Background: Locally advanced non-small cell lung cancer (LA-NSCLC) is mainly diagnosed in elderly patients. Although multimodality treatments are effective and have demonstrated clinical benefits in terms of OS and DFS, these options are frequently denied to elderly patients. **Method:** This is a single institution retrospective study with an observation period from January 2015 to December 2017. The primary endpoint was to investigate mortality, morbidity and short-term outcomes of pulmonary resection, after induction therapy (IT), for NSCLC elderly patients. The secondary endpoint was to identify risk factors for post-operative complications. Inclusion criteria were as follows: patients who received pre-operative chemotherapy (+/- radiation therapy) and subsequent pulmonary resection. The multimodal treatment was established by a multidisciplinary team. Comparisons between two groups were made: patients <70 years (group A) and patients ³70 years (group B). Categorical variables were analyzed by means of chi-square tests and Multivariable logistic regression was used to identify pre-operative factors associated with overall morbidity. The variables included into the logistic regression model were chosen based on clinical relevance (age, sex, PS, ASA score, mCCI, clinical stage and pneumonectomy). **Result:** In the study, 70

patients (male/female=42/28; adenocarcinoma 58.6% vs squamous-cell carcinoma 33%) underwent pulmonary resection after IT; among these, 26 were aged 70+ (median age 72.5 years [range: 70-80]). No significant differences in baseline characteristics as PFTs, PS, ASA score, number of comorbidities, clinical stages. 66 patients were treated with platinum-based chemotherapy. Chemoradiation therapy was used more frequently in group A (25% vs 3.8%; p=0.02). Surgical procedures were similar in both groups, the percentage of pneumonectomies was comparable (15.9% vs 19.2%), while chest wall resections were more frequent in group A (18.2% vs 3.8%). Pathological stages were comparable between the two groups. In-hospital mortality (2.3% vs 0%) and median hospitalization were not different. The percentage of patients who suffered from any complication (36.4% vs 42.3%, p=0.8) and the complication rate (43.1% vs 69.2%, p=0.06) were higher in group B. In group B there was a significantly higher incidence of atrial fibrillation (p=0.049). Despite these findings, the severity of complications was comparable between the two groups. The multivariable analysis demonstrates the absence of any significant factors associated with overall morbidity. **Conclusion:** Lung resection, for LA-NSCLC after IT, can be performed safely in appropriately selected elderly patients. There is a strong need to standardize the preoperative evaluation in order to reach an effective and tailored multimodal treatment for LA-NSCLC elderly patients.

Keywords: non-small cell lung cancer, locally advanced, multimodal treatment

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
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P3.17-10 OUTCOME OF SURGICAL RESECTION FOR SUPERIOR SULCUS TUMOR: EXPERIENCE AT A SINGLE INSTITUTION.

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Background: Superior sulcus tumors are some of the most challenging thoracic malignant disease to treat because of their proximity to vital structures at the thoracic inlet. The aim of this study was to investigate the outcome of surgical treatment for the patients with superior sulcus tumor who underwent surgery in our institution. **Method:** Between 2006 and 2017, 8 patients with non-small cell lung cancer with invasion of the superior sulcus underwent surgical resection, and their clinical and pathological data were retrospectively reviewed. Postoperative complications were defined as events of grade 2 or more according to the Clavien-Dindo classification. Overall survival (OS) rates were compared using a log-rank test and survival curves were plotted using the Kaplan–Meier method. **Result:** Participants comprised 6 men and 2 women, ranging in age from 46 to 76 years (median, 69 years). Median observation period in the survivors was 61.0 months (range, 10-125 months). One patient underwent surgical resection with median sternotomy and posterolateral thoracotomy, and all otherswith posterolateral thoracotomy. One patient underwent combined resection of left innominate vein and chest wall, and all others underwent combined resection of chest wall, respectively. The histologic types were adenocarcinoma, squamous cell carcinoma and large cell carcinoma in 3, 3 and 2 cases, respectively. A complete resection was achieved in seven patients (87.5%), and there was no fatal complication and no postoperative mortality. The 5-year overall survival rate for all the patients were 62.5%. **Conclusion:** In our institution, 87.5% of patients with superior sulcus tumor could achieve complete resection. There was no postoperative mortality, and no postoperative complication of grade3 or more. Our result indicated that complete resection could impact the overall survival of the patients with superior sulcus tumor, as well as the patients with lung cancer with chest wall invasion except superior sulcus tumor.

Keywords: non-small cell lung cancer, Surgery, superior sulcus tumor

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
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P3.17-11 DUO SYNCHRONOUS PRIMARY LUNG TUMOURS MIMICKING A SOLITARY SPICULATED CAVITATORY MASS ON COMPUTED TOMOGRAPHIC IMAGING

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Background: Multiple primary lung cancer (MPLC) is a well-established clinical entity with an incidence ranging 1-8%. It is the simultaneous presence of two or more primary lung cancers in an individual. Although the current high-resolution imaging tools have enabled such lesions to be readily detectable, we report a rare case of two synchronous primary lung adenocarcinomas that presented as a single lesion on computed tomographic (CT) imaging. **Method:** A 60-year-old Chinese gentleman, smoker, had an incidental finding of 2.4 cm lesion in the right lower zone on chest X-ray. CT of the thorax demonstrated 2.2 x 2.7 x 3.1 cm right lower lobe spiculated soft tissue mass with a small central cavitation and enlarged right hilar and pre-carinal lymph nodes measuring 1.5 x 1.6 cm and 1.8 x 1.8 cm respectively. Positron emission tomography – CT showed 3.1 cm spiculated lung mass in the right lower lobe (maxSUV 7.5), with metastatic FDG-avid right hilar node, right tracheo-bronchial node (maxSUV 4.8) and right paratracheal node. CT guided biopsy was done and histology showed primary lung adenocarcinoma. **Result:** The patient underwent completely portal robotic right lower lobectomy with mediastinal lymph node dissection. His recovery was uneventful and was discharged on post-operative day 5. Histological examination revealed R0 resection of two distinctly separate adenocarcinomas measuring 2.3 x 2 x 1.5cm and 2.5 x 2.5 x 2.2cm respectively. The former showed acinar (40%), lepidic (30%), micropapillary (20%) and solid (10%) growth patterns while the latter showed solid (80%) and acinar (20%) growth patterns. Lymph node stations 2, 4, 7, 9, 10, 11 were dissected and analysed. Station 7 and 11 nodes were found to contain metastases. Final pathological staging was Stage 3A (pT1cN2M0). Subsequently, he underwent adjuvant chemotherapy (Carbo/Alimta #4) followed by radiotherapy (50.4Gy/28#). There was no tumour recurrence at the 1 year follow-up. **Conclusion:** Despite current state of the art imaging modalities for lung cancer, there remains the possibility of MPLC mimicking a solitary cavitatory lung lesion during clinical staging.

Keywords: Solitary nodule, Multiple primary lung tumours, Adenocarcinoma

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
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P3.17-12 PHASE II TRIAL OF ATEZOLIZUMAB BEFORE AND AFTER CHEMORADIATION FOR UNRESECTABLE STAGE III NSCLC (AFT-16): TRIAL IN PROGRESS

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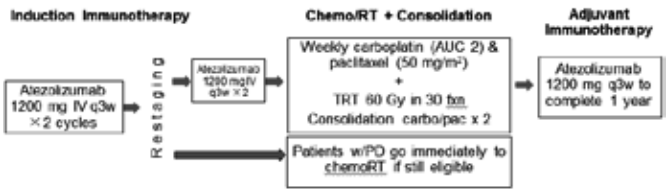
Background: Cure is possible for a substantial minority of stage III NSCLC patients, but most will relapse after conventional chemoradiation (CRT). Combining checkpoint inhibition through PD-L1 blockade with CRT may attenuate tumor related immunosuppression via depletion of Tregs and clonal expansion of effector T-cells, thereby improving tumor immunogenicity. Further, CRT may reveal hidden antigens that can present additional targets to the reconstituting immune system. Whether anti-PD-L1 therapy before CRT will improve outcomes in this setting is the subject of this trial. **Method:** This phase II single arm Alliance Foundation Trials study (AFT-16, NCT03102242) explores safety and efficacy of atezolizumab before and after definitive CRT. 63 patients with stage III NSCLC, PS 0-1, no active autoimmune disease and no significant organ dysfunction will enroll at 15 Alliance sites. Participants receive 4 cycles of neoadjuvant atezolizumab 1200 mg IV q 21 days with restaging after cycles 2 and 4. Non-progressing patients undergo carboplatin and paclitaxel (C/P) weekly with 60 Gy RT followed by 2 cycles of C/P consolidation and adjuvant atezolizumab to complete one year of therapy. The primary endpoint is disease control rate (CR+PR+SD) after neoadjuvant atezolizumab. Secondary endpoints include ORR, PFS, OS, safety and QoL by the EORTC QLQ-30.



Correlatives include the role of PD-L1 and tumor mutation burden as predictive biomarkers. Tumor tissue is obtained at study entry, and plasma and immune cells are isolated at study entry, post neoadjuvant atezolizumab, post CRT, during adjuvant atezolizumab and at study end.

Explorative endpoints include potential predictive biomarkers development that may define how atezolizumab affects the proportions of immunologic subtypes and immune activation using flow cytometry and T cell receptor immunophenotyping, multiplex immunohistochemistry and cytokine analysis. The trial was activated on 11/1/17. As of 5/4/18, the trial is open at 8 centers with 14 patients enrolled. **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Stage III NSCLC, neoadjuvant immunotherapy, clinical trial

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
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P3.17-13 SAKK 16/14: DURVALUMAB IN ADDITION TO NEOADJUVANT CHEMOTHERAPY IN PATIENTS WITH STAGE IIIA(N2) NSCLC — A MULTICENTER SINGLE-ARM PHASE II TRIAL.

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Background: Improving the outcome of locally advanced non-small cell lung cancer (NSCLC) is one of the major challenges in thoracic oncology. SAKK substantially contributed to establish a standard of care for patients with stage III NSCLC: The trial SAKK 16/96 established neoadjuvant chemotherapy with three cycles of cisplatin and docetaxel. The randomized trial SAKK 16/00 showed no benefit by adding neoadjuvant radiotherapy as third treatment modality. Our results consistently showed a 5-year overall survival (OS) of 37%. Recently, the PACIFIC trial showed significantly improved progression-free survival for durvalumab as consolidation therapy after definitive chemoradiotherapy in unresectable stage III NSCLC. **Method:** This is a single-arm phase II clinical trial designed to evaluate the addition of perioperative immunotherapy with durvalumab to the previously established standard of care for stage IIIA(N2) patients. Eligible patients with WHO performance status 0-1 and age of 18-75 years must have pathologically proven NSCLC stage IIIA(N2) (T1-3 N2 M0) according to the 7th edition of the TNM classification, irrespective of histological subtype, genomic aberrations or PD-L1 expression status. Tumor tissue has to be available for the mandatory translational research. Patients whose tumor is deemed resectable at diagnosis receive three cycles of chemotherapy with cisplatin 100 mg/m^2 and docetaxel 85 mg/m^{2}every three weeks followed by two cycles of durvalumab 750 mg every two weeks. Following surgery, patients will be treated with durvalumab 750 mg every two weeks for 12 months. The primary endpoint of the trial is event-free survival at 12 months. Secondary endpoints include OS, objective response, nodal down-staging, complete resection, pattern of recurrence and toxicity. Additionally, a large translation research program accompanies the trial investigating potential predictive biomarkers of anti-PD-L1 therapy. Based on the data of first 25 operated patients and given that the results showed that their 30-day post-operative mortality is less than 10%, according to the decision rule described in the protocol of the trial there is no reason for further detailed safety analysis (evaluated by an IDMC) and thus shall continue as per protocol. **Result:** "Section not applicable" **Conclusion:** "Section not applicable"

Keywords: neoadjuvant immunotherapy, Stage IIIA, immune checkpoint inhibitor

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
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P3.17-14 A CASE OF A PATIENT HARBORING AN EGFR -T790M MUTATION POSITIVE IN SQUAMOUS CELL LUNG CANCER

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Lima, Aliada Clinic, Lima/PE

Background: Actually, the treatment of lung cancer who express driver mutations consist in block this target, the majority of this patients has an adenocarcinoma histology only few of them has the squamous type. **Method:** We describe a case report of a 58-year-old female, non smoker, with a persistent cough of 2 months of evolution. On May 2016, the CT scan reported an irregular solid lesion of 72x56mm in right segment 6, infiltration of hilum, pulmonary artery and mediastinal lymph nodes. No extrathoracic disease. Biopsy: squamous cell carcinoma. Since the lesion was considered unresectable, she initiates concurrent ChT-RT (cisplatin / gemzar). After the 4th application, local progression was evidenced. Mutation studies, showed EGFRm Exon 19. She starts treatment with Afatinib (40mg / d) but, after 2 weeks, presented G3 gastrointestinal toxicity, so a dose-adjustment to 30mg / d was performed, G2 dermal toxicity also was reported. By december 2016, due to the response obtained, a medial and inferior lobectomy was performed. Pathological report (PR): middle lobe: pneumonitis. Lower lobe: squamous carcinoma. T: 3.5cm, G1, LVI (+), parenchymal margin (+). A PET / CT scan 4 weeks after the surgery, demonstrating right parahilar hypermetabolic lesion, pleural nodules and subcarinal adenopathy. The systemic treatment was restart in January 2017 with erlotinib 150mg /d. A PET / CT control 2 months later just showed slight metabolism in subcarinal adenopathy. She remains asymptomatic until october 2017, when presented aphasia and behavioral alterations. MRI: single left cortico-subcortical lesion of 2.2 x 2 cm with edema and subfalcial herniation. An hypo-fractionated radiotherapy scheme with corticoids was programmed but with minimal benefit. Six weeks after having completed RT (December 2017), greater neurological involvement is evidenced associated with weakness in lower limbs. MRI: lesion of 17.6 x17.3mm with contrast hyper-uptake and edema. CT thorax: no evidence of disease. Considering these findings and clinical deterioration a cerebral metastasectomy was performed. PR: squamous cell carcinoma. EGFRm deletion 19 (+) T790M (+). **Result:** Due to the post-surgery clinical deterioration, the patient did not receive systemic treatment until march 2018, CT scan: multiple subcarinal adenopathies, contralateral pulmonary nodules and a 6mm nodule in the right lobe of the cerebellum. Patient is currently under treatment with osimertinib, with clinical neurological recovery and no respiratory symptoms. **Conclusion:** The use of TKI in SQCLC has a benefit in this patients, but the magnitude of this could be lower than adenocarcinoma according with a few series. However, this does not seem to be the case.

Keywords: EGFR, SQCLC, T790M mutation

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
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P3.17-15 THERAPEUTIC OUTCOME OF SURGERY FOR SUPERIOR SULCUS TUMOR

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Background: Treatment of superior sulcus tumor (SST) is challenging and often requires multidisciplinary approach. Accumulation of treatment outcome is a principal issue for the future. **Method:** We retrospectively reviewed clinical records of the patients those who were clinically diagnosed to have SST which involved to the 1st rib but was resectable. From 2000 to 2017, 16 patients were eligible in our hospital. Average age of the patients was 62.3 (40-74). The number of the patients with various properties was following; men 16/ women 3, right lung 5/ left lung 11, squamous cell carcinoma 5/ adenocarcinoma 9/ pleomorphic carcinoma 1, induction chemoradiotherapy 12/ induction chemotherapy 3/ no induction treatment 1, and clinical stage T3N0M0 9/ T3N2M0 2/ T4N0M0 4/ T4N3M0 1. Pathological information and clinical information regarding recurrence and survival were collected. Correlation between prognosis and clinicopathological factors were statistically evaluated by both univariate and multivariate analysis. P value was regarded as statistically significant when it was less than 0.05. **Result:** Undertaken surgical approach was posterolateral for 8 cases/ median sternotomy for 6 cases/ transmanubrial approach (TMA) + thoracoscopy for 2 cases. Combined resection extended to the 1st rib for 6 cases/ 2nd rib for 4 cases/ parietal pleura for 4 cases/ vessels for 4 cases. For curativity, pathological curative (R0) was achieved in 12 cases, while macroscopic curative (R1) was noted in 4 cases. Effect of induction treatment was revealed as Ef1 for 4 cases/ Ef2 for 7 cases/ Ef3 for 2 cases. There was no death within 30 days after surgery. Morbidity (grade3) occurred in 6. Postoperative recurrence was observed in 8 cases and 7 of them dead from lung cancer. 5-year survival rate was 48.8%. By multivariate analysis, R0 resection was a statistically significant factor which correlates with survival. **Conclusion:** R0 resection was a critical factor for postoperative survival. Thoracoscopic approach combined with TMA might contribute to reduce surgical invasiveness according to the location of the disease.

Keywords: multidisciplinary treatment, Surgery, superior sulcus tumor

P3.17-16 ADENOCARCINOMA OR EPIDERMOID? THE IMPORTANCE OF THE HISTOLOGICAL SUBDIVISION

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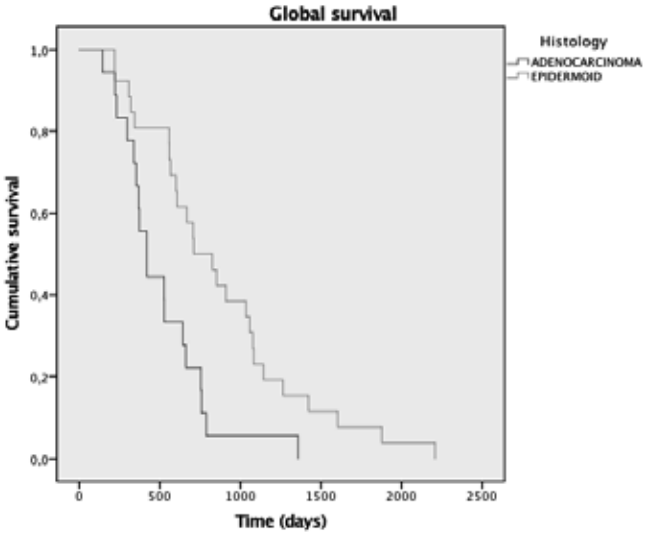
Background: Lung cancer is the leading cause of cancer death. Most studies focus on metastatic disease, and the complementary treatment in localized disease has limited evidence. This study aims to highlight the factors that influence the survival of lung cancer in localized phase. **Method:** A retrospective study was conducted on 96 patients (14% women and 86% men, median age of 66 years) with localized lung cancer treated in our center between 2009 and 2017. At the end of the data collection, 44 patients had died (46 %) but 52 (54%) remained alive until today. All the medical histories were reviewed in order to analyze different parameters related to histology, stage, tumor biology, imaging tests, surgery and treatment. A statistical data analysis software (SPSS) was applied to find statistically significant relationships between the variables. **Result:** From the 49 patients with adenocarcinoma, 18 (37% of the total) died with a median overall survival (OS) of 35 months (27-43 months with CI <0.05%). From the 47 epidermoids, 26 died (55% of the total) although with a median OS of 59 months (40-78 months with CI <0.05%). By stages I and II: The median OS for the adenocarcinoma group was 12.33 months (3.6-21 months with CI <0.05%) versus the squamous cell group, with a median of 28.75 months (12.6-57, 8 months with CI <0.05%). Between stages III: The median OS in the adenocarcinoma group was 14 months (11.7-16.2 months with CI <0.05%) compared to the squamous group with 22.26 months (15.7-28.8 months with CI <0.05%). The median OS among the patients with some inflammation data was 65.7 months (57-74 months with CI <0.05%).



Conclusion: Adenocarcinomas seem to present a worse prognosis in localized stage, in contrast to metastatic stage. Inflammation seem to play an important role in the evolution of the tumor, regardless of the treatment.

Keywords: adenocarcinoma, epidermoid, global survival

P3.17-17 STAGE III: ANALYSIS TO ASSIST IN THE DECISION OF SURGERY AGAINST QUIMIO-RADIOTHERAPY

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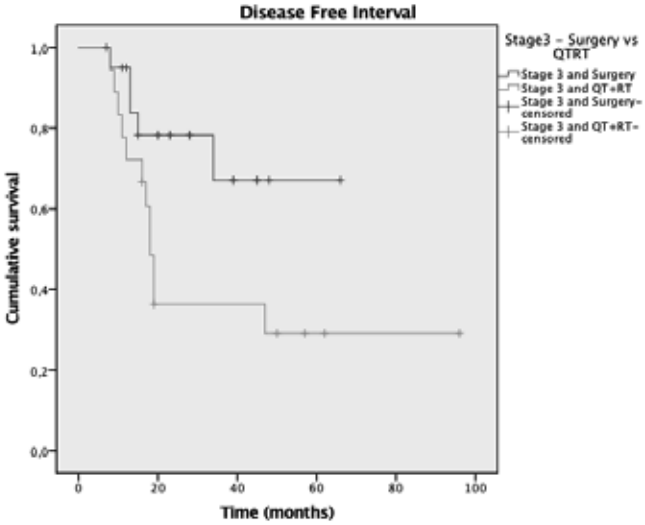
Background: The treatment of localized stage lung cancer offers limited succes in terms of increase survival. This study aims to find out if there are differences in disease-free survival (DFS) between surgery and chemo-radiotherapy in lung cancer Stage III. **Method:** A retrospective study was conducted on 96 patients with localized lung cancer treated in our center between from 2009 to and 2017, selecting only patients in Stage III. All the clinical medical histories were reviewed in order to analyze different parameters related to demography, histology and treatment. A statistical data analysis software (SPSS) was applied to search for relationships statistically significant among the variables. For the survival analysis, They used Kaplan-Meier curves and the Log-Rank test. **Result:** 39 cases of patients in Stage III were collected. The surgery group (with neoadjuvant or adjuvant chemotherapy) covers 21 patients (54%). The group treated with Chemo-Radiotherapy includes 18 patients (46%). For the surgery group, the mean for the DFS is estimated at 51 months (39.5-62.3 months), the median has not yet been reached.The mean DFS in the Chemo-Radiotherapy group is 40.2 months (22.6-57.8 months); the median being 18.2 months (15.75-20.65 months). These differences are statistically significant. The group treated with surgery: median age of 66.5 years, 94% male smokers. The adenocarcinoma represented the 61% of the group compared to the epidermoids, which account for 39%. In 44% of the tumors, signs of inflammatory infiltration were found. The Standard Uptake Value (SUV) average was 11.19 (2.72-18 SUV). The group treated with Chemo-Radiotherapy: median age of 66 years, 95% male smokers, 57% epidermoid tumors versus 43% of adenocarcinomas. Only 14% had signs of histological inflammation. The average SUV was 15.94 (3-48 SUV).



Conclusion: Patients candidates for surgery not only have optimal respiratory function tests. They seem to present less pulmonary pathology, a better immune response against tumors and a lower SUV value.

Keywords: surgery, quimio-radiotherapy, disease free survival

P3.17-18 TOWARDS INDIVIDUALIZING PATIENT SELECTION IN PROTON THERAPY FOR LUNG CANCER USING THE MODEL-BASED APPROACH

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Background: Intensity modulated proton therapy (IMPT) has the potential to reduce dose to adjacent normal tissue compared to photon therapy. Although dosimetric advantages can be seen, these results need to translate to clinically meaningful benefit. We aim to identify patients who would benefit from IMPT over photon volumetric modulated arc therapy (VMAT) in locally advanced lung cancer using recently published normal tissue complications probabilities (NTCP) models for heart and lung. **Method:** VMAT and robust optimised-IMPT plans were assessed to a physical dose of 70Gy in 35 fractions according to RTOG 1308 protocol. Risk estimates of grade 3+ cardiac toxicities and dyspnoea were calculated based on NTCP models which incorporated dose metrics and individual patients' baseline risk-factors (RF) (cardiac: pre-existing heart disease (HD), lung: patient-reported outcome dyspnoea grade). Risk estimates were calculated and compared based on the pre-treatment patients' RF and in the hypothetical scenarios where all patients had baseline HD or grade 1 dyspnoea. The difference between the probability estimates of VMAT and IMPT were determined (ΔNTCP). The models were applied in the different scenarios to ten proxy patients. These patients were retrospectively identified to ensure different anatomical locations (lobes and mediastinal/hilar regions) were represented (GTV median:

106cc, range: 15–404cc). Five patients had planning target volume (PTV) overlapping with the heart. **Result:** There was no significant difference in target coverage between VMAT and IMPT. Protons delivered a lower dose and to heart and lung in all patients (p<0.05, lung: V20, V5, mean lung dose; heart: V30, V5 and mean heart dose). When the risk estimates were calculated according to the patients' baseline RF, only three had an estimated ΔNTCP≥5%- all based on cardiac toxicities (AR VMAT vs IMPT: 38% vs 10%, 13% vs 10%, 18% vs 9%). Of the three, two patients had pre-existing HD. The relative risk reduction with IMPT varied between none to 0.74. Using ΔNTCP≥5% as a threshold, when all patients were considered to either have baseline HD or grade 1 dyspnoea, the same three patients were selected based on cardiac toxicities and two based on lung toxicity. Predictors of ΔNTCP≥5% for cardiac toxicities were pre-existing cardiac disease, tumour volume extending to the level of T7 vertebrae or below, degree of overlap between PTV and heart. **Conclusion:** In an unselected patient group, not all patients would benefit from IMPT. Although the validity of photon NTCP models in proton is unclear, appropriate models could be used to aid randomised control trial design.

Keywords: Cardiac toxicity, model-based patient selection, intensity modulated proton therapy

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.17-19 FIRST RELAPSE AND SURVIVAL FIVE YEARS AFTER RADICAL RADIOTHERAPY FOR LUNG CANCER.

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Background: Whilst local and distant control rates for both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) have been described for the immediate years following curative-intent radiotherapy, the natural history in patients with long-term disease-free survival (DFS) has not been established. Late relapse has been described in limited, small series (e.g. following surgery or SABR) but there is a paucity of data on relapse and survival after radical radiotherapy for all-comers. With improved radiotherapy planning and delivery, systemic therapy personalisation and surveillance strategies, survival rates at five years are improving. We describe the outcomes in patients with at least five years DFS from the commencement of radiotherapy. **Method:** Patients with DFS >5 years post-radiotherapy between 1st December 2000 and 1st March 2013 were identified from a prospective database of patients treated with curative-intent radiotherapy at a tertiary centre. Electronic records were interrogated for information pertaining to disease status and cause of death. **Result:** 680 patients received curative-intent radiotherapy; 503 NSCLC, 176 SCLC. At 5 years, 108 (16%) patients were alive; 66 males, 42 females. Mean age of survivors at treatment 67 years, median ECOG PS 1. SCLC for accounted 32 cases (18% total SCLC); NSCLC for accounted 76 cases (15% total NSCLC). SCLC (n=32 limited-stage) were managed with sequential chemoradiotherapy (n=20), concurrent chemoradiation (n=12). NSCLC (n=37 stage I; n=9 stage II; n=27 stage III; n=3 stage IV) were managed with radiotherapy alone (n=47), sequential chemoradiotherapy (n=19), concurrent chemoradiotherapy (n=7), SABR (n=5). With 80 months total median follow-up 16 (15%) patients surviving 5 years relapsed, 14 NSCLC (2.7% total treated radically), 2 SCLC (1.9% total treated radically). Of 23 patients reaching the 5-year time-point and thereafter developing a further malignancy, 4 were cases of second lung primary. **Conclusion:** Approximately 1 in 6 patients (all-comers) survived for 5 years after radical radiotherapy. Approximately 1 in 6 patients with 5 year DFS will later go on to relapse, suggesting that such patients should receive active follow-up.

Keywords: late relapse, lung cancer, radical radiotherapy

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.17-20 IMPACT OF SIGNIFICANT PRIMARY TUMOR SIZE REDUCTION ON RADIATION DOSE TO NORMAL STRUCTURES IN PATIENTS RECEIVING DEFINITIVE CHEMORADIOTHERAPY

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Background: Kilo-voltage cone beam computed tomography (kV-CBCT) allows for tumor localization and response assessment during definitive chemoradiotherapy (CRT) for locally advanced non-small cell lung cancer (LA-NSCLC). Previously we have analyzed patients with LA-NSCLC treated with definitive CRT accompanied with daily CBCT in our department and found that significant primary tumor volume loss occurs relatively early during treatment; and that greater tumor volume loss during treatment correlates with improved disease control and overall survival. It is not a standard practice to re-simulate patients for smaller target volume; but decreased tumor volume and consequent increase in air density could lead to increased radiation dose to the surrounding normal tissue such as the spinal cord. We hypothesize that increased air density secondary to tumor size reduction leads to increased dose to normal tissue including spinal cord, heart, esophagus and normal lung. **Method:** kV-CBCT images were imported to Eclipse treatment planning system. Primary tumors were re-contoured, and all normal tissue structures were readjusted based on the new images. Doses to the spinal cord, esophagus, normal lung, original planning target volume (PTV) as well as the new, smaller, PTV were re-calculated based on the original prescription dose and compared with the original plan by paired student t-test. The Acuros XB advanced dose calculation algorithm was used for all patients. **Result:** Nine patients with greater than 40% target volume reduction after 4 weeks of CRT were analyzed. There is a mean size reduction of 425.1 cc (55.6%) in PTV (p=0.002). Mean dose to the new PTV is 50 cGy (0.8%) less than the prescription dose (average 6088 cGy) (p=0.07). 0.03 cc of PTV receiving the highest dose is 110 cGy (1.8%) less than originally planned. There is no significant dose difference to the normal tissue, including esophagus (D0.03cc, DMean, V105%, V50 Gy and V60 Gy), heart (D0.03cc, DMean, V30Gy and V45Gy), ipsilateral lung (DMean, V5Gy, V10 Gy, V20 Gy, V30 Gy) and total lung (DMean, V5Gy, V10 Gy, V20 Gy, V30 Gy). **Conclusion:** Despite significant primary tumor size reduction, there is no clinically significant difference in dose delivered to the primary tumor or to the radiation sensitive critical organs. Therefore the orinigal treatment plan can be safely used.

P3.17 TREATMENT OF LOCOREGIONAL DISEASE - NSCLC
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.17-21 SURGICAL TREATMENT FOR CENTRALLY LOCATED OR HILAR INVASIVE LOCALLY ADVANCED LUNG CANCER.

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Background: In cases of centrally located or hilar invasive lung cancer(CLHILC), it is quite difficult to decide the treatment strategy whether pneumonectomy, sleeve-lobectomy and/or pulmonary angioplastic procedure, or lobectomy is necessary or not. Especially in the patients with inadequate pulmonary functions, the treatment strategy is hard to be decided. To clarify the surgical outcomes for CLHILC, we retrospectively investigated our experiences in Setouchi Lung Cancer Study Group (SLCG). **Method:** In order to show the clinical results of (CLHILC), we retrospectively investigated the patients' medical records from January 2010 to December 2011 in SLCG. The definition of CLHILC; clinical tumor size is more than 3cm (T2 or more) and located in main bronchus or lobar orifice, or hilar nodal invasion is shown around lobar bronchial orifice or pulmonary arterial branch without mediastinal nodal metastasis. That is, the simple lobectomy is not easy or inadequate to complete resection for CLHILC. **Result:** Ninety-seven patients' records were collected, the men were 78, the mean age was 67. Twenty- four cases underwent preoperative treatment (induction chemotherapy in 8, induction chemoradiotherapy in 13, and radiotherapy in 3 cases). Except 1 exploratory thoracotomy cases, the surgical procedure was as following; lobectomy in 37, lobectomy with broncho-vascular plasty in 4, bronchoplasty in 11 and pulmonary angioplasty in 16, bilobectomy in 12, and pneumonectomy in 15 cases. The post-operative complications were occurred in 39 cases (40%), and there were 2 30-days mortal cases. The survival rate was 65% at 3 years and 60% at 5 years. **Conclusion:** We reviewed CLHILC in SLCS Group and showed the surgical procedure variety, the morbidity and survival rate. The pneumonectomy was performed in 15% and the complicated surgical procedure such as broncho-vasucular platy were chosen in 30% with acceptable morbidity and mortality.

Keywords: Hilar invasive lung cancer, Pneumonectomy, Broncho-vascular plastic surgery

P3.17-22 NIVOLUMAB PLUS CISPLATIN/PEMETREXED OR CISPLATIN/ GEMCITABINE AS INDUCTION IN RESECTABLE NSCLC

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Background: For patients (pts) with stage IB (>4cm)-IIIA Non-small-cell lung cancer (NSCLC), multi-modality therapy yields a modest improvement in 5 year post-surgical overall survival (OS), with comparable benefit for induction and postoperative adjuvant chemotherapy (chemo). Induction can speed the discovery of promising regimens by using pathologic response as a surrogate for OS. About 20% of pts treated with induction chemo have major pathologic response (MPR) (< 10% viable tumor) at primary and lymph nodes while pathologic complete responses (pCR) average 4%. MPR was strongly associated with improved OS (Hellmann MD, Lancet, 2014). PD-1 checkpoint inhibitors (CI), nivolumab (nivo), pembrolizumab (pembro), and the PD-L1 CI, atezolizumab, are established in advanced NSCLC as 2nd line therapy, and pembro is approved as a single agent as 1st line treatment of pts with PD-L1 high expressing tumors. In a phase III 1st line NSCLC study, pts with high mutational burden tumors had superior OS with nivo plus ipilimumab compared to doublet chemo. Pembro plus carboplatin with pemetrexed (P) was approved as 1st line therapy based on a randomized phase II study in advanced NSQ NSCLC showing improved clinical response and PFS compared to chemo alone with no increase in grade III toxicity. We therefore hypothesize that the addition of nivo to induction cisplatin (C) P or C gemcitabine (G) will increase the MPR rate over induction chemo alone compared to historical controls. **Method:** This is an investigator initiated trial for pts with newly diagnosed clinical stage I-IIIA (stage I > 4cm) SQ and NSQ NSCLC. Induction is C 75mg/m2 IV q 3w x 3 plus either P 500 mg/m2 IV q 3wks x 3 or G 1250mg/m2 IV d1, d8 q 3 wks x 3 plus nivo 360mg IV q 3w x 3. Surgery is planned 3 wks after the last dose. The primary outcome is MPR. Secondary outcomes include safety, pCR, overall clinical response rate, clinical CR, 1 year PFS, OS and exploratory outcomes assessing markers of immune bias. Enrollment will be 34 pts. NCT03366766 **Result:** Section not applicable **Conclusion:** Section not applicable

Keywords: Non-small-cell lung cancer, induction, Surgery

P3.17-23 ROLE OF SURGERY IN LOCOREGIONAL ADVANCED NSCLC; A CASE OF AGGRESSIVE SALVAGE SURGERY AFTER DEFINITIVE CHEMORADIATION

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Background: Prognosis of patients with locally advanced NSCLC is limited. Multimodality approach can be effective in highly selected patients. **Method:** The present report describes an interesting case treated with aggressive salvage surgery after definitive chemoradiation. **Result:** Case: 72 year-old male was found to have a centrally located tumor in right upper lobe at a regional hospital. The carina and lower trachea, and subcarinal lymph node was directly infiltrated with the tumor. Finally, the tumor was diagnosed as a cT4(carina & trachea) N2(#7 direct invasion) M0 squamous cell carcinoma. With thought of unresectable disease due to long invasion of central airway, definitive chemoradiation consisted of 4 cycles of Carboplatin and Paclitaxel in combination with 60Gy concurrent radiotherapy was performed. The tumor response was limited, and Docetaxel was used as 2nd line therapy. However, the disease was progressive, the tumor occluded the right main bronchus totally and also obstructed an orifice of the left main bronchus partially. The patient was referred to us for palliative airway stenting. Y-shaped silicon stent was inserted urgently, and his respiratory status was improved immediately. The patient strongly hoped to receive further therapy, a precise systemic workup was performed at our hospital. The tumor was still locoregional disease and length of the airway invasion was about 3cm, which was considered as resectable with right carinal upper lobectomy or carinal pneumonectomy. Although risk of the resection was extremely high not only due to complex surgical procedure but due to poor patient status and history of full-dose irradiation, our multidisciplinary team decided to perform aggressive salvage surgery. To minimize the risk of surgery, our plans were follows; 1: trying to preserve right lung, 2: modified clamshell approach to make tension-free reconstruction of carina with bilateral hilar release, 3: a tight covering of anastmosis with omentum and thymus. Macroscopic R0 resection was acheived with right carinal upper lobectomy. However, remaining right lung had severe fibrotic change due to irradiation, right carinal pneumonectomy was performed ultimately. Although postoperative tracheostomy and long-term respiratory support were required, his general condition was improved slowly. Most part of the anastomosis became necrosis, however the intensive covering avoided anastomotic problems except for mild stricture. He was finally discharged at 5 months after surgery, and was free from recurrence at 1-year. **Conclusion:** In the present case, aggressive salvage surgery achieved a successful outcome. A careful evaluation of patient and an elaborate plan of surgery were essential.

Keywords: salvage surgery, multimodality approach, Locally advanced NSCLC

P3.CR-01 TO BETTER UNDERSTAND THE ANATOMICAL PROXIMITY OF CARDIAC PLEXUS TO PREVENT LETHAL ARRHYTHMIAS ASSOCIATED WITH LUNG CANCER SURGERY

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Background: Arrhythmias are known as one of the complications after surgery, and most of them are not lethal. But life-threatening bradycardic arrhythmias, such as complete AV block and asystole, have been described in the literature, but in reality very rare. **Method:** To consider the relationship between arrhythmias and the involvement of cardiac plexus during lymph node dissection from anatomical viewpoint by presenting two patients who were complicated with life-threatening arrhythmias during and after surgery. **Result:** A 71 year-old Japanese woman had an abnormality in a chest X ray on the annual medical checkup. A CT scan and a bronchoscopic biopsy led to the diagnosis of adenocarcinoma in left lower lobe, cT2aN0M0 StageIB. A preoperative electrocardiogram showed a heart rate of 55 per minute with normal sinus rhythm, and the echocardiography was normal. The patient underwent a thoracoscope-assisted left lower lobectomy and lymph node dissection. Post-operatively the patient was noticed to have lower heart rates of 40s, and when the patient sat up on the next morning, the bradycardia progressed to asystole for 10 seconds. CPR was performed and sinus rhythm was resumed. Having a temporary then a permanent pacemaker been implanted, the patient was uneventfully discharged from hospital on postoperative day (POD) 22. The second patient was a 67 year old Japanese man who presented with bloody sputum. An X ray and a bronchoscopic biopsy led to the diagnosis of squamous cell carcinoma in left lower lobe, cT2bN0M0 StageIIA. A preoperative electrocardiogram showed a heart rate of 73 per minute with normal sinus rhythm and the echocardiography was normal. The patient underwent a left lower lobectomy and bilateral mediastinal lymph node dissection through a median sternotomy. During lymph node dissection along the right vagus nerve, the patient's heart rate and blood pressure dropped suddenly and an electrocardiogram monitor showed ST elevation. These abnormalities returned to normal soon after cardiac massage was performed and a coronary vasodilator was given. A temporary pacing wire was inserted at the end of the surgery. The postoperative course was uneventful and the patient was discharged on POD 11. **Conclusion:** The cause of arrythmias is probable that cardicac plexus was stimulated inadvertently during lymph nodes dissection around the vagus nerve, considering a role of cardicac plexus from the anatomical viewpoint. It is important to be familiar not only with the course of phrenic, vagus and recurrent laryngeal nerve but also the anatomy of cardiac plexus in lung cancer surgery.

Keywords: lung surgery, bradycardia, cardiac plexus

P3.CR-02 SBRT OF LUNG PRIMARY AFTER COMPLETE RESOLUTION OF METASTATIC DISEASE IN CASE OF EGFR MUTATED ADENOCARCINOMA LUNG: A CASE REPORT

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Background: Lung cancer accounts for the highest malignancy related mortality among males worldwide. The prognosis of metastatic lung cancer is dismal and as per data from United States of America, the 5-year survival of metastatic lung cancer patients stands at mere 5 percent. Loco-regional management in metastatic lung cancer is not routinely practiced, however exceptions are made in patients who have very good response to systemic treatment. In such cases loco-regional treatment is expected to improve disease free survival. **Method:** Section Not applicable **Result:** Fifty-six year old male, known hypothyroid[on thyroxine supplementation] without any significant history of addiction/ family history presented with chronic non-productive cough and acute breathlessness. On evaluation left lung upper lobe primary mass [adenocarcinoma on histopathology] and left sided pleural and pericardial effusion[malignant on cytology]as well as multiple cervical lymphadenopathy was found on PET-CT. Hundred percent of the primary tumour tissue was found to harbour EGFR mutation while being negative for ALK mutation. After six cycles of chemotherapy with Carboplatin and Pemetrexed combination chemotherapy regimen, the patient was kept on Erlotinib for 9 months. All the metastatic diseases were found to be resolved and primary was shrunken on assessment PET-CT. Patient was advised for SBRT to primary 50Gy in 5 fractions,10Gy per fraction on alternate days over a period of 10 days following which he has been kept on Tab Erlotinib. The patient has a survival of 18 months calculated from the time of diagnosis till compilation of data and is disease free. **Conclusion:** High percentage of EGFR mutation can provide very good response to tyrosine kinase inhibitor therapy in case of metastatic adenocarcinoma lung. Partial response at primary with resolution of metastatic disease throws a challenge for use of loco-regional modality of management in tandem with systemic treatment.

Keywords: Metastatic adenocarcinoma lung, SBRT, EGFR mutation positive

P3.CR-03 PULMONARY SPINDLE CELL NEOPLASM - NEOADJUVANT TREATMENT AND RESPONSE

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Background: Sarcomatoid carcinoma (SC) of the lung comprises a small subset of non-small cell lung cancer (NSCLC) accounting for no more than 3% of all lung tumors. **Method:** Section not applicable **Result:** A 66-year-old Caucasian man was seen in the ED for the complaints of shortness of breath, productive cough, and fever. He had a 70 pounds unintentional weight loss over 5 months and generalized weakness. His medical history included COPD, HTN, HLD, and tobacco abuse (108 pack years of smoking). He denied alcohol or illicit drug use. He was treated with antibiotics for COPD exacerbation with symptomatic improvement; However, he had a chest X-ray finding notable for an 8 cm right upper lung mass. Chest CT showed 6.3 x 7.9 x 8 cm RUL pleural-based mass with areas of low density changes and irregular opacity measuring 3.7 x 6.5 x 7.5 cm abutting the pleura in the right lower lobe. A right hilar node was also seen measuring up to 2.3 x 2.9 cm in size. Abdomen/pelvis CT and MRI brain showed no gross evidence of metastatic disease. The bone scan was negative for blastic or lytic bone disease. He had a CT guided biopsy which identified a spindle cell neoplasm. Histopathology confirmed spindle cells with markedly atypical nuclei amid a hyalinized background, with areas of necrosis. Immunoperoxidase stains were positive for CKAE1/AE3 and vimentin with diffuse staining. CK7 was focally positive in very few cells, as were Ber-EP4 and calretinin. PAX8 was negative. Transthoracic echocardiogram showed grade I diastolic dysfunction with preserved ejection fraction. Pulmonary function testing showed severe obstructive pattern consistent with severe COPD, making him a poor surgical candidate. The final decision was made to start the patient on concurrent chemoradiation. Initial chemotherapy regimen was Ifosfamide 1200 mg/m2 along with Mesna 240 mg/m2 to be given for a total of 15 doses. He was also planned to have Intensity-modulated radiation therapy of 3000 Centigray over 15 fractions to the lung. He finished 6 cycles of chemotherapy. He tolerated his regimen well with only mild neutropenia. Repeat CT chest showed interval decrease of the right upper lobe mass (now 4.5 x 1.7 cm instead of 7.9 x 4.7 cm) and a hilar lymph node that measured 1.3 x 1.3 cm (previously measuring 2.3 x 2.9 cm). **Conclusion:** We present a patient that received concurrent chemoradiotherapy with initial response on CT imaging. This can provide an acceptable alternative to patients presenting with non-resectable tumors.

Keywords: Neoadjuvant treatment, Spindle cell neoplasm

P3.CR-04 LUNG CANCER WITH CONCURRENT ROS1 REARRANGEMENT AND KRAS MUTATION: A CASE REPORT

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Background: ROS1 rearrangement has recently emerged as a new molecular subtype in non-small cell lung cancer (NSCLC), and is predominantly found in lung adenocarcinomas compared with other oncogenes such as EGFR, KRAS, or ALK. Patients who have both mutations are extremely rare. **Method:** A 42-year-old female diagnosed with adenocarcinoma (IIIB, $T_2N_3M_0$), who was shown to have ROS1 and KRAS mutations by next generation sequencing. **Result:** The patient was prescribed oral crizotinib and a CT scan show a partial response in the pulmonary lesions after one month. Unfortunately, a CT scan show progression of the pulmonary lesion after three months. And the patient was treated with the MEK inhibitor, selumetinib (AZD6244), combined with pemetrexed. The patient was alive at now. **Conclusion:** We reviewed the related literature to determine the frequency of gene mutations in NSCLC patients. A better understanding of the molecular biology of NSCLC with multiple driver genomic aberrations will assist in determining optimal treatment.

Keywords: non-small cell lung cancer, KRAS gene mutation, ROS1 fusion gene

P3.CR-05 THE ROLE OF PATIENT ENGAGEMENT IN IMPROVED OUTCOMES IN LUNG CANCER CARE

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Background: Anne Marie Cerato, the primary author, is the patient in this case study. Lung cancer patients tend to have a high disease burden as many are diagnosed at a late stage and require extensive treatment. As such, they are required to make life-altering decisions during and after treatment. The level of their engagement and participation in that decision-making process can differ greatly thus effecting their quality of care and quality of life. **Method:** Patient was diagnosed in 2009 with stage 3A adenocarcinoma of the right lung. Treatment decisions were required at three different time points within this patient's experience (at time of original diagnosis, at recurrence, and at progression). Two different models of engagement were experienced. At diagnosis, the patient as a passive participant model was experienced, and upon recurrence and progression, the patient was an active participant in the decision making process. **Result:** In the patient as a passive participant model, the patient felt duress to follow prescribed treatment resulting in feelings of isolation, anxiety, anger, and depression. In contrast, when the patient was an active participant and involved in the decision making process, the patient felt more in control of their treatment, which resulted in feelings of inclusion, hopefulness, and decreased anxiety. **Conclusion:** It is difficult to determine the difference whether or not there was improvement in patient clinical outcomes. However, qualitatively as a result of increased patient engagement and shared decision making, patients experienced improved outcomes as they felt less isolated, anxious, and more involved in their care. As a result of increased patient engagement, this patient explored additional treatment avenues and sought connections with the larger patient community. Clinicians can work with patients to enable or improve engagement and involvement by considering the following recommendations: 1. Patients should be given access to clinical notes, results and reports, and given time to consider the information provided. 2. Patients should be encouraged to ask questions. 3. Connect patients to a lung cancer patient group for additional support 4. Ensure patients are supported post treatment and through transitions in care.

Keywords: Patient Engagement, Case Study, Advocacy

P3.CR CASE REPORTS
WEDNESDAY, SEPTEMBER 26, 2018 - 09:45-13:30

P3.CR-06 EFFECT OF PALLIATIVE CARE AND CANCER REHABILITATION ON LUNG CANCER SURVIVORSHIP - PATIENT'S PERSPECTIVE

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Background: Pate *et al*,(1995) and Bryan *et al*,(2007) reported that approximately 30% of total cancer deaths are related to poor exercise and nutrition. Though importance of palliative care, cancer rehabilitation and nutritional advice has been recognized, those information tend to be fragmented. Considering the importance of palliative care and cancer rehabilitation in patients' treatment outcome and survivorship, joint and comprehensive advocacy to strengthen those intervention is necessary. **Method:** Case study of a 56-year old Japanese male patient diagnosed with pulmonary adenocarcinoma NSCLC (stage 4) metastases and worked with cancer for 7 years. **Result:** Various treatment were used including chemotherapy, EGFR Tyrosine kinase inhibitor, and immunotherapy. Bone metastases and brain metastases were observed and palliative radiotherapy and strontium were used. Vertebroplasty was considered but not conducted. Irradiation to whole brain was considered but not done. Early introduction of palliative care and cancer rehabilitation helped to improve the patient QOL and enable patient to continue his work. Though ADL decreases over the period, the patient continued to receive support from rehabilitation team, try to exercise and manage his QOL. Patient kept his own record on urine, defecation, medication, meals, mental condition, in daily basis. Patient's conditions and effectiveness of treatment were examined regularly at the consultation based on the laboratory result and the patient's record. Regular feedback towards the patient's condition and his record from the Palliative care and the rehabilitation team gave patient better perspective and understanding of his changing condition and enable him to coop with advancing stage. **Conclusion:** The life of the patient has had its ups and downs. The case shows effect of palliative care and cancer rehabilitation on patent's QOL and survivorship. More integrated approach of cancer rehabilition into palliative care and lung cancer treatment need to be explored. It also suggest that more study from patients' perspective could contribute towards comprehensive understanding and advocacy.

Keywords: working with cancer, palliative care, cancer rehabilitation

P3.CR CASE REPORTS
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P3.CR-07 COMPREHENSIVE GENOMIC PROFILES FOR A MEDIASTINAL TUMOR SUSPECTED OF SYNOVIAL SARCOMA: A CASE REPORT

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Background: Synovial sarcoma (SS) is an aggressive malignant tumor and accounts for 5 to 10% of all types of soft tissue sarcomas. SS commonly occurs in the deep tissue adjacent to the joints or tendons in the limbs while SS rarely occurs in the mediastinum. Most of SS harbor t(X;18) (p11.2;q11.2), which leads to chimeric fusion of *SYT* with one of the *SSX* genes. Furthermore, somatic mutations of cancer-related genes such as *PIKC3A, TERT, CDH1,* and *PTEN* have also been reported in the SS even though the frequencies of these genetic alterations were not high. Recently, the comprehensive genomic profile (CGP) using the next-generation sequencing (NGS) is widely used for better understanding of tumorigenesis and it can also provide clinically actionable information to guide treatment decisions for patients. **Method:** In this study, the clinical and histological records of an anterior mediastinal tumor suspected of SS were reviewed, and a reverse transcript polymerase chain reaction (RT-PCR) assay and NGS using a high sensitivity amplicon-based targeted sequencing method incorporating molecular barcodes (a panel designed for hotspots of 47 cancer-related genes) were performed to identify the genetic alterations. **Result:** A 78 years old woman was referred to our hospital because of approximately 9 cm anterior mediastinal tumor. A positron emission tomography showed the high fluorine-18-fluorodeoxyglucose uptake. The patient underwent median sternotomy and resection of the tumor combined with wedge resection of the left upper lobe of lung. Histological examination revealed a monomorphic spindle cell growth and immunohistochemical stains (AE1/AE3, CAM5.2, CD34, CD99, Desmin, Nestin, a-SMA, CDK4, CD56, c-kit, EMA, and S-100) were negative, so the tumor was suspected of SS. We performed a RT-PCR assay for *SYT-SXX* fusion, however, it was not detected. NGS analysis revealed the presence of hotspot mutations in 4 cancer-related genes (*PIK3CA, CDKN2A, PTEN,* and *MAP2K4*). Because the tumor was completely resected, an adjuvant therapy had not been planned and the scheduled medical checkup has been performed. Fortunately, the patient is alive without any recurrence for 5 years. **Conclusion:** The genetic features of a mediastinal tumor suspected of SS, without *SYT-SSX* fusion, were evaluated by CGP analysis. In case of the rare tumor especially when it occurs in the unusual location and the histological and molecular assessments are not conclusive, a CGP assay may be helpful to reveal the genetic feature of the tumor and to determine the effective targeted drugs.

Keywords: next-generation sequencing, SYNOVIAL SARCOMA, anterior mediastinal tumor

P3.CR CASE REPORTS
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P3.CR-08 CLONALLY RELATED PRIMARY ALK REARRANGEMENT ADENOCARCINOMA AND ASSOCIATED METASTATIC LESIONS: A CASE REPORT

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Background: Anaplastic lymphoma kinase (*ALK*) rearrangement is a driver gene in non-small cell lung cancer (NSCLC). *ALK*-positive tumors are sensitive to ALK tyrosine kinase inhibitors (TKIs). Detecting key driver genes is crucial to personalized treatment. Different histomorphological patterns have different driver genes. **Method:** A 42-year-old male diagnosed with adenocarcinoma (III), who was shown to have ALK fusion by reverse transcription polymerase chain reaction (RT-PCR). **Result:** The patient diagnosed with adenocarcinoma, who had different histomorphologies in the primary lung site (mucinous type) and lymph node metastasis (solid type), but had the same genotype, which both presented with an *ALK* rearrangement, while negative for an *EGFR* mutation.This histological heterogeneity did not necessarily indicate a genomic difference. **Conclusion:** Genomic analysis may be a supplement of the histological feature of ALK-rearranged tumors. These gene alterations could help patients to choose an appropriate TKI and its impact on the therapeutic responses.

Keywords: ALK fusion, histology, Non-small-cell lung cancer

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P3.CR-09 MET-UBE2H FUSION AS A NOVEL MECHANISM OF ACQUIRED EGFR RESISTANCE IN LUNG ADENOCARCINOMA" WITH "MET FUSION AS A NOVEL MECHANISM OF ACQUIRED EGFR RESISTANCE IN LUNG ADENOCARCINOMA

W. Wang[1], C. Xu[2], Q. Zhang[3], W. Zhuang[4], Y. Zhu[5], Z. Song[1], Y. Chen[3], G. Chen[6], M. Fang[1], T. Lv[7], Y. Song[7]
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Background: As we all known, the most common mechanism of acquired resistance to EGFR-TKIs treatment is the development of the EGFR T790M mutation, which occurs almost one half of cases of acquired resistance. Other previously described resistance mechanisms include HER2 amplification, MET amplification, PIK3CA mutation, epithelialmesenchymal transition (EMT), and small cell transformation. **Method:** A 43-year-old female diagnosed with adenocarcinoma including brain and bone metastases, who was shown to have MET fusion after erlotinib acquired resistance by next generation sequencing. **Result:** The patient with left lung tumor. Cytological examination of sepecimens from primary focus show adenocarcinoma." with "A bronchoscopic biopsy sepecimens from primary foucus show adenocacrcinoma. By next generation sequencing we found EGFR 19 exon E746_S752delinsV and MET-UBE2H fusion after erlotinib acquired resistance, and the patient experienced a remarkable tumor response to crizotinib remains at 6

months on therapy. **Conclusion:** We report the occurrence of MET-UBE2H fusion along with EGFR 19del at disease progression after treatment with erlotinib. Hence we attribute the emergence of MET-UBE2H fusion as a possible mechanism of acquired resistance to first generation EGFR-TKI in EGFR mutated NSCLC.

Keywords: EGFR resistance, MET fusion, non-small cell lung cancer

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P3.CR-10 HIP1-ALK FUSION VARIANT IN NON-SMALL-CELL LUNG CANCER AND RESPONSE TO CRIZOTINIB

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Background: Several fusion partners of ALK have been reported in patients with non-small cell lung cancer (NSCLC). And huntingtin interacting protein 1 (HIP1)-ALK is one kind of ALK fusion types. **Method:** We reported a case of HIP1-ALK fusion variant in non-small-cell lung cancer and further reviewed the clinical characteristic and the efficacy of crizotinib to this type fusion of NSCLC patients. **Result:** A 56-year-old Chinese woman with multiple lung metastases NSCLC(T1N0M1, stage IV). Histological examination of the tumor showed lung adenocarcinoma. Ventana (D5F3) ALK IHC assay (Ventana Medical Systems, Roche, Inc) analysis of the left lung tissue revealed the presence of an ALK rearrangement. Then the patient experienced a remarkable tumor response to crizotinib. By using next generation sequencing assay, we found that tumor had HIP1-ALK (H21; A20) rather than the most common kind of Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK). Considering this rare ALK fusion and remarkable response to crizotinib treatment, we conclude that the incidence of HIP1-ALK in NSCLC patients with ALK rearrangement should be attentive. NSCLC patients with HIP1-ALK fusion gene response to treatment with ALK inhibitors. **Conclusion:** With the guidance of precise diagnosis, it is important that we should realize other rare ALK fusions and novel diagnostic method.

Keywords: HIP1-ALK, NSCLC, crizotinib

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P3.CR-11 ROS1 FUSION AND MET AMPLIFICATION DUAL DRIVE COEXISTENCE IN LUNG ADENOCARCINOMA AND RESPONSE TO CRIZOTINIB: A CASE REPORT

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Background: The c-ros oncogene 1 (ROS1) fusion is almost mutually exclusive to MET amplication in non-small cell lung cancer (NSCLC), and it is not seen in the literature for patients to exhibitthree mutations. **Method:** A 66-year-old female diagnosed with IV stage adenocarcinoma, who was shown to have ROS1 fusion and MET amplication by fluorescence in situ hybridization (FISH), and verified by next generation sequencing. **Result:** The patient with right lung tumor and brain metastases NSCLC. Histological examination of surgical sepecimens from primary focus show adenocarcinoma. By fluorescence in situ hybridization (FISH), we found ROS1 fusion and MET amplication. Then we verified a novel ROS1fusion: ZCCHC8-ROS1, and the patient experienced a remarkable tumor response to crizotinib for 6 months (PFS). **Conclusion:** To the best of to our knowledge, this is the first case report of a patient with concurrent ROS1 fusion and MET amplication, and ZCCHC8-ROS1. This patient had an excellent response to crizotinib, suggesting that concurrent ROS1 fusion and MET amplication response to crizotinib was less than ROS1 fusion single driver.

Keywords: ROS1 fusion, MET amplication, non-small cell lung cancer

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P3.CR-12 A NOVEL ONCOGENIC DRIVER IN A LUNG ADENOCARCINOMA PATIENT HARBORING AN EGFR-KDD AND RESPONSE TO AFATINIB

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Background: Oncogenic mutations in the epidermal growth factor receptor (EGFR) are found in a subset of patients with non-small cell lung cancer (NSCLC) and serve as important predictive biomarkers in this disease. EGFR exon 18-25 kinase domain duplication (EGFR-KDD) mutations has rencently emerged as a new EGFR gene molecular subtype in non-small cell lung cancer(NSCLC) is extremely rare. **Method:** A 59-year-old male diagnosed with adenocarcinoma, who was shown to have gene detected by the next generation sequencing (NGS) and treatment with afatinib. **Result:** Histopathological observations with hematoxylin and eosin staining was shown adenocarcinoma, immunohistochemical staining for the expression of TTF-1, NapsinA and CK7. The gene detected by NGS that found an EGFR-KDD, CTNNB1 p.S37Y and TP53 p.R282W. Our case is the second report EGFR-KDD in Chinese populations. The patient was treated with afatinib therapy. And afatinib therapy showed a good response. **Conclusion:** The cases presented here highlight that adjusting our strategy and using newly available tools, such as comprehensive NGS tests, could prove useful in detecting alternative ways in which the EGFR pathway is altered (and can be targeted) in tumors.

Keywords: afatinib, NSCLC, EGFR-KDD

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P3.CR-13 DUAL DRIVE COEXISTENCE OF EML4-ALK FUSION AND TPM3-ROS1 FUSION LUNG ADENOCARCINOMA: A CASE REPORT

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Background: Recent reports of overlap between ROS1 fusions and other oncogenic driver alterations have still been controversial. We reported a case of concomitant EML4-ALK fusion and TPM3-ROS1 in non-small-cell lung cancer (NSCLC) and further reviewed the clinical characteristic in this type double fusion of NSCLC patients. **Method:** A 47-year-old male diagnosed with adenocarcinoma (IA, T1aN0M0), who was shown to have ALK and ROS1 fusion by next generation sequencing. **Result:** The patient presented with a locally tumor of the left upper lobe with physical examination. He received lung cancer surgery with thoracoscopic. by using next generation sequencing assay, we found that tumor had concomitant EML4-ALK fusion and TPM3-ROS1. No recurrence was observed from a follow-up of 7 months in the case. Considering this rare ALK fusion and ROS1 double rearranged, we conclude that the incidence of this double mutation in NSCLC patients should be attentive. **Conclusion:** With the guidance of precise diagnosis, it is important that we should realize the incidence of concomitant ROS1 fusion and other driver genes including ALK or EGFR. And it should further explore treatment model and provides additional therapeutic options.

Keywords: Anaplastic lymphoma kinase, ros1, Concomitant

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P3.CR-14 A CASE OF EGFR TYROSINE KINASE INHIBITOR (TKI), OSIMERTINIB INDUCED PNEUMONITIS IN A PATIENT WITH RECURRENT FEVERS OF UNKNOWN ORIGIN

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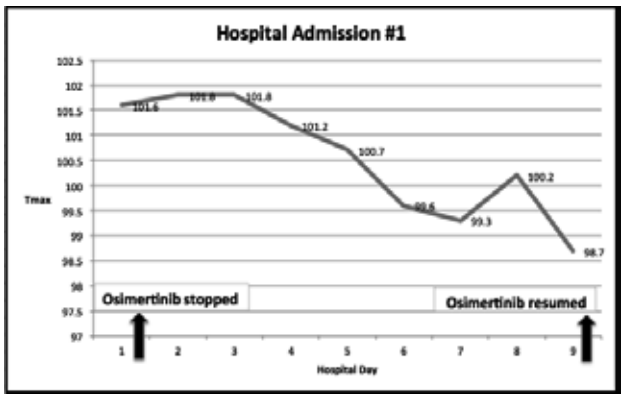
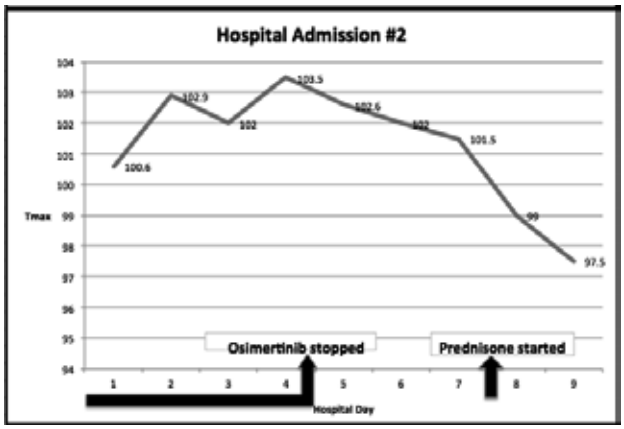
Background: 64-year-old female with stage IV EGFR exon 19 mutated adenocarcinoma of lung on osimertinib presented with recurrent fevers of unknown origin. **Method:** Section not aplicable. **Result:** Ms. M presented

to the hospital with fevers. Osimertinib was held on admission. Imaging showed a possible pneumonia and she started IV antibiotics. Her fevers subsided and she was discharged on IV antibiotics. She resumed osimertinib upon discharge. The following day, she spiked fevers to 103.9F. She was admitted to the hospital with fevers and new hypoxia requiring 4 liters of supplemental oxygen. Osimertinib was continued on admission. The results of her infectious workup, including bronchoscopy studies, were negative and she continued to spike high fevers despite broadened coverage for atypicals and fungi. Osimertinib was stopped on hospital day #4 due to QTc prolongation likely from its interaction with other QT prolonging antimicrobials. Given persistently high fevers despite broad antibiotics and a negative infectious workup, Osimertinib-induced pneumonitis became a likely explanation. Anti-microbials were stopped and prednisone 1mg/kg daily was started. She deferversed and had a rapid symptomatic improvement.





Conclusion: Osimertinib toxicity has been investigated in the literature. In the AURA3 trial, pneumonitis resulted in 1/4 reported fatal adverse events. ILD–like events were reported in 10 patients (4%, 9 events were grade 1 or 2, 1 death). The FLUARA trial showed similar findings, with ILD-like adverse events in 11 patients (4%) with 7 "recovered" and 4 "recovering". There were no reported fatal outcomes from ILD. After stopping Osimertinib during her 2 hospitalizations, our patient defervesced after 4 days and 3 days, respectfully. This correlates with the 48-hour half-life of Osimertinib. Our case demonstrates that determining drug toxicity can be challenging, especially when other etiologies such as infection are more common. For Ms. M, her lack of improvement with anti-microbials coupled with a significant response to steroids makes the case for Osimertinib-induced pneumonitis.

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P3.CR-15 SQUAMOUS CELL CARCINOMA DIAGNOSED WHILE ON IMMUNOTHERAPY FOR LUNG ADENOCARCINOMA: A UNIQUE CLINICAL CASE.

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Background: In the first-line setting, pembrolizumab is used in non-small lung cancer (NSCLC), when the expression of PD-L1 is 50% or more, and the tests for EGFR, BRAF V600E mutations and ALK and ROS1 rearrangements are negative. In this setting, pembrolizumab showed higher response rates, overall survival benefit and fewer severe adverse events when compared with chemotherapy. Also, there is increasing evidence of the efficacy of immunotherapy in other types of cancer, namely, locally advanced unresectable or metastatic cutaneous squamous cell carcinoma (cSCC). **Method:** A literature and patient clinical information review was performed. **Result:** A 72 years-old man, former smoker (60 pack-year), was admitted to our hospital for treatment of a stage IIIA (cT1N2M0) lung adenocarcinoma, diagnosed in November 2015 following screening exams. Concurrent chemoradiotherapy was administered between 7th January and 14th February 2016 (70Gy in 35 fractions, using Intensity-modulated radiation therapy technic with carboplatin-paclitaxel duplet) followed by consolidation chemotherapy. Ten months later, a sub-carinal adenopathy recurrence confirmed by biopsy was diagnosed. The tumor was highly positive to PD-L1 (expression over 90%) and showed no predictive mutations/rearrangements of sensitivity to molecular target EGFR, ALK or ROS1 drugs. Radical radiotherapy to the mediastin was administered between 9th January and 17th February 2017 (60Gy in 30 fractions, using volumetric modulated arc radiotherapy technic). Metastatic disease was diagnosed 7 months later, with right hilar and mediastinal adenopathies, bilateral pulmonary nodules and right pleural metastasis. Pembrolizumab 200mg every 21 days was initiated in 10th November 2017 until 20th March 2018 (7 cycles), due to disease progression and to grade 3 xerostomia (CTCAE v4.03). Second-line palliative treatment with platin-pemetrexed duplet was proposed. In January 2018, while on pembrolizumab, the patient noticed an ulcerated and growing lesion in the right *ala* of the nose. The lesion was surgically removed in 29th March 2018, with the diagnosis of an invasive cSCC. **Conclusion:** The patient developed a cSCC while on treatment with pembrolizumab for metastatic lung adenocarcinoma. The reason for this does not seem to be associated with immunotherapy as there is no current description in the literature of development of second neoplasia while on immunotherapy. Innate resistance to immunotherapy could be a possible explanation, with unsuccessful reactivation and poor clonal-proliferation of antigen-experienced T cells present in the tumor micro-environment.

Keywords: Immunotherapy, cutaneous squamous cell carcinoma, lung adenocarcinoma

P3.CR CASE REPORTS
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P3.CR-16 A CASE OF TOXIC HEPATIC EVENT OCCURRING IN COMBINATION TREATMENT WITH NIVOLUMAB AND ANTI-TUBERCULOSIS IN ADVANCED LUNG CANCER

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Background: Nivolumab, an immune checkpoint inhibitor, has been considered one of the standard treatments for previously treated advanced non-small-cell lung cancer. There is a not well known about the treatment and complications of tuberculosis in advanced lung cancer patients treating with nivolumab. We report a new case, toxic hepatic event occurring in combination treatment with nivolumab and anti-tuberculosis in advanced lung cancer patient. **Method:** The patient was 60-year-old man with advanced lung cancer. He had been treated for lung cancer stage IV by nivolumab for 15 months. Chest computed tomography showed a new developed wedge shaped consolidation in right upper lobe posterior segment. However, there was grossly no interval change of residual tumoral lesion in left upper lobe. Nivolumab treatment was discontinued to confirm metastasis. In bronchoscopic examination, we found endobronchial mass like lesion in right upper lobe anterior segment posterior portion, and bronchoscopic biopsy was done for pathologic diagnosis. The specimen showed chronic granulomatous inflammation with necrosis, suggestive of tuberculosis, but PAS and AFB stains was negative. However, Mycobacterium tuberculosis polymerase chain reaction (TB-PCR) revealed positive finding, so the new consolidative lesion was confirmed as pulmonary tuberculosis infection, not metastasis. The patient began receiving anti-tuberculosis treatment. **Result:** After 1 month anti-tuberculosis treatment, he complained no adverse effect and the laboratory finding was normal range. Thus, he resumed nivolumab treatment. However, abnormalities in liver function tests (LFT) were observed after 2 weeks nivolumab treatment. Anti-tuberculosis medication and nivolumab was discontinued for control the elevated LFT. In further evaluation, he was likely to be drug-induced toxic hepatitis, and no other causative factor was found to affect hepatic function. **Conclusion:** This is the first report of toxic hepatic event occurring in combination treatment with nivolumab and anti-tuberculosis in lung cancer patient. Anti-PD L1 antibody immunotherapy is known to upregulate the immune response against micro-organisms, but the

patient was infected with the pulmonary tuberculosis. Although the mechanism is unknown, nivolumab combination treatment seems to increase the risk of toxic hepatitis in tuberculsis treatment. Thus, we should pay attention to liver function changes in combination treatment with nivolumab and anti-tuberculosis.

Keywords: tuberculosis, Nivolumab, hepatitis

P3.CR CASE REPORTS
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P3.CR-17 AN INTERESTING CASE OF LONG-TERM IMMUNOTHERAPY RESPONSE IN METASTATIC NSCLC

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Background: Immunotherapy has improved survival in advanced non-small cell lung cancer but optimal duration of treatment is unknown. We present a case of metastatic squamous cell carcinoma of lung, who continued to respond, in spite of short exposure to immunotherapy. **Method:** A 71 year old male was diagnosed with T2N2M1 squamous cell carcinoma of lung in May, 2012. CT revealed right lung mass 4 cm and left lung lesion 1 cm but no distant metastasis. PET scan revealed FDG-avid lesion in the right lung with SUV of 18.5, sub carinal lymph node and contralaetral nodule with SUV 3.4. His case was reviewed in Lung MCC and the consensus was to treat as stage 4 due to FDG avid contralateral lung nodule. **Result:** He received 4 cycles of carboplatin and gemcitabine from May to July of 2012, with good response. He had progressive disease in October 2012 and received palliative radiation to the chest. He responded well. Further progression was observed on a PET scan to 7.2 cm hypermetabolic lesion in right lung, right hilar and sub carinal lymph nodes with persistent hypermetabolic activity in the left lung. Chemotherapy with taxotere was offered form July to October of 2013. CT scan revealed reduction in size of lesion to 5 cm. In July 2014 CT revealed progressive disease with 9.1 cm right lung mass. Standard of care, Erlotinib was offered from August, 2014 to June, 2015 with good response. Further progression was revealed in July,2015 to 9.3 cm with adrenal metastases. Erlotinib was discontinued. Immunotherapy with Nivolumab was given from September to December of 2015. CT from December,2015 revealed index lesion in the right lung 6.9 cm compared to 9.6 cm. However, the patient developed grade 3 pneumonitis requiring admission to the hospital and was teated with steroids with discontinuation of Nivolumab.The index lesion remained stable on CT in April, 2016. Subsequently he remained stable till progression was observed on CT in May, 2017 to 9.8 cm. **Conclusion:** The immunotherapy has revolutionized the treatment of lung cancer. Nivolumab was offered to this gentleman as a 4th line of treatment. His exposure to immunotherapy was only 3 months, which achieved a durable response of 18 months. Duration of treatment required to achieve durable response might be diffrent for each patient. More studies are needed to find out the optimal exposure to immunotherapy. This might enable a huge cost saving in a publicly funded health system.

Keywords: Durable response, Immunotherapy

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P3.CR-18 CENTRAL NERVOUS SYSTEM ACTIVITY OF CHECKPOINT INIHIBITOR IN NON-SMALL-CELL LUNG CANCER

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Background: Data regarding the activity of atezolizumab in the central nervous system (CNS) and its toxicity in combination with radiotherapy in patients with brain metastases (BM) of non-small cell lung cancer (NSCLC) is limited. Most clinical trials adopt strict selection criteria excluding patients with active BM and the blood–brain barrier (BBB) seems responsible for limiting the distribution of agents into the CNS. Method: Here we present a 51 yr-old female patient with the diagnosis of stage IV NSCLC with an isolated BM (T3 N3 M1b, non-mutated EGFR). She received stereotactic radiosurgery (SRS) to the isolated brain lesion (figure 1) and sequential palliative first-line systemic monotherapy with atezolizumab (1200mg/dose q21d, 15 doses).

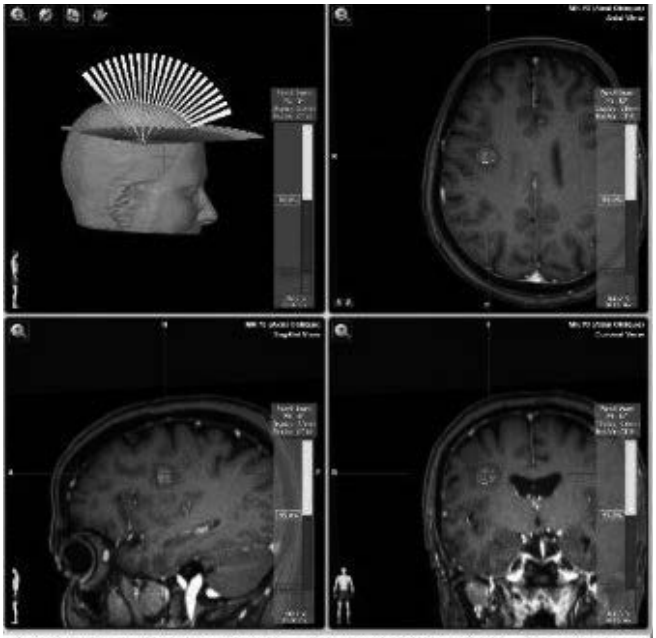

FIGURE 1. Right frontal lesion treated with SRS, linac-based, to a dose of 20Gy in one fraction. Yellow contour represents the 95% isodose line and blue contour the 50% isodose line.

Result: Control brain MRI 3-month post SRS showed a new lesion in the thalamus (figure 2) while on atezolizumab. Medical team decided to continue systemic treatment and the repeat brain MRI demonstrated complete response to the new lesion. Additionally, treated lesion showed evidence of pseudoprogression. While on follow-up, the patient continued to respond in the brain for 14 months.

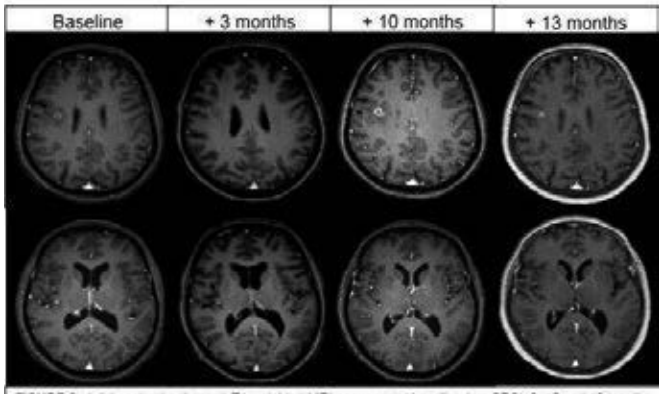

FIGURE 2. Axial contrast-enhanced T1-weighted MRI sequence at baseline (pre SRS), 3, 10 and 13 months at follow up after SRS a) right frontal lesion, treated with SRS to a dose of 20Gy. During follow up this lesion increased in size as seen in the 10 months MRI, but there was no increased perfusion and it reduced in the later MRI, suggesting radiation effect. b) left thalamic lesion (red arrow), evidenced in the 3 months follow up MRI demonstrating sustained complete response in the subsequent MRI.

Conclusion: This case reports activity of atezolizumab in CNS. The advent of immunotherapy in the therapeutic algorithm of NSCLC has raised the need to identify patients that could mostly benefit from checkpoint inhibitors.

Keywords: Immunotherapy, brain, Metastases

P3.CR-19 THROMBOEMBOLIC EVENTS RELATED TO IMMUNOTHERAPY IN A NSCLC PATIENT: A CASE REPORT

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Background: Despite the significant clinical benefits, checkpoint inhibition is associated with a unique spectrum of immune-related adverse events. It is sometimes difficult to distinguish a rare adverse effect from a cancer progression, so such effects should be reported to be diagnosed in clinical practice. **Method:** A 56-year old male patient, former smoker, was diagnosed with adenocarcinoma of lung with bone metastasis. He did not have EGFR mutation or ALK translocation, but a PD-L1 expression of 80%. The patient started first line treatment with Pembrolizumab in January 2018, and it is side effects were followed prospectively and reported. **Result:** After second cycle he developed a grade 2 colitis, which was treated with antibiotic and corticosteroid. After the third cycle he was admitted in the hospital with worsening of dyspnea and acute confusional state. The CT scan showed focus of pneumonitis adjacent to lung lesion and signs of acute pulmonary thromboembolism, splenic and renal infarction and bilateral deep vein thrombosis. His brain MRI revealed multiple signal changes involving the juxtacortical and periventricular white matter, suggestive of an embolic event. His physical exam showed multiple petechial lesions in both arms and legs, neurological exam was consistent with left homonymous hemianopsia, left hemineglect and mild left appendicular ataxia. Cardioembolic and atheroembolic causes were discarded. His cerebrospinal fluid was negative for malignant cells. Because of the suspicion of pneumonitis and vasculitis, he received metilprednisolone 2 mg/kg and enoxaparin, with progressive improvement of the symptoms. After 10 days, he received hospital discharge and Pembrolizumab was permanently discontinued. **Conclusion:** Our case demonstrated that the PD-1 blockade has potential life threatening adverse events, with the necessity of suspension. To the best of our knowledge, that is the first case of thromboembolic events related to immunotherapy in a patient with no previous history of thrombophilia or autoimmune disease.

Keywords: Non Small Cell Lung Cancer, Thromboembolism, Immunotherapy

P3.CR-20 THE EFFECT OF PEMBROLIZUMAB IN EGFR MUTATED LUNG ADENOCARCINOMA PATIENTS WITH PD-L1 OVEREXPRESSION: TWO CASES REPORT

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Background: Recently, the immune checkpoint inhibitor (ICI) pembrolizumab was demonstrated to be superior to platinum doublet chemotherapy in the first-line setting in patients with tumor PD-L1 expression of at least 50%.However, because patients with epidermal growth factor receptor (EGFR) mutations of anaplastic lymphoma kinase (ALK) rearrangements were not included in that study, the efficacy of this agent in lung cancers carrying EGFR mutations could not be determined. **Method:** We retrospectively evaluated the clinical effects of pembrolizumab treatment for EGFR mutated lung adenocarcinoma patients with PD-L1 overexpression. **Result:** Between March 2017 and February 2018, 343 cases were evaluated immunohistochemical analysis of PD-L1 expression by tumor cells according to findings of transbronchial lung biopsies or surgically resected lung specimens at our institution. Of the 343 tumors analyzed, 12 had both TPS of at least 50% and positive for EGFR mutations. Only 2 cases of EGFR mutant NSCLC patients with PD-L1 overexpression treated with pembrolizumab. We describe two cases of response to pembrolizumab in EGFR mutated lung adenocarcinoma patients with PD-L1 overexpression. Case 1 involved a 75-year-old male, diagnosed with stage IVB lung adenocarcinoma. The tumor was found to have a PD-L1 tumor proportion score (TPS) of almost 100% and was EGFR mutation positive. First line treatment with erlotinib yielded no response. Case 2 involved an 83-year-old female, diagnosed with Stage IVA pulmonary adenocarcinoma with EGFR mutation, as determined from left pleural effusion cytology. Gefitinib was selected for the initial treatment. The tumor regressed remarkably, but then slightly progressed 11 months later. We performed re-biopsy and the tumor was found to have a PD-L1 TPS of at least 95% and to be harboring the same EGFR mutation as that in the initial biopsy but was negative for T790M. In both cases, second-line therapy was commenced using pembrolizumab after failure of first-line EGFR-TKI therapy. After administering pembrolizumab, both tumors were observed to be reduced on chest radiography. Therefore, pembrolizumab was observed to be effective. **Conclusion:** The cases presented in this report indicate that ICIs are an effective treatment for EGFR mutated lung adenocarcinoma patients with PD-L1 overexpression.

Keywords: Programmed death-ligand 1, Non-small-cell lung cancer, Epidermal growth factor receptor

P3.CR-21 UTILITY OF THORACOSCOPY IN DIAGNOSIS OF LUNG TUMOUR IN PLEURAL EFFUSION

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Background: Papillary adenocarcinoma of the lung is a rare malignancy accounts]ing for 7.4%–12% of the lung adenocarcinomas . A pleural metastasis is often accompanied by a malignant pleural effusion (MPE),can be one of the presentations of this disease. Differential diagnosis of exudative recurrent pleural effusion is often a lengthy process brimming with various snags. Contrary to thoracocentesis and closed pleural biopsy, thoracoscopy allows biopsy with direct visualization., Medical thoracoscopy increases the diagnostic yield in patients with pleural disease especially when thoracocentesis and closed pleural biopsy are non diagnostic **Method:** We present case of 75 year old female housemaker with complaint of breathlessness and chest pain for the last 3 months. She was a never smoker and did not have any significant personal history. On physical examination and chest xray – a massive pleural effusion was seen on the left side. A chest tube was inserted. Because of unilateral haemorrhagic pleural fluid with an exudative pattern, medical thoracoscopy was performed . We observed a hepatized lung with severe pleural inflammation, medical thoracoscopy was done and biopsy was taken. Because of the family's low economic status, we could not perform immunohistochemistry. Smear and culture of the pleural fluid were negative for tuberculosis. Cytology of the pleural fluid was positive for malignancy. On histopathology, Sections from the biopsy taken showed a malignant neoplasm with atypical cells arranged in a branching papillary pattern with fibrovascular cores .The papillae are lined by columnar cells with moderate amount of cytoplasm showing nuclear overlapping hyperchromasia and coarse chromatin. Few of the nuclei appear optically clear. Invasion into the deeper tissues is seen in the form of different sized angular and malignant glands surrounded by a dense desmoplastic stoma .Areas of necrosis, neutrophilic exudate and hemorrhage were also seen. **Result:** Hence a diagnosis of stage IV papillary type of adenocarcinoma lung was made. And the patient was started on Chemotherapy but unfortunately she expired in the course of treatment. **Conclusion:** High index of suspicion should be kept for the possibility of malignancyin a massive pleural effusion especially when its being refilled – recurrently. Medical thoracoscopy is always helpful in diagnosis and management of these cases as seen in the present case report. In developing nations where interventional pulmonology is still not a routine procedure , by this case report we wish to highlight its importance.

Keywords: papillary adenocarcinoma, pleural disease, Thoracoscopy

P3.CR-22 PULMONARY TUBERCULOSIS – A CHAMELEON; MIMICKING LUNG CANCER ON IMAGING

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Background: Tuberculosis (TB) often mimics other diseases including malignancy, and has been rightly called a benign imposter. Most common radiographic appearances seen in TB are cavitary, fibroproductive, exudative, acinary, micro and macronodular and miliary types.The typical presentation of pulmonary tuberculosis is easily recognisable but the disease, a well-known masquerader, can be a source of diagnostic confusion radiologically when the presentation is atypical., especially in the regions in which the tuberculosis is endemic. Tuberculosis may be radiographically revealed as mass formation in the cases clinically and radiographically examined, difficulties may be encountered in the differential diagnosis due to the similar constitutional symptoms such as fatigue, breathlessness , and anorexia both in tuberculosis and carcinoma, and the radiologic appearance is also confusing. **Method:** A 65 year old female patient was referred to our department with a 3 months history

of breathlessness, chest tightness, intermittent non-productive cough and unintended weight loss of 5 kg in the past 2 months. She had no reported fever or any prior medical history. A presumptive diagnosis of lung cancer was made from elsewhere based on her radiological appearance on computed tomography (CT) scan of chest which showed a large peripherally located enhancing solid mass lesion in the posterobasal segment of right lower lobe and another solid necrotic lesion in right middle lobe abutting the pericardium along with multiple nodular opacities. CT guided fine needle aspiration cytology was done from the lesion and it showed acute on chronic inflammation. The next diagnostic step was bronchoscopy with negative results regarding malignancy. The bronchial wash samples were also sent to microbiology with negative results for bacteria, fungi, even negative on direct microscopy but Cartridge based nucleic acid amplification test (CBNAAT) (Polymerase Chain Reaction based) for *Mycobacterium tuberculosis* provided the diagnosis by showing growth of the *Mycobacterium tuberculosis*. **Result:** The patient was diagnosed as pulmonary tuberculosis and started on standard anti-TB-therapy and she responded symptomatically as well as with clearing of the lesion, radiologically. **Conclusion:** In conclusion, tuberculosis emerging as a large nodular or mass-like radiographic appearance is uncommon and this can be easily confused with the tumoral formations. Differentiation from lung cancer based on imaging findings alone may be challenging and often ambiguous, thereby highlighting the importance of use of interventions like bronchoscopy in suspecting cases.

Keywords: bronchoscopy, lung cancer, tuberculosis

P3.CR CASE REPORTS
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P3.CR-23 MULTILOBAR ADENOCARCINOMA: A CASE REPORT AND REVIEW OF THE LITERATURE OF PAPILLARY ECCRINE ADENOCARCINOMA PRESENTING WITH RESPIRATORY FAILURE

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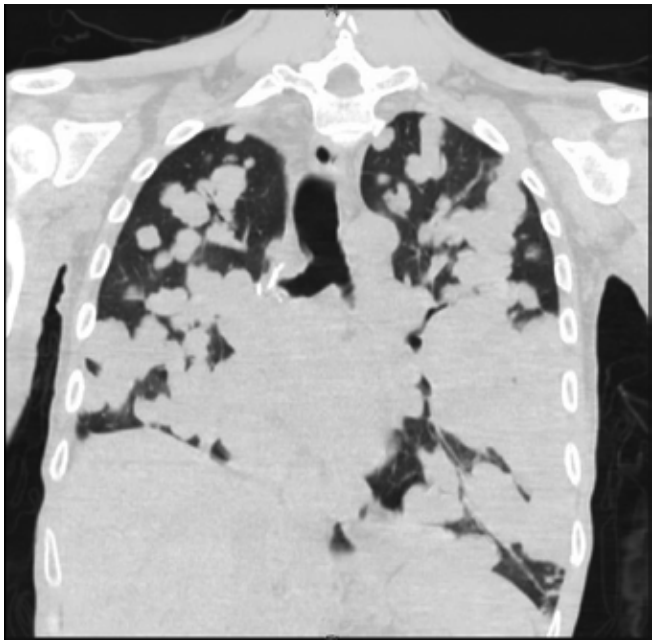
Background: Aggressive digital papillary adenocarcinoma (ADPAca) is a rarely recognized neoplasm of the sweat gland duct that has a high metastatic potential with metastasis seen in the lymph nodes, liver, lungs, and bones. Originally described in 1865, this tumor represents a rare group of sweat gland carcinomas. We report the uncommon presentation of a patient with metastatic eccrine adenocarcinoma and hypoxic respiratory failure with a review of the literature.

Method: A 52-year-old Caucasian male was brought to the emergency room by his wife appearing cyanotic and with a saturation of 82%. The respiratory exam demonstrated coarse breath sounds and a well-healed right thoracotomy scar. His extremities demonstrated a prior amputation of the second finger of the left hand. He was subsequently intubated and imaging obtained (Fig. 1).

The wife noted he had a slowly growing lesion on the left second finger approximately 10 years before initial presentation with primary amputation and a diagnosis of papillary eccrine adenocarcinoma. Concurrently, a right upper lobe mass was found and, with his strong history of tobacco abuse, a right upper lobectomy was performed with negative lymph nodes and margins but the pathology consistent with metastatic papillary eccrine adenocarcinoma. He first presented at our facility 3 years later with a chest wall mass and biopsy, again, demonstrated metastatic papillary eccrine adenocarcinoma. Pathology of the mass demonstrated multiple fragments of tissue containing metastatic adenocarcinoma. Immunohistochemistry disclosed these to be tumor cells positive for pancytokeratin, S100, SOX-10, and p63, and negative for TTF-1, CK20, Napsin, and CDX2. In review, with the initial left index finger excision, this was diagnostic of metastatic papillary eccrine adenocarcinoma.



Result: Section not applicable **Conclusion:** Aggressive digital papillary adenocarcinoma is a rare tumor of the eccrine sweat glands with marked metastatic potential often affecting the hands and presenting as a slowly growing mass or cystic lesion.

Keywords: Adenocarcinoma, eccrine, metastatic

P3.CR CASE REPORTS
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P3.CR-24 SURGICAL RESECTION OF 30 YEARS' RECURRING PNEUMONIA: 1 CASE OF GIANT BRONCHOPULMONARY SEQUESTRATION

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Background: Bronchopulmonary sequestration is easily omitted or missed diagnosed as recurrent pulmonary infection or pneumonia due to having no specific symptoms. Recurring pulmonary infection is the most common manifestation for bronchopulmonary sequestration. Enhanced CT is useful for diagnosis by revealing clearly the aberrant vessel from aorta to the sequestered mass. Surgery is of the best choice for treatment. Here we report one rare case of giant tumor-like bronchopulmonary sequestration, with three aberrant thicker vessels from descending aorta to the sequestered mass. **Method:** A male aged 38 in Nov 2017, with recurring pneumonia, breath with difficulty, fatigue for more than 30 years, until recently enhanced CT revealed three aberrant thicker vessels from descending aorta connecting to the 20x15x12cm3 giant solid tumor-like mass in left lower-lobe suggested the possibility of pulmonary sequestration. Heart and lung function test showed normal; there was no contraindication for surgery. Surgical resection became first of choice. **Result:** Standard posterolateral thoracotomy was performed, and severe adhesion closed the thoracic cavity. The normal pulmonary fissure was not existed. Whole left lower lobe became a 20x15x12cm3 solid giant tumor-like mass, with sever inflammatory edema on pulmonary surface, rich lateral wall circulation between the lung and chest wall. Three aberrant thicker vessels 2.5, 1.5, 1.2cm in width were found from descending aorta connecting into the left lower lobe, confirming the diagnosis of bronchopulmonary sequestration. Severe adhesion prevented separating left lower-lobe from diaphragm. Left lower pulmonary vein was first separated, ligated and cut; left lower-lobe bronchus, left lower-lobe arteries branches were then separated, ligated and cut. The widest one of the three aberrant thicker vessels was almost as same as the descending aorta in width. Three vessels were 2.5, 1.5, 1.2cm in width were separated, ligated and then cut, respectively. The patient recovered rapidly. Six months' follow-up revealed that the patient recovered better than before, pneumonia, dyspnea, and fatigue were all completely disappeared. **Conclusion:** Bronchopulmonary sequestration is less common and easily omitted or missed diagnosed as recurrent

pulmonary infection. Bronchopulmonary sequestration with three aberrant thicker and larger vessels was rare. Enhanced CT is useful for diagnosis. Once diagnosed, surgery is of the best choice for treatment. (This study was partly supported by Science Foundation of Shenyang City, China, No. F16-206-9-05, 17-230-9-71)

Keywords: surgery, recurring pneumonia,bronchopulmonary sequestration

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P3.CR-25 FINDING THE WAYS TO DETERMINE THE PROGNOSIS OF PULMONARY CARCINOIDS WITH CERTAIN GENES/MARKERS IN PAKISTAN

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Background: Pulmonary neuroendocrine tumors are classified into four subtypes from well differentiated to poorly differentiated high grade large cell neuroendocrine carcinomas. Because of the difficult histological classification and a cancer free period following surgery, it is often difficult to predict certain prognostic factors. We aim to analyse the prognostic factors of pulmonary carcinoids. In our study we also aim to find the the patterns of CD44, OTP and RET. **Method:** The study was conducted in tertiary care. CD44, OTP and RET were analysed in 70 frozen carcinoids by using PCR. mRNA expression of these genes were assessed. Methylation and mutation analysis was used to assess RET proto oncogene. Immmunohistochemistry for CD44 and protein expression for OTP was conducted **Result:** Downward regulation of CD44 and OTP in carcinoid patients exhibited poor prognosis with distant metastasis whereas the RET was upregulated. This subsequently shows that these genes had a large negative impact on 20-year overall survival. Absence of CD44 was also strongly correlated with distant metastasis A strong positive CD44 effect on patient outcome was observed when membranous staining CD44 was present. We determined that RET expression was not related to promoter methylation or gene mutations. The absence of nuclear OTP followed by complete loss of expression was also significantly associated with unfavorable disease outcome in all carcinoids. Other independent prognostic predictors were also determined **Conclusion:** We found that loss of CD44 or OTP expression shows adverse patient outcomes. We conclude that these strong prognostic markers should be implemented in the routine diagnosis so that we can determine the prognosis of pulmonary carncioids

Keywords: CD44, cancer prognosis, pulmonary carcinoids

P3.CR CASE REPORTS
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P3.CR-26 MEDIASTINAL LIPOMA IN ADULT: A CASE REPORT

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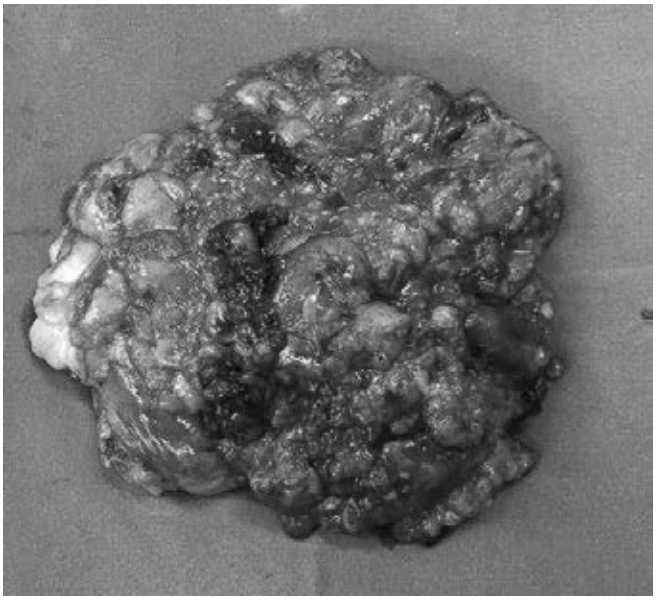
Background: Lipoma is mesenchymal tumor originated from adipose tissue resembling normal fat. Lipoma mostly found in subcutaneous tissues but only 2% found as primary mediastinal tumor locatedbmainly in anterior medistinum. There were no spesific symptoms and definitive diagnosis require invasive surgical therapy.



Method: Section not applicable **Result:** We report a 50 years old lady presented with persistent cough and palpitation, difficult to braeth and got worsen with daily activities since 3 months. There was no fever, no weight loss and normal appetite. The left lung sound was decrease but no rales and wheezing. Chest X-Ray showed mass suspected bulky adipose tissue consistent with medistinal lipoma. Thoracotomy was perfomed and 2,8 kilograms intramedisatinal mass was removed and pathological evaluation confirmed intramediastinal lipoma. Pasien wa recovered with minimal symptoms. **Conclusion:** Mediastinal Lipoma is a rare case and usually found in adult with no spesific symptoms, but could be evaluated by thoracic CT Scan and/or MRI and could be succesfully removed by surgical resection.

Keywords: Mesenchymal Tumor, Mediastinal Lipoma, resection

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P3.CR-27 SURGICAL TREATMENT OF A RARE CASE OF MEDIASTINAL MASSON'S TUMOR MIMICKING A THYMOMA

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Background: Masson's tumor or intravascular papillary endothelial hyperplasia (IPEH) is a rare non-malignant pseudotumoral disease, characterized by an exuberant endothelial proliferation usually arising as a reactive process within a normal blood vessel. The pathogenesis of intravascular papillary endothelial hyperplasia is still unclear, but it seems that the exuberant tissue derives from an autocrine stimulation of the endothelial cells due to the secretion of basic Fibroblast Growth Factor (bFGF). There are three types of papillary endothelial hyperplasia: primary or intravascular form, secondary or mixed form and tertiary or extravascular (rarer) form. Mediastinal localization is exceptional. We report a rare case of antero-superior mediastinal Masson's tumor mimicking a thymoma, successfully treated with surgery. **Method:** A 48-year old man presented to our institution with computerized tomography (CT) evidence of a 4 x 3 cm antero-superior mediastinal mass, extending up to the right thyroid lobe, resembling a thymoma. Total body 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT revealed a SUV max of 3.5. Despite complaining of a myastheniform syndrome (asthenia and slight palpebral ptosis) laboratory (anti-MUsk and anti-AChR antibodies) and instrumental evaluation (electromyography) were found to be normal. The patient had previously undergone resection of a right supraclavicular Masson's tumor and of a sublingual angioma. After cardio-respiratory function evaluation, through a sternotomy, the patient underwent thymectomy and challenging resection of a hypervascularized mediastinal lesion adjacent to the right upper horn of the thymus, but apparently independent from it, and tenaciously adherent to the right innominate vein. **Result:** Postoperative course was uneventful. Histopathology revealed a normal adipose thymic involution and a Masson's tumor or intravascular papillary endothelial hyperplasia with mediastinal localization. The patient underwent hemocoagulative and genetic tests, as Masson's tumor may be associated with thrombophilia and genetic syndromes. **Conclusion:** Masson's tumor can clinically and radiologically mimic various benign and malignant mediastinal lesions, such as thymomas. The definitive diagnosis can be obtained only with the histological examination, demonstrating the presence of endothelial papillae, with a thin fibrous stroma, protruding into the vessel lumen. To the best of our knowledge, this is the first reported case of surgical treatment of a mediastinal Masson's tumor. However, surgical resection may be technically difficult due to the intrinsic hypervascularized nature of these pseudotumoral lesions.

Keywords: Surgical treatment, Thymoma, Masson's tumor

P3.CR CASE REPORTS
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P3.CR-28 SIMULTANEOUS PRESENTATION OF MEDIASTINAL MALIGNANT PERIPHERAL NERVE SHEATH TUMOR WITH INTRAPULMONARY METASTASIS, AN EXTREMELY RARE CASE

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Background: Malignant peripheral nerve sheath tumors (MPNST) are sarcomas originating from the cells constituting the nerve sheaths and occupy 5-10% of all soft tissue sarcomas. MPNSTs may occur in any peripheral nerve. They are often found in the chest wall and the posterior mediastinum. Their simultaneous existence with intrapulmonary metastasis is not commonly seen. **Method:** In this report, we present a rare patient with Simultaneous presentation MPNST located in the right posterior mediastinum and having contralateral Lung metastasis both treated with minimally invasive surgery. **Result:** Clinical summary: A 57-year-old woman had no history of smoking had respiratory symptoms sputum and dyspnea. Chest computed tomography revealed a posterior mediastinal solid mass of 55mm on the right hemi thorax also a 33mm solid mass lesion located on the left upper lobe. She first underwent video assisted thoracoscopic surgery (VATS) resection of the lesion on the right. The histopathological examination revealed malignant peripheral nerve sheath tumor (MPNST). Just after the first intervention she underwent left VATS lingual sparing upper lobectomy . The histopathological examination revealed the lesion as intrapulmonary metastasis of the previous MPNST. Patient did not have any problem related with surgery and discharged quickly in both surgeries. She had a chemotherapy afterwards. **Conclusion:** Simultaneous presentation of MPNST with lung metastasis are extremely rare clinical cases with very poor prognosis. Our patient is doing well on the 11th months after resection. This may be a good example of the synergic effect of surgery with chemotherapy with successful outcomes.

Keywords: malignant peripheral nerve sheath tumor,Intrapulmonary metastasis, minimally invasive surgery

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P3.CR-29 EN-BLOC EXCISION OF INTRAPERICARDIAL THYMOMA USING SINGLE PORT VIDEO-ASSISTED THORACOSCOPIC SURGERY. A RARE CASE

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Background: Thymomas are located in the normal location of the thymus in the anterior mediastinum. It is very rare for thymomas to arise primarily intrapericardialy. There had been only few reports for this unusual localization. We report a case of a patient with an entirely intrapericardial thymoma. **Method:** A 76-year-old man with a known human immunodeficiency virus (HIV) positivity and has been under close follow up for the recent 5 years . The patient had a computerized tomography of the thorax due to suspicious mediastinal enlargement .The radiological evaluation revealed an intrapericardial mass of 3x3x2.5 cm dimensions. **Result:** We have performed right uniportal videoassisted thoracoscopic surgery(VATS) for the intrapericardial mass resection. Histopathological examination revealed the tumor as type A thymoma, according to the World Health Organization classification (1999). The biopsied adjacent pericardial tissue in relation with the tumour showed thymic gland. As the patient was evaluated again he did not have any signs of symptoms of myasthenia gravis. The patient was discussed in tumour board and aggreed for a local radiation treatment on the site of excision. The patient is in his early post operative period with no clinical problem. **Conclusion:** HIV positive patients are in higher risk for opportunistic infections and other tumoral lesions including malignant thymic tumours . Unexpected localization for thymoma might be the question of HIV and needs to be proven with more patients and clinical data .

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P3.CR-30 PLEURAL DISEASES ON SINGLE LUNG AFTER PNEUMONECTOMY FOR CANCER

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Background: After pneumonectomy for cancer, the residual lung can be affected by pleural disorders, which usually produce severe respiratory distress and impose emergency treatment. **Method:** Between 2000 and 2016 we identified 11 patients with previous pneumonectomy for cancer, who presented with pleural disease; 9 of them needed emergency treatment. **Result:** There were 2 cases of pneumothorax: one developed in first postoperative day after left completion pneumonectomy with chest wall re-resection (for relapsed squamous cell carcinoma); the second pneumothorax developed after CT-guided needle biopsy of a left pulmonary nodule (single left lung after right pneumonectomy for cancer) – in both cases the pneumothorax needed emergency chest tube drainage. Also, there were 8 cases with liquid pleural effusions – 6 malignant, 1 tuberculous and 1 empyema. We performed 2 thoracoscopies and 6 chest drain insertions; in one case the patient with previous left pneumonectomy presented with right pleural and pericardial effusion, for which a pericardial percutaneous left parasternal drainage with ultrasound guidance, and a right pleurotomy, were performed. In another case a left tension loculated pleural effusion needed CT-guided percutaneous drainage. In 3 cases talc pleurodesis was performed. Finally, one patient with previous pneumonectomy presented with left pulmonary nodule and he was prepared for resection. At thoracotomy a pleural entrapment of the inferior lingular segment was found and a decortication was performed; no pulmonary nodule was found neither intraoperatory nor at postoperatory CT-scan. **Conclusion:** The pleural disease developed on single surgical lung (pneumonectomy for cancer) may be malignant or benign, correlated or not with the primary

malignancy which imposed previous pneumonectomy. In endemic areas for TB specific pleural effusions and pleural retraction may appear and surgical treatment is necessary. Special attention is needed for nodules on single lung proposed for CT-guided biopsy – the pneumothorax on single lung has indication for drainage.

Keywords: pleural disease, single lung, pneumonectomy

P3.CR CASE REPORTS
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P3.CR-31 A CASE OF THYMOMA WITH AUTOIMMUNE HEPATITIS FOLLOWING PREOPERATIVE CHEMOTHERAPY

T. Nishimura, H. Tsunezuka, N. Miyata, S. Okada, S. Ishihara, S. Ikebe, H. Suzuki, C. Nakazono, N. Ishikawa, A. Uchibori, D. Kato, J. Shimada, M. Inoue

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Background: We encountered a case of thymoma with autoimmune hepatitis. **Method:** *A 63-year-old woman was found to have an abnormal finding on chest radiography during a medical checkup, but did not seek further care. She was referred to our hospital one year later when a bilateral hilar abnormality was again found during a checkup. Chest computed tomography (CT) showed a 4.6 × 3.0 × 5.6 cm mass with calcifications in the anterior mediastinum. The tumor invaded the right lung and middle lobe, in association with a 2.0-cm daughter nodule in the head of the main tumor, with multiple pleural seeding lesions in the right thoracic cavity. Although she was asymptomatic, the anti-acetylcholine receptor antibody level was elevated to 33 nmol/L and the soluble IL-2 receptor antibody was elevated to 1,700 U/mL. The mass was diagnosed with CT-guided biopsy as a type-B2 thymic tumor (cT3N0M1a, c-Stage IV). She underwent induction chemotherapy (ADOC, 2 courses). After chemotherapy, abnormal liver enzyme levels (aspartate aminotransferase: 451 U/L, alanine aminotransferase: 529 U/L) were noted on preoperative examination. She was diagnosed with autoimmune hepatitis based on liver biopsy findings and treated with oral prednisolone 30 mg.* **Result:** *Surgery was performed after prednisolone dose was gradually decreased to 20 mg. Extended thymectomy and pulmonary wedge resection using median sternotomy were performed. Pleural dissemination was resected using video-assisted thoracoscopic surgery. The pathological findings showed type-B3 thymic carcinoma (pT3N0M1a, p-Stage IV, Masaoka classification IVa). She was placed under observation without any additional treatment. Prednisolone dose has been gradually decreased to 15 mg without exacerbation of liver function. The anti-acetylcholine receptor antibody level decreased after surgery.* **Conclusion:** *Autoimmune diseases in association with thymoma are well known, but reports of autoimmune hepatitis are very rare. Autoimmune hepatitis must be considered when acute liver damage is observed.*

Keywords: Surgery, Thymoma, autoimmune hepatitis

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P3.CR-32 AMYLOID DEPOSITION IN THYMIC EXTRANODAL MARGINAL ZONE LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE: A CASE REPORT

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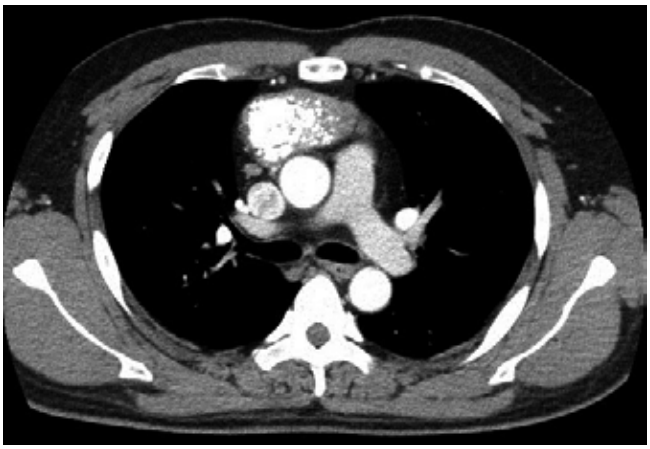
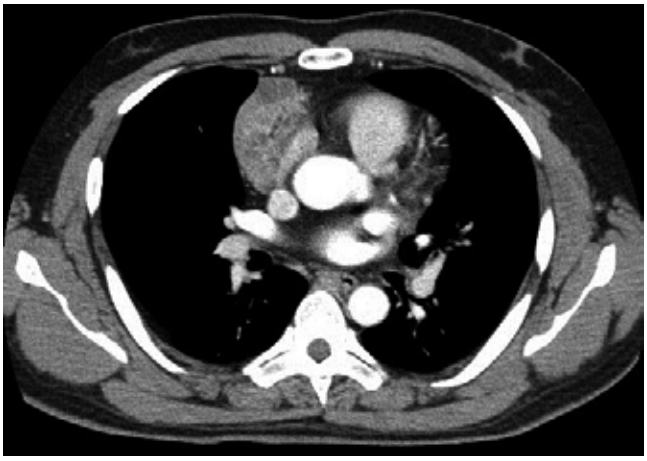
Background: Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) is a rare thymic tumor with a few cases described to date. Amyloid deposition can be unusually associated with MALT lymphoma, and those cases have been reported arising from the lung, soft tissue, ocular adnexa, skin, and aerodigestive tract. To our knowledge, our case is the first report of thymic MALT lymphoma with amyloid deposition. **Method:** A 35-year-old East Asian male presented with dyspnea on exertion. He did not have any history of autoimmune disease. His CT scan showed a 7.5-cm mass in the anterior mediastinum with extensive conglomerated calcification (Fig 1a and b). Acetylcholine receptor antibody titer was elevated up to 7.83 nmol/L. The mass was removed by median sternotomy and histologically diagnosed as extranodal marginal zone lymphoma of MALT arising from the thymus. Extensive amyloid deposition was noted within the tumor with a positive stain to Congo red, apple-green birefringence on polarized microscopy and binding of antibodies predominantly to kappa light chain.





Result: Section not applicable **Conclusion:** We report a case of thymic MALT lymphoma with extensive amyloid deposition. Unusual CT manifestation of extensive calcification can lead to difficulties in differential diagnosis of mediastinal masses.

Keywords: lymphoma, Amyloid, thymus

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P3.CR-33 TRICHOPTYSIS, HEMOPTYSIS AND CHEST PAIN: A VERY RARE PRESENTATION OF ANTERIOR MEDIASTINAL TERATOMA IN A YOUNG PATIENT

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Background: 1/Case History: A 28-year old patient who presented to the Emergency Department for a 2-week history hemoptysis, right chest pain and intermittent sebaceous expectorations. He had such intermittent chest pain for the last 2 months. He had no fever, breathlessness, loss of weight, joint pain or renal symptoms. He had no significant personal or family history of tuberculosis. On examination, he was afebrile.Full clinical examination revealed decreased breath sound in the left lung with a dull-percussion note. **Method: 2/Investigations:** Laboratory investigations were normal.The coagulation tests were normal. The Tuberculin skin test was negative. The Chest CT-scan revealed a large well-circumscribed anterior mediastinal mass with heterogeneous mixed density (fat, soft tissue and calcifications), in the left hemi-thorax. It also showed intra-tumoral bleeding associated with a left massive hemomediastinum. This radiological aspect suggested a teratoma. Preoperative labs showed normal carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), CA-125 and beta-HCG level were normal. **Result: 3/Treatment:** The multidisciplinary team decision was to perform surgery. A standard posterolateral thoracotomy was performed in the 5th intercostal space. Immediately upon entering the thoracic cavity, a bulky mediastinal mass was found to have a strong adhesion to the upper left lobe. The mass itself was originating from the thymus and extending down to the left lung. A complete thymectomy with a total removal of the tumor was

therefore performed. The total amount of bleeding was about 900ml. This was completely evacuated from the thoracic cavity. The patient is currently doing well one year from his initial diagnosis. Although he had a benign teratoma, he was referred to a medical geneticist for further evaluation and management. **Conclusion: 4/Discussion and conclusion:** Teratomas are germ cell tumors arising from pluripotent cells. Most of them are asymptomatic. Hemoptysis is rare. It may result either from communication with tracheobronchial tree or they may result from bronchial bleeding due to the irritation caused by the tumor. In this case, the presence of hypervascularisation depending on the left internal mammary artery in the chest CT-scan suggests that the teratoma developed systemic blood supply which make our case original. Another pathognomonic symptom is **Trichoptysis** which is extremely rare . All these symptoms may mimic a pulmonary tuberculosis in young patients especially in our tuberculosis-endemic country. In our case, the tuberculin tests were negative. To conclude, it is a rare case of Teratoma of the anterior mediastinum. It should be considered in the differential diagnosis of Hemoptysis.

Keywords: Oncology Teratoma Surgery

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P3.CR-34 A GIANT GANGLIONEUROMA OF THE THORACIC SPINE

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Background: 1/Case History: A 9-year old girl presented to our Department for a chronic cough. Her medical history revealed that she had pneumonia at the age of 2 years. The family history was marked by an allergic rhinitis in the father. On examination, she was afebrile.Full clinical examination revealed decreased breath sound in the left lung. **Method: 2/Investigations:** Laboratory investigations were normal. The Chest CT-scan revealed a well-circumscribed mediastinal mass measuring 8.6cm*7.8cm*6.8cm. It extended through the neural foramen of T9 and also in the left chest cavity behind the aortic cross and the esophagus. Magnetic Resonance imaging showed a long intra-dural extra-medullary tumor extending from T6 to T11 levels. It extended through the left T9 neural foramen into the left thoracic cavity. The intervertebral foramen was enlarged. The thoracic aorta was totally sheathed. The lesion was mildly hypo-intense on T1-weighted imaging and heterogeneously hypo-intense on T2-weighted imaging. This radiological aspect could suggest a ganglioneuroma or a shwannoma. **Result: 3/Treatment:** The multidisciplinary team decision was to perform surgery. **Final histology** demonstrated a well-circumscribed ganglioneuroma with negative margins. The case was reviewed at the Oncology multidisciplinary team. The decision was made to proceed with active follow-up without any adjuvant therapy given that it's benign. The patient is currently doing well 2 years from her initial diagnosis. **Conclusion: 4/Discussion:** Thoracic intradural extra medullary Ganglioneuromas are very rare benign tumors of the autonomic nerve fibers. Most of them are incidentally discovered. In this case, our patient had no significant clinical symptoms apart from a chronic cough. The thoracic location, the potential of growth the large-size of the tumor (extending to the left chest wall with an intra-dural component) and the radiological profile, makes it therefore rare and unusual. It also illustrates the complexities of the management of this rare tumor. In fact, surgical treatment is usually safe and efficient. But, it can be more complicated in case of a such large-sized mass. So, a 2-step surgical intervention should be performed. Ganglioneuroma has commonly a good prognosis given its low-risk of recurrence and low-metastatic potential. However, it can become cancerous and spread to other organs. Conclusion: To conclude, it is a rare case of giant Ganglioneuroma of the Thoracic spine with intra-dural extension. It should be considered in the differential diagnosis of a mediastinal mass. We also underline that the surgical treatment is safe and efficient.

Keywords: Oncology Ganglioneuroma Surgery

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P3.CR-35 A RARE GIANT THORACIC DESMOID TUMOR /A CASE REPORT

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Background: 1/Case history: A 43-year old lady who presented to the Emergency Department with a 2-month progressively worsening chest pain associated with dyspnea. There was no remarkable past history. On examination, she was in significant distress due to pain. She was afebrile, Full clinical examination revealed decreased breath sound in the left lung and dull-percussion note of the left hemi-thorax. **Method:** 2/ Investigations A Computed-Tomography Scan (CT) revealed an expansile soft –tissue density mass locating in the left hemi-thorax. The large mass invaded the posterior arches of the 6th and 7th ribs and the 6th and 7th vertebral bodies with an 'hour-glass'-like extension through the growth foramen including the bone; with partial osteolytic lysis. The left-lung was compressed. She had a Transthoracic Needle biopsy of the tumor. The histological aspect can be perfectly fitted with a fibromatosis. **Result:** 3/Treatment: After a strict work-up and assessment of the prognosis, that results in establishment of an indication for surgery in 2 times. Final pathology showed a well-circumscribed, white- pearly, bulky tumoral mass measuring 28*19*12cm. The case was reviewed on the **Multidisciplinary team**. The decision was made to proceed with the second surgical time. The patient is currently doing well 6 months after the initial diagnosis. **Conclusion:** 4/ Discussion and Conclusion: Desmoid Tumors are rare tumors which originate from fibroblasts. They typically arise in the abdominal wall. However, the chest wall is the second location of these rare tumors. Most of them are asymptomatic. Rarely, patients can develop a wide range of symptoms due to tumoral mass effect on surrounding organs that result in cough, dyspnea. The thoracic location of the tumor, the pattern of growth, the large-sized tumor, as well as the radiological profile makes this case rare and unusual. **Surgical excision** is considered as the best treatment for most desmoid tumors. In our patient, surgery was therefore necessary to establish the diagnosis and to remove the tumor. However, it can become more complicated in case of a such large-sized mass. So, a 2-step wise surgical intervention should be therefore performed. To conclude, this case demonstrates the complexities involved in the presentation and the management of these rare tumors. We also underline that surgical treatment is safe and efficient.

Keywords: Oncology Desmoid Surgery

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P3.CR-36 INTRAPERICARDIAL THYMOMA: A CASE REPORT

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Background: Thymomas are located in the normal location of the thymus in the anterior mediastinum. It is very rare for thymomas to arise primarily intrapericardialy. There had been few reports for this unusual localization. **Method:** We report a case of a patient with an entirely intrapericardial thymoma. A 76-year-old man with a known human immunodeficiency virus (HIV) positivity and has been under close follow up for the recent 5 years **Result:** The patient had a computerized tomography of the thorax due to suspicious mediastinal enlargement .The radiological evaluation revealed an intrapericardial mass. We have performed right uniportal videoassisted thoracoscopic surgery(VATS) for the intrapericardial mass resection. Pathological evaluation revealed a Type A thymoma with a 3x3x2.5 cm dimensions. He was discharged on the 3rd day op operation. He underwent pericardial irradiation. He has been doing well for 5 months. **Conclusion:** Whether unusual localization of thymoma could be attributable to HIV infection remains unknown and needs to be confirmed with case series.

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P3.CR-37 EXTENSIVE RESECTION FOR INVASIVE ATYPICAL CARCINOID OF THYMUS: 1 CASE REPORT

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Background: Atypical carcinoid of thymus (ACT) is extremely rare. Patients with ACT usually have no specific symptoms, and mostly are found as mediastinal tumors when taking chest X-ray or CT scanning. ACT is usually aggressive and extensive surgical resection is of first choice, even though chemo-radiation is recommended but showing less effects. Here we report one case of ACT invading adjacent organs and tissues received extensive radically surgical resection. **Method:** A male aged 53 in Mar 2018, with chest distress, fatigue for 1 month; chest CT revealed a round 5x4x3cm3 mediastinal tumor sitting on superior vena cava, aortic arch. Thymoma was diagnosed. Heart and lung function test showed normal; there was no contraindication for surgery.

Surgical resection became first of choice. **Result:** Median sternotomy was performed, and the 5x4x3cm3 tumor was confirmed invading into adjacent superior vena cava and left innominate vein, invading aortic adventitia, pericardium, right mediastinal pleural and right upper lobe of the lung. Extensive and radical en block resection was performed including resection and followed plasty of the lateral wall of the superior vena cava and right innominate vein, resection of being-invaded aortic adventitia, pericardium, right mediastinal pleural, right upper lobe of the lung, and resection of the whole thymoma and fat tissues of thymus body and four feet. The surgical resection was evaluated as perfect, being resected completely and radically. Postoperative adjuvant radiation was followed one month later. No chemotherapy was added. The patient is now recovering rapidly and healthily. Long term follow-up is needed to monitor recurrence and metastasis. **Conclusion:** Atypical carcinoid of thymus is extremely rare. Surgical resection is of first choice. Complete en bloc resection of the whole tumor, the whole fat tissues of thymus body and four feet, and adjacent being-invaded organs and tissues, is the key point to avoid recurrence, to cure ACT. (This study was partly supported by Science Foundation of Shenyang City, China, No. F16-206-9-05, 17-230-9-71)

Keywords: extensive resection, atypical carcinoid, thymoma

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Mary Beth	Beasley	Honoraria	Genentech, Merck, Bristol-Meyers Squibb
Hubert	Beaumont	Employee (full time or part time)	Median Technologies

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
John	Beeler	Employee (full time or part time)	Inivata
Mike	Beggs	Employee (full time or part time)	MagArray
Jill	Bell	Other	Millennium Pharmas, Takeda
Tim	Bell	Employee (full time or part time)	VisionGate
R. Joseph	Bender	Employee (full time or part time)	Perthera
Jaafar	Bennouna	Speakers or Advisory Board	Roche, Boehringer Ingelheim, AstraZeneca, Bristol-Meyers Squibb
		Honoraria	Roche, Boehringer Ingelheim, AstraZeneca, Bristol-Meyers Squibb
Sadia	Benzaquen	Other	Medtronic
Christine	Berg	Honoraria	Medial Early Sign LLC, GRAIL
Emily	Bergsland	Supported/Contracted Research/Grant	Novartis, Merck
		Royalty, Intellectual Property/Patent Holder	UpToDate
Peter	Berzinec	Speakers or Advisory Board	Boehringer Ingelheim, Roche, Merck
Benjamin	Besse	Supported/Contracted Research/Grant	Roche, AstraZeneca
Akihiro	Bessho	Honoraria	Chugai Pharma, Eli Lily
		Speakers Bureau	Chugai Pharma
Christine	Bestvina	Speakers or Advisory Board	AbbVie
Prabhu	Bhagavatheeswaran	Employee (full time or part time)	Bristol-Meyers Squibb
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Meyers Squibb
Mandar	Bhonde	Employee (full time or part time)	Lupin
Rafia	Bhore	Employee (full time or part time)	Celgene Corporation
Paolo	Bidoli	Other	Eli Lilly, Bristol-Meyers Squibb, Boehringer Ingelheim
Paolo	Bironzo	Speakers or Advisory Board	Bristol-Meyers Squibb, Boehringer Ingelheim
		Honoraria	Bristol-Meyers Squibb
Normand	Blais	Speakers or Advisory Board	AstraZeneca, Merck, Sanofi Canada, Bristol-Meyers Squibb, Roche Canada, Boehringer Ingelheim, Bayer, Pfizer
Collin	Blakely	Other	Jazz Pharmas
		Supported/Contracted Research/Grant	Mirati, Ignyta, MedImmune, Novartis, Clovis, AstraZeneca
Ken	Bloom	Employee (full time or part time)	Human Longevity
		Other	Human Longevity
		Honoraria	Genentech, Roche, Ventana Medical Systems, Merck, Bristol-Meyers Squibb
		Speakers or Advisory Board	Ventana Medical Systems, Roche, Bristol-Meyers Squibb
		Speakers Bureau	Genentech
George	Blumenschein	Supported/Contracted Research/Grant	Xcovery Holding Company
		Speakers or Advisory Board	Bristol-Meyers Squibb, Bayer, Clovis, Merck, Celgene, AbbVie, Ariad
Paolo	Boffetta	Honoraria	Nucleix
		Contracted/Support Research Grant	National Institute for Occupational Safety and Health
Zeev	Bomzon	Employee (full time or part time)	Novocure
Steven	Boniol	Honoraria	Janssen
		Speakers or Advisory Board	Janssen
		Speakers Bureau	Janssen, Bristol Meyers-Squibb
		Other	Johnson & Johnson

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Philip	Bonomi	Honoraria	AstraZeneca, Bristol-Meyers Squibb, Biodesix, Merck, Pfizer, Roche Genentech, Trovagene, Eli Lilly, Clovis, Imedex
		Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb, Biodesix, Merck, Pfizer, Roche Genentech, Trovagene, Eli Lilly, Clovis, Imedex
		Supported/Contracted Research/Grant	AstraZeneca, Bristol-Meyers Squibb, Corvus Pharmas, Five Prime Therapeutics, Biodesix, Roche Genentech, Eli Lilly, Merck, Pfizer
		Other	Data Monitoring Committee: Genentech, Pfizer
Anne-Marie	Boothman	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Hossein	Borghaei	Supported/Contracted Research/Grant	Bristol-Meyers Squibb, Eli Lilly, Genentech, Celgene, Merck, Pfizer, Millennium
		Speakers or Advisory Board	Bristol-Meyers Squibb, Eli Lilly, Genentech, Celgene, Merck, Pfizer, Boerhinger Ingelheim, AstraZeneca, Genmab, Trovagene, Novartis, Regeneron, Cantargia AB, BioNTech
		Other	University of Pennsylvania MIllennium
		Employee (full time or part time)	Fox Chase Cancer Center
Diana	Borthwick	Speakers or Advisory Board	Boerhinger Ingelheim, Novartis, Merck, Bristol-Meyers Squibb
Joaquim	Bosch Barrera	Speakers or Advisory Board	Boheringer Ingelheim
Nandita	Bose	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Biothera
Johan	Botling	Honoraria	AstraZeneca, Merck, Roche, Pfizer, Bristol-Meyers Squibb, Boehringer Ingelheim, Novartis
Dean	Bottino	Employee (full time or part time)	Millennium Pharma
Souheil	Boubia	Speakers Bureau	Medtronic
		Honoraria	Medtronic
Nicole	Bouchard	Supported/Contracted Research/Grant	Pfizer, Bristol-Meyers Squibb, Merck
		Speakers or Advisory Board	Bristol-Meyers Squibb, Merck, Roche
J. Philip	Boudreaux	Speakers Bureau	Ipsen BioPharmas, Novartis, Lexicon Pharma
Jill	Bowman	Employee (full time or part time)	Incyte
Michael	Boyer	Honoraria	Roche, Bristol-Meyers Squibb, Merck, AstraZeneca, Novartis
		Speakers or Advisory Board	Merck, Amgen, Roche, Bristol-Meyers Squibb, Pfizer, AstraZeneca
		Contracted/Support Research Grant	Merck, Amgen, Genentech, Roche, Bristol-Meyers Squibb, AstraZeneca, Novartis, Pfizer
Penelope	Bradbury	Honoraria	AbbVie, Merck, Pfizer
Anthony	Brade	Speakers or Advisory Board	AstraZeneca
		Other	Eli Lilly
Jeffrey	Bradley	Speakers or Advisory Board	AstraZeneca, ViewRay, Varoian
		Supported/Contracted Research/Grant	Mevion Medical Systems, Viewray
Manisha	Brahmachary	Employee (full time or part time)	Eli Lilly
Julie	Brahmer	Speakers or Advisory Board	Merck, Genetech, Bristol-Meyers Squibb, Syndax, AstraZeneca, Celgene, Amgen Oncology
		Other	Celgene, Eli Lilly, MedImmune, AstraZeneca, Bristol-Meyers Squibb
		Supported/Contracted Research/Grant	Medimmune, AstraZeneca, Bristol-Meyers Squibb
Rachael	Brake	Employee (full time or part time)	Millennium Pharmas, Cambridge, MA, Takeda
Rolf	Brekken	Honoraria	BerGenBio ASA

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Emilio	Bria	Honoraria	Merck, AstraZeneca, Celgene, Pfizer, Helsinn, Eli Lilly, Bristol-Meyers Squibb, Novartis, Roche
		Supported/Contracted Research/Grant	Associazione Italiana Ricerca sul Cancro, IASCL, Lega Italiana per la Lotta contro i Tumori, Fondazione Cariverona, Astra-Zeneca, Roche, Open Innovation
		Speakers Bureau	Merck, Pfizer, Helsinn, Bristol-Meyers Squibb, Novartis
		Speakers or Advisory Board	Celgene, AstraZeneca, Roche
John	Bridges	Other	ICON
		Supported/Contracted Research/Grant	Lungevity
		Honoraria	Bayer, Boehringer Ingelheim
J. Michelle	Brockman	Employee (full time or part time)	Genentech
Stephen	Broderick	Other	Bristol-Meyers Squibb
Susan	Brouwer	Employee (full time or part time)	Syndax
Anthony	Brown	Employee (full time or part time)	BerGenBio ASA
Helen	Brown	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Wolfram	Brugger	Other	AstraZeneca
Rolf	Bruns	Employee (full time or part time)	Merck
Odd Terje	Brustugun	Speakers or Advisory Board	Novartis, Merck, Boehringer Ingelheim, Ariad
		Honoraria	AstraZeneca, Bristol-Meyers Squibb, Roche, PierreFabre, Novartis, Pfizer, Boehringer Ingelheim, Merck, Eli Lilly
		Supported/Contracted Research/Grant	Roche, AstraZeneca, GlaxoSmithKline, Novartis
Lukas	Bubendorf	Speakers or Advisory Board	Roche, Bristol-Meyers Squibb, AbbVie, AstraZeneca, Novartis, Pfizer, Takeda, Merck
		Honoraria	Roche, Pfizer, Bristol-Meyers Squibb, Merck
		Supported/Contracted Research/Grant	Roche, Merck
		Other	Roche, Roche, Pfizer, Bristol-Meyers Squibb
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche, Novartis
		Employee	Roche, Pfizer, Bristol-Meyers Squibb, Merck
		Financial Support from Tobacco Company(ies)	Merck, Roche, Novartis
Raphael	Bueno	Supported/Contracted Research/Grant	NIH U01 SPECS II
Paul	Bunn, Jr.	Other	AstraZeneca, Bristol-Meyers Squibb, Genentech, Eli Lilly, Pfizer, Merck, Novartis, Merrimack, Daiichi
		Supported/Contracted Research/Grant	Genentech, Roche
		Honoraria	AstraZeneca, Guardant Health
		Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb, Eli Lilly, Genentech, Merck, MerckSerono, Takeda
Mark	Burkard	Speakers or Advisory Board	Strata Oncology
Thomas	Burke	Employee (full time or part time)	Merck
Ronald	Burkes	Speakers or Advisory Board	AstraZeneca, Roche, Boehringer Ingelheim, Merck, Eli Lilly, Amgen
Charles	Butts	Honoraria	Pfizer, Boehringer Ingelheim, AstaZeneca, Bristol-Meyers Squibb, Merck, Takeda
		Speakers or Advisory Board	Pfizer, AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Merck, Takeda
Jacques	Cadranel	Speakers or Advisory Board	Boerhinger Ingelheim, AstraZeneca, Roche
Junliang	Cai	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Meyers Squibb
		Employee (full time or part time)	Bristol-Meyers Squibb

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Wilson	Caldwell	Employee (full time or part time)	Regeneron Pharmas
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Regeneron Pharmas, Bristol-Meyers Squibb, Merck
Raffaele	Califano	Other	AstraZeneca, Bristol-Meyers Squibb, Roche, Merck, Boehringer Ingelheim, Takeda, Novartis, Pfizer, Eli Lilly
		Speakers Bureau	Bristol-Meyers Squibb, AstraZeneca, Medimmune, Roche, Novartis, Merck, Eli Lilly
		Speakers or Advisory Board	Bristol-Meyers Squibb, AstraZeneca, Medimmune, Roche, Takeda, Novartis, Merck, Eli Lilly
		Honoraria	Bristol-Meyers Squibb, AstraZeneca, Medimmune, Roche, Takeda, Novartis, Merck, Eli Lilly
Kim	Caliri	Employee (full time or part time)	Merrimack Pharma
Emiliano	Calvo	Supported/Contracted Research/Grant	Boehringer Ingelheim, Roche, Genentech, Bristol-Meyers Squibb, Novartis, PsiOxus, Nanobiotix, Janssen, AbbVie, PharmaMar, PUMA, Sanofi, Eli Lilly, Pfizer, Merck, Nektar, Amcure, Amgen, AstraZeneca, Principia, Bayer, CytomX, H3, Incyte, Kura, Loxo, Macrogenics, Menarini, Serono, Merus, Millenium, Rigontec, Tahio, TesaroReceipt
		Honoraria	Novartis, Nanobiotix, Janssen-Cilag, PsiOxus Therapeutics, Seattle Genetics, Pierre Fabre, Boehringer Ingelheim, Cerulean Pharma, EUSA, AbbVie, Celgene
		Speakers Bureau	Novartis, Nanobiotix, Janssen-Cliag, PsiOxus, Genetics, Pierre Fabre, Boehringer Ingelheim
Ross	Camidge	Honoraria	Takeda, G1 Therapeutics, Mersana Therapeutics, Roche, Genentech, AstraZeneca, Arrys/Kyn, Genoptix, Ignyta, Daichii Sankyo, Hansoh SRC, Bio-Thera, Lycera, Revolution Med, Orion, Clovis, Celegene, Novartis
		Supported/Contracted Research/Grant	Ariad, Takeda, Pfizer
		Speakers or Advisory Board	AstraZeneca, Takeda, Arrys/Kyn, Genoptix, G1 Therapeutics, Mersana Therapeutics, Roche, Genentech, Takeda, Ignyta, Daichii Sankyo, Hansoh SRC, Bio-Thera DSMB, Lycera, Revolution Med
Jeroen	Cant	Employee (full time or part time)	Agfa HealthCare
Andrew	Capen	Employee (full time or part time)	Eli Lilly
Federico	Cappuzzo	Speakers or Advisory Board	Bristol-Meyers Squibb, Merck, AstraZeneca, Pfizer, Roche
William	Capra	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche
		Salary	Genentech
		Employee (full time or part time)	Genentech
		Other	Roche
David	Carbone	Other	Genentech
		Supported/Contracted Research/Grant	Merck, Bristol-Meyers Squibb
		Speakers or Advisory Board	AbbVie, Adaptimmune, Agenus, Amgen, Ariad, AstraZeneca, Biocept, Boehringer Ingelheim, Bristol-Meyers Squibb, Celgene, EMD Serono, Inc, Foundation Medicine, Genentech, Roche, Gritstone, Guardant Health, Inovio, Merck, Novartis, Palobiofarma, Pfizer, prIME Oncology, Stemcentrx, Takeda
		Honoraria	AbbVie, Adaptimmune, Agenus, Amgen, Ariad, AstraZeneca, Biocept, Boehringer Ingelheim, Bristol-Meyers Squibb, Celgene, Foundation Medicine, Genentech, Roche, Gritstone, Guardant Health, Inovio, Merck, Novartis, Palobiofarma, Pfizer, prIME Oncology, Stemcentrx, Takeda
Luis	Carbonell	Employee (full time or part time)	MagArray
Cynthia	Card	Speakers or Advisory Board	Boehringer Ingelheim
Carmine	Carpenito	Employee (full time or part time)	Eli Lilly
Marina	Carpentieri	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Philippe	Carriere	Employee (full time or part time)	Boehringer Ingelheim

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Marion	Carrigan	Employee (full time or part time)	Merck
Ken	Carson	Employee (full time or part time)	Flatiron Health
Francesca	Cavallo	Employee (full time or part time)	Personal Genome Diagnostics
Pilar	Cazorla Arratia	Employee (full time or part time)	Novartis
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Novartis
Fabiola	Cecchi	Employee (full time or part time)	NantOmics
Anne Marie	Cerato	Honoraria	AstraZeneca, Roche, Takeda
		Other	Bristol-Meyers Squibb
Giovanni	Ceresoli	Supported/Contracted Research/Grant	Bayer
Andres	Cervantes	Speakers or Advisory Board	Roche
		Honoraria	Roche
		Supported/Contracted Research/Grant	Genentech, Roche
Jamie	Chaft	Other	Genentech, Roche, AstraZeneca, MedImmune, Merck, Bristol-Meyers Squibb
		Supported/Contracted Research/Grant	Genentech, Roche, Bristol-Meyers Squibb, AstraZeneca, MedImmune
		Speakers or Advisory Board	Genentech, Bristol-Meyers Squibb, Merck, AstraZeneca
Carlos	Chaib	Employee (full time or part time)	Bristol-Myers Squibb
Yajnaseni	Chakraborti	Employee (full time or part time)	Novartis
Oscar S.H.	Chan	Speakers or Advisory Board	AstraZeneca, Merck
		Honoraria	Bristol-Meyers Squibb, AstraZeneca
Sheenu	Chandwani	Employee (full time or part time)	Merck
Gee-Chen	Chang	Honoraria	Roche, Eli Lilly and Company Oncology, AstraZeneca, Pfizer, Boehringer Ingelheim, Bristol-Meyers Squibb, Merck
Joe	Chang	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Global Oncoloe One
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb
Bo	Chao	Employee (full time or part time)	Eli Lilly
Sandra	Chaplan	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Janssen
		Salary	Janssen
		Employee (full time or part time)	Janssen
Haris	Charalambous	Supported/Contracted Research/Grant	Merck
Aafia	Chaudhry	Employee (full time or part time)	Eli Lilly
Parneet	Cheema	Speakers or Advisory Board	Pfizer, AstraZeneca, Roche, Merck, Novartis, Takeda, Boehringer Ingelheim, Bristol-Meyers Squibb
Nabil	Chehab	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Hui	Chen	Employee (full time or part time)	OrigiMed
Shuquan	Chen	Employee (full time or part time)	Daiichi Sankyo
Paul Ning-Man	Cheng	Royalty, Intellectual Property/Patent Holder	Bio-cancer Treatment
		Salary	Bio-cancer Treatment
Carol	Cheung	Honoraria	Merck, Bristol-Meyers Squibb
Anne	Chiang	Speakers or Advisory Board	AstraZeneca, AbbVie
		Other	AstraZeneca
		Supported/Contracted Research/Grant	AstraZeneca, AbbVie
		Speakers Bureau	Bristol-Meyers Squibb

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Alberto	Chiappori	Speakers or Advisory Board	Genentech, Merck, Takeda, AstraZeneca, Bristol-Meyers Squibb, Novartis
		Supported/Contracted Research/Grant	Novartis, Bristol-Meyers Squibb, AstraZeneca
		Speakers Bureau	Genentech, Takeda, Merck, Boehringer Ingelheim, Celgene, Pfizer
James	Chih-Hsin Yang	Honoraria	Boehringer Ingelheim, Eli Lilly, Roche, Genentech, Chugai, Merck, Pfizer, Novartis, Celgene, Bristol-Meyers Squibb, Ono Pharma, AstraZeneca, Takeda, Hansoh Pharmas
Darin	Chin	Employee (full time or part time)	Eli Lilly
Marc	Chioda	Employee (full time or part time)	Pfizer
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
Michael	Chisamore	Employee (full time or part time)	Merck
Juliann	Chmielecki	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Byoung Chul	Cho	Honoraria	AstraZeneca, Boehringer Ingelheim, Novartis, Ono Pharmas
		Other	AstraZeneca, Janssen, MedImmune, Merck, Novartis, Ono Pharma, Pfizer, Roche, Yuhan
		Speakers Bureau	Novartis
Krishna	Chodavarapu	Employee (full time or part time)	Eli Lilly
Soongyu	Choi	Employee (full time or part time)	Yuhan Corporation
Quentin	Chometon	Employee (full time or part time)	Optellum
Teh-Ying	Chou	Speakers or Advisory Board	Merck, Foundation Medicine, Roche, Novartis
Christos	Chouaid	Speakers or Advisory Board	Roche, Boehringer Ingelheim, AstraZeneca, Eli Lilly, Novartis, Merck, Bristol-Meyers Squibb, GlaxoSmithKline, Amgen
Jouhara	Chouitar	Employee (full time or part time)	Millennium Pharmas, Cambridge, MA, Takeda
Laura	Chow	Speakers or Advisory Board	Bristol-Meyers Squibb, Merck, Genentech, Astra-Zeneca, Seattle Genetics, Pfizer, Novartis, Dynavax
		Other	Bristol-Meyers Squibb
		Honoraria	Amgen, Sanofi-Genzyme, Takeda
		Supported/Contracted Research/Grant	Bristol Meyers Squibb, Merck, Genentech, Astra-Zeneca, Pfizer, Seattle Genetics, Novartis, Dynavax, VentiRx, Eli Lilly, Imclone, Incyte
Edna	Chow-Maneval	Employee (full time or part time)	Ignyta
Hak	Choy	Speakers Bureau	AstraZeneca
		Honoraria	AstraZeneca, Merck
Paula	Chu	Employee (full time or part time)	Roche
Shannon	Chuai	Employee (full time or part time)	Burning Rock Biotech
Mattia	Cinelli	Supported/Contracted Research/Grant	Inivata
		Employee (full time or part time)	Inivata
Andrew	Ciupek	Speakers or Advisory Board	Takeda Pharmas, AbbVie, Grail, Genentech
Jill	Clancy	Employee (full time or part time)	Pfizer
Jeffrey	Clark	Supported/Contracted Research/Grant	Pfizer
C	Clifford	Employee (full time or part time)	Blueprint Medicines
Roger	Cohen	Supported/Contracted Research/Grant	Merck
Esther	Conde	Speakers or Advisory Board	Pfizer, Roche
Henry	Conter	Other	Roche, Eli Lilly, Janssen
Keegan	Cooke	Employee (full time or part time)	Amgen
Wendy	Cooper	Speakers or Advisory Board	Bristol-Meyers Squibb, Merck, AstraZeneca
		Other	Travel support

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Romain	Corre	Speakers or Advisory Board	Bristol-Meyers Squibb
Stefani	Corsi-Travali	Employee (full time or part time)	Loxo
Alexis	Cortot	Speakers or Advisory Board	AstraZeneca, Roche, Pfizer, Takeda, Novartis
Daniel	Costa	Speakers or Advisory Board	Tadeka, AstraZeneca
		Honoraria	Pfizer, Tadeka
		Supported/Contracted Research/Grant	Pfizer
		Other	Ariad
Christian	Couture	Speakers or Advisory Board	AstraZeneca, Merck, Bristol-Meyers Squibb, Pfizer
		Honoraria	AstraZeneca, Merck, Bristol-Meyers Squibb, Pfizer
		Supported/Contracted Research/Grant	AstraZeneca, Merck, Bristol-Meyers Squibb, Pfizer
		Honoraria	AstraZeneca, Merck, Bristol-Meyers Squibb, Pfizer
Michael	Cox	Employee (full time or part time)	Loxo
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Loxo
Angela	Coxon	Employee (full time or part time)	Amgen
Jeffrey	Crawford	Speakers or Advisory Board	Amgen
Diana	Cripps	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
		Employee (full time or part time)	AstraZeneca
Marka	Crittenden	Supported/Contracted Research/Grant	Jounce, Nanobiotix
Victoria	Crossland	Employee (full time or part time)	Takeda
Scott	Cruickshank	Employee (full time or part time)	Loxo
Agnieszka	Cseh	Employee (full time or part time)	Boehringer Ingelheim
J. Jean	Cui	Employee (full time or part time)	TP Therapeutics
Na	Cui	Employee (full time or part time)	Roche, Genentech
Zhanglin	Cui	Employee (full time or part time)	Eli Lilly
Alessandra	Curioni Fontecedro	Other	Bristol-Meyers Squibb, Merck, Roche, AstraZeneca, Pfizer, Takeda, Novartis, Boehringer Ingelheim
		Speakers or Advisory Board	Roche, Merck, Bristol-Meyers Squibb, Boehringer-Ingelheim, Pfizer, AstraZeneca, Takeda
		Supported/Contracted Research/Grant	Novartis
Martin	Curtis	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Janssen
		Employee (full time or part time)	Janssen
		Salary	Janssen
Paul	Curtis	Employee (full time or part time)	Regeneron Pharma
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Regeneron Pharma
Sanja	Dacic	Speakers or Advisory Board	Bristol-Meyers Squibb, Astra-Zeneca
		Honoraria	Bristol-Meyers Squibb, AstraZeneca
Ibiayi	Dagogo-Jack	Honoraria	Foundation Medicine
		Other	Boehringer Ingelheim
Suzanne	Dahlberg	Other	AstraZeneca
Samir	Dalia	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	32nd Street Surgery Center
		Speakers or Advisory Board	New Century Health
		Supported/Contracted Research/Grant	Novartis Bristol-Meyers Squibb, Calithera, Helsinn, Genentech, Celgene
Deepa	Dalvi	Employee (full time or part time)	Roche

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Bita	Damadzadeh	Employee (full time or part time)	Roche
Gina	D'Amato	Speakers or Advisory Board	Novartis, Bayer, Eisai, Eli Lilly, Janssen
		Speakers Bureau	Novartis, Eisai, Eli Lilly, Janssen
Thomas	D'Amico	Other	Consultant for Scanlan Instruments
		Speakers or Advisory Board	Scanlon
Kathleen	Danenberg	Employee (full time or part time)	Nant Health, Liquid Genomics
Peter	Danenberg	Employee (full time or part time)	Liquid Genomics
Thao	Dang	Employee (full time or part time)	Merck
Jeannie	Daniel	Employee (full time or part time)	Incyte
Marianne	Davies	Speakers Buerau	AstraZeneca, Genentech, Bristol-Meyers Squibb, Merck
Gilberto	De Castro	Speakers or Advisory Board	AstraZeneca
Floris	De Jong	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Amgen, Shire
		Employee (full time or part time)	Shire
Filippo	De Marinis	Honoraria	Bristol-Meyers Squibb, AstraZeneca, Roche, Merck
Cisio	De Oliveira Brandao	Employee (full time or part time)	Amgen
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Amgen
Peter	De Porre	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Johnson & Johnson
		Employee (full time or part time)	Johnson & Johnson
Michael	De Rosa	Employee (full time or part time)	Adelphi Values
		Other	Bristol-Meyers Squibb
Maike	De Wit	Supported/Contracted Research/Grant	AstraZeneca
		Speakers or Advisory Board	AstraZeneca
Jerome	Declerck	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Optellum
		Employee (full time or part time)	Optellum
Chantal	Decroisette	Speakers or Advisory Board	Roche, Bristol-Meyers Squibb, Boehringer Ingelheim, AstraZeneca, Pierre Fabre, Novartis
Justine	Degrandpre	Employee (full time or part time)	Thermo Fisher Scientific
Angelo	Delmonte	Other	AstraZeneca, Boehringer Ingelheim
Todd	Demmy	Other	Medtronic
Phillip	Dennis	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
		Other	AstraZeneca
Charuhas	Deshpande	Speakers Bureau	Merck
Frank	Detterbeck	Speakers or Advisory Board	Spiration
		Supported/Contracted Research/Grant	Medela
Geeta	Devgan	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Rasvan	Diaconescu	Honoraria	Merck, Bristol-Meyers Squibb
Sven	Diederichs	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Biotech, Martinsried

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Maximilian	Diehn	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	CiberMed
		Honoraria	Roche
		Supported/Contracted Research/Grant	Varian Medical Systems
		Royalty, Intellectual Property/Patent Holder	Patents on Cancer Biomarkers
Martin	Dietrich	Speakers Bureau	AstraZeneca, Novartis
		Speakers or Advisory Board	AstraZeneca, Novartis, Takeda
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
Beiying	Ding	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche
		Salary	Roche/Genentech
		Employee (full time or part time)	Roche, Genentech
		Other	Roche
Lieming	Ding	Employee (full time or part time)	Bettapharma Pharmas
Yan	Ding	Employee (full time or part time)	Geneseeq Technology
Winand	Dinjens	Supported/Contracted Research/Grant	AstraZeneca
		Honoraria	Thermo Fisher, Life, Roche, Bristol-Meyers Squibb
		Speakers or Advisory Board	Amgen
Robert	Doebele	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Rain Therapeutics
		Speakers or Advisory Board	Ignyta, AstraZeneca, Bayer, Takeda, Bristol-Meyers Squibb, Ariad
		Supported/Contracted Research/Grant	Ignyta
		Other	Pfizer, OncoMed, Trovagene, Ignyta, GreenPeptide, AstraZeneca, Ignyta, Ariad, Guardant Health
		Honoraria	Pfizer, AstraZeneca, Ariad, Guardant Health, Takeda, Spectrum Pharmas, Trovagene
		Royalty, Intellectual Property/Patent Holder	Abbott Molecular, Rain Therapeutics, Igynta
Toshihiko	Doi	Supported/Contracted Research/Grant	Daiichi Sankyo
Thompson	Doman	Employee (full time or part time)	Eli Lilly
Yu-An	Dong	Employee (full time or part time)	OrigiMed
Jessica	Donington	Honoraria	AstraZeneca
Gregory	Donoho	Employee (full time or part time)	Eli Lilly
Frank	Dorsey	Employee (full time or part time)	Eli Lilly
Helene	Doubre	Speakers or Advisory Board	Novartis
		Supported/Contracted Research/Grant	Merck, Bristol-Meyers Squibb, Boehringer Ingelheim, AstraZeneca
Afshin	Dowlati	Other	AbbVie, Stemcentrx, Ariad, Amgen, Bristol-Meyers Squibb, Mercl, Eli Lilly, MedImmune, OncoMed
Nick	Dowson	Employee (full time or part time)	Optellum
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Optellum
Alexander	Drilon	Speakers or Advisory Board	Ignyta, Loxo, TP Therapeutics, AstraZeneca, Pfizer, Blueprint Medicines, Genentech, Roche, Takeda, Helsinn Therapeutics, BeiGene
		Honoraria	TP Therapeutics, Loxo, Ignyta, Roche, Genentech, Pfizer
		Supported/Contracted Research/Grant	Foundation Medicine
		Other	Ignyta, Loxo, TP Therapeutics, AstraZeneca, Pfizer, Blueprint Medicines, Genentech, Roche, Takeda, Helsinn Therapeutics, BeiGene

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Erik Jan	Dubbink	Supported/Contracted Research/Grant	AstraZeneca
		Speakers or Advisory Board	Pfizer, Personal Genome Diagnostics
Steven	Dubinett	Speakers or Advisory Board	T-Cure, EarlyDiagnostics, AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	EarlyDiagnostics
		Royalty, Intellectual Property/Patent Holder	Patent holder DC-CCL21
Elizabeth	Dudnik	Other	Boehringer Ingelheim, Merck, Roche, AstraZeneca, Pfizer, Bristol-Meyers Squibb, Novartis
Mei Sheng	Duh	Supported/Contracted Research/Grant	AstraZeneca
		Other	AstraZeneca
Gary	Dukart	Speakers or Advisory Board	Xcovery Holding Company
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Xcovery Holding Company
Addie	Dvir	Employee (full time or part time)	Oncotest Teva Pharmas
Rafal	Dziadziuszko	Speakers or Advisory Board	Roche, AstraZeneca, Pfizer, Bristol Meyers-Squibb, Ignyta
		Honoraria	Roche, Pfizer, Novartis, Ignyta, AstraZeneca, Bristol-Meyers Squibb
		Speakers Bureau	Roche, Bristol-Meyers Squibb, AstraZeneca
Beth	Eaby-Sandy	Speakers Bureau	Helsinn, Merck, AstraZeneca, Takeda
		Other	Consultant- AbbVie
Kevin	Ebata	Employee (full time or part time)	Loxo
Wilfried Ernst Erich	Eberhardt	Speakers or Advisory Board	Bristol-Meyers Squibb, Roche, AstraZeneca, Merck, Boehringer Ingelheim, Celgene, Eli Lilly, Pfizer, Novartis, Takeda, AbbVie
		Honoraria	Bristol-Meyers Squibb, Roche, AstraZeneca, Merck, Boehringer Ingelheim, Celgene, Eli Lilly, Pfizer, Novartis, Takeda, AbbVie
		Supported/Contracted Research/Grant	Eli Lilly, Bristol-Meyers Squibb, AstraZeneca
		Other	Bristol-Meyers Squibb, Roche, AstraZeneca, Boehringer Ingelheim
François	Eisinger	Honoraria	Roche
Martin	Edelman	Speakers or Advisory Board	Bristol-Meyers Squibb, Eli Lilly
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Andarix, Biomarker
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb
		Other	Eli Lilly, Boehringer Ingelheim, AstraZeneca
David	Eiznhamer	Salary	Kadmon Corporation, LLC
Ehab	Elgabry	Employee (full time or part time)	Roche
Ivy	Elkins	Speakers or Advisory Board	Astrazeneca
		Honoraria	Boehringer Ingelheim, AstraZeneca, AbbVie
Barbara	Ellers-Lenz	Employee (full time or part time)	Merck KGaA
Peter	Ellis	Honoraria	AbbVie, AstraZeneca
		Other	Celegene, Mylan
Sotaro	Enatsu	Employee (full time or part time)	Eli Lilly
Masahiro	Endo	Honoraria	AstraZeneca
Judson	Englert	Employee (full time or part time)	MedImmune, LLC
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	MedImmune, LLC
Rachel	Erlich	Employee (full time or part time)	Foundation Medicine
Carin	Espenschied	Employee (full time or part time)	Guardant Health

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Janet	Espirito	Employee (full time or part time)	McKesson
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	McKesson
E	Evans	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Blueprint Medicines
		Employee (full time or part time)	Blueprint Medicines
		Supported/Contracted Research/Grant	AstraZeneca, Celgene, Roche, Boehringer Ingelheim, Eli Lilly
Tracey	Evans	Speakers Bureau	Genentech
		Honoraria	Genentech
William	Evans	Speakers or Advisory Board	AbbVie, Astellas, Bristol-Meyers Squibb, Eisai, Eli Lilly, Janseen, Gilead, Takeda, AstraZeneca, Janssen, Boehringer Ingelheim, Roche, Celgene
		Other	AstraZeneca, Janssen, Boehringer Ingelheim, Roche, Celgene
Corinne	Faivre-Finn	Supported/Contracted Research/Grant	Merck, AstraZeneca, Elekta
		Other	Merck, AstraZeneca, Elekta, Pfizer, Respective Meeting-Related Travel Support
		Speakers or Advisory Board	Pfizer, Merck
		Honoraria	AstraZeneca, Merck
		Speakers Bureau	AstraZeneca, Merck
lionel	Falchero	Speakers or Advisory Board	Roche, Boehringer Ingelheim, Bristol-Meyers Squibb, Novartis, AstraZeneca, AbbVie
Markus	Falk	Speakers or Advisory Board	Boehringer Ingelheim, Pfizer, Roche
Minhao	Fan	Employee (full time or part time)	AstraZeneca
Anna	Farago	Supported/Contracted Research/Grant	AbbVie, Stemcentrx, PharmaMar, Ignyta, Bristol-Meyers Squibb, Merck, AstraZeneca, Novartis, Bayer, Loxo
		Honoraria	Foundation Medicine
		Other	AbbVie, PharmaMar, Takeda, Stemcentrx, Loxo, Bayer
		Speakers or Advisory Board	AbbVie, Loxo, Pharmamar
Ori	Farber	Employee (full time or part time)	Novocure
Claire	Faure	Employee (full time or part time)	Roche Diagnostics
Emily	Fay	Employee (full time or part time)	Optellum
Nathalie	Faye	Employee (full time or part time)	Median Technologies
Bruce	Feinberg	Employee (full time or part time)	Cardinal Health
Enriqueta	Felip	Other	AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb Celgene, Eli Lilly, Guardant Health, Novartis, Pfizer, Roche, Takeda, Merck
		Speakers or Advisory Board	Boehringer Ingelheim, Eli Lilly, Pfizer, Roche, AstraZeneca, Bristol-Meyers Squibb, Novartis, AbbVie, Takeda, Celegene, Guardant Health, Merck
		Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, MSD, Novartis, Pfizer, Roche, Takeda, AbbVie, Merck, Celegne, Eli Lilly, Guardant Health
Federico	Felizzi	Employee (full time or part time)	Roche
Minjie	Feng	Employee (full time or part time)	Regeneron
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Regeneron, Bayer
Dean	Fennell	Speakers or Advisory Board	AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Meyers Squibb, Clovis, Eli Lilly, Lab21, Oncos, Polaris, Bristol-Meyers Squibb, Epizyme, Roche
		Supported/Contracted Research/Grant	Boehringer Ingelheim, Bergen Bio, Bayer, Bristol-Meyers Squibb, Pierre Fabre, Eli Lilly, Roche-Genentech, Astex
		Speakers Bureau	Boehringer Ingelheim, Roche, Bristol-Meyers Squibb, Merck, AstraZeneca
		Honoraria	AbbVie, Boehringer Ingelheim, Bayer, Bristol-Meyers Squibb, Epizyme, Roche, AstraZeneca

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Ancilla	Fernandes	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Mary Jo	Fidler	Honoraria	Genentech, Celgene, Merck, AbbVie
		Speakers or Advisory Board	AstraZeneca, AbbVie, Takeda, Genentech
		Supported/Contracted Research/Grant	Biodesix
John	Field	Speakers Bureau	Roche
		Speakers or Advisory Board	Epigenomics, VisonGate
Joseph	Fiore	Employee (full time or part time)	Bristol-Meyers Squibb
		Other	Merck
Martin	Filipits	Speakers or Advisory Board	AstraZeneca, Boehringer Ingelheim, Myriad
		Homoraria	AstraZeneca, Boehringer Ingelheim, Merck, Eli Lilly, Ratiopharm, Novartis
Juergen	Fischer	Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb, Celgene, Roche, Merck, Boehringer Ingelheim,
		Speakers Bureau	AstraZeneca, Celgene, Roche
		Honoraria	AstraZeneca, Bristol-Meyers Squibb, Celgene, Roche, Merck, Boehringer Ingelheim
		Other	Celgene
Amanda	Fish	Employee (full time or part time)	MagArray,
Javier	Flandes	Other	Medtronic, Olympus, BTG-PulmonX
		Supported/Contracted Research/Grant	BTG-PulmonX
Emuella	Flood	Employee (full time or part time)	ICON
Marie	Florescu	Speakers Bureau	Roche, Bristol Meyers Squibb, AstraZeneca
		Speakers or Advisory Board	AstraZeneca, Roche, Bristol-Meyers Squibb, Merck, Boehringer Ingelheim
Erik	Folch	Other	Medtronic
		Speakers or Advisory Board	Medtronic
Patrick	Forde	Supported/Contracted Research/Grant	AstraZeneca, Bristol-Meyers Squibb, Novartis, Kyowa, Janssen
		Other	Merck, Inivata, AbbVie, Boehringer Ingelheim
		Speakers or Advisory Board	Bristol-Meyers Squibb, AstraZeneca, Novartis, Merck
Tim	Forshew	Employee (full time or part time)	Inivata
Martin	Forster	Speakers or Advisory Board	Eli Lilly, Pfizer, Clovis, Novartis, Merck, AstraZeneca
Stefan	Foser	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche
		Salary	Roche
		Employee (full time or part time)	Roche
		Other	Roche
Paul	Foster	Employee (full time or part time)	Genentech
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche, Exelixis
Garrett	Frampton	Employee (full time or part time)	Foundation Medicine
Fabio	Franke	Speakers or Advisory Board	Bristol-Meyers Squibb
		Other	Bristol-Meyers Squibb
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb
Stuart	Fraser	Employee (full time or part time)	Oncimmune LLC
Elke K.	Friedman	Speakers Bureau	Gilead Pharma
		Employee (full time or part time)	Virginia Cancer Institute
Matthias	Friedrich	Employee (full time or part time)	Amgen

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Osvaldo	Frontera	Other	Bristol-Meyers Squibb, Roche, AstraZeneca, Regeneron
		Honoraria	Bristol-Meyers Squibb, Roche, Novartis
Nobukazu	Fujimoto	Honoraria	Ono Pharmacuticals, Eli Lilly, Chugai, Taiho, Hisamitsu
		Speakers or Advisory Board	Boehringer Ingelheim, Bristol-Meyers Squibb, Kyorin
		Supported/Contracted Research/Grant	Ono Pharmas, Novartis, GlaxosmithKline, Merck
Yuka	Fujita	Speakers Bureau	Eli Lilly, Chugai Pharma
		Supported/Contracted Research/Grant	Eli Lilly, Chugai Pharma, Taiho Pharma, Pfizer
Minoru	Fukuda	Supported/Contracted Research/Grant	AstraZeneca
		Honoraria	Taiho Pharma, Merck, Chugai Pharma, Boehringer Ingelheim
Tatsuro	Fukuhara	Supported/Contracted Research/Grant	AstraZeneca, Merck, Ono Pharma, Bristol-Meyers Squibb, Chugai Pharma, Novartis
Tomoya	Fukui	Honoraria	Chugai Pharma, Novartis Pharma, Ono Pharma, Taiho Pharma
Matthew	Fury	Employee (full time or part time)	Regeneron Pharmas
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Regeneron Pharmas
		Royalty, Intellectual Property/Patent Holder	Regeneron Pharmas
Rabab	Gaafar	Supported/Contracted Research/Grant	Roche, Boehringer Ingelheim, AbbVie, AstraZeneca
Louis	Gaboury	Supported/Contracted Research/Grant	AstraZeneca
Shirish	Gadgeel	Speakers or Advisory Board	Astra-Zeneca, Genentech, Roche, Ariad, Takeda, AbbVie, Bristol Meyers-Squibb
Justin	Gainor	Other	Bristol-Meyers Squibb, Genentech, Roche, Novartis, Loxo, Theravance, Clovis, Merck, Boehringer Ingelheim, Incyte, Affymetrix, Pfizer, Amgen, Agios
		Honoraria	Bristol-Meyers Squibb, Merck, Genentech, Roche, Pfizer, Array Biopharm, Loxo, Ariad, Takeda, Agios, Amgen, Novartis
		Speakers or Advisory Board	Bristol-Meyers Squibb, Array Biopharma, Ariad, Takeda, Theravance
		Supported/Contracted Research/Grant	Genentech
Thomas	Gajewski	Speakers or Advisory Board	Merck, Roche, Genentech, Jounce Therapeutics, Bayer, AbbVie, Amgen, Aduro Biotech, Forma Therapeutics
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb, Merck, Roche, Genentech, Incyte, Seattle Genetics, Ono Pharma
Aaron	Galaznik	Employee (full time or part time)	Millennium Pharmas, Takeda Pharma
Domenico	Galetta	Speakers or Advisory Board	Bristol-Meyesr Squibb
Hui	Gan	Speakers or Advisory Board	AbbVie
		Speakers Bureau	Ignyta, Bristol-Meyers Squibb
		Supported/Contracted Research/Grant	AbbVie
David	Gandara	Honoraria	AstraZeneca, Celgene, Genentech, Guardant Health, Eli Lilly, Liquid Genomics, Nant Health
		Other	Genentech, AstraZeneca, Celgene, Guardant Health, Eli Lilly, Liquid Genomics
		Supported/Contracted Research/Grant	AstraZeneca, Genentech
		Speakers or Advisory Board	AstraZeneca, Celgene, Genentech, Gaurdant Health, Eli Lilly, Liquid Genomics, Nant Health
Mayank	Gandhi	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Merck, Neurocrine, Acadia Pharmas, Spark Therapeutics
		Employee (full time or part time)	Roche, Genentech
Gérard	Ganem	Honoraria	Roche
Apar Kishor	Ganti	Supported/Contracted Research/Grant	Merck, AstraZeneca, Bristol-Meyers Squibb, Amgen, NewLink Genetics, Novartis
		Speakers or Advisory Board	Takeda, Pfizer

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Bo	Gao	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Regeneron Pharmas
		Employee (full time or part time)	Regeneron Pharmas
Yuki	Gao	Employee (full time or part time)	Amoy Diagnostics
Marina	Garassino	Other	Merck, Bristol-Meyers Squibb AstraZeneca, Roche
		Honoraria	Merck, Bristol-Meyers Squibb, AstraZeneca, Roche, Boehringer Ingelheim
Maria Rosario	Garcia Campelo	Honoraria	Ariad, AstraZeneca, Roche, Pfizer, Bristol-Meyers Squibb, Boehringer Ingelheim
		Speakers or Advisory Board	Ariad, AstraZeneca, Roche, Pfizer, Bristol-Meyers Squibb, Boehringer Ingelheim
Chad	Garner	Employee (full time or part time)	Nantomics
Edward	Garon	Other	Bristol-Meyers Squibb, Eli Lilly, AstraZeneca, Genentech, Merck, Novartis, Pfizer, Boehringer Ingelheim, Mirati, Dynavax
		Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb, Eli Lilly, Genetech, Merck, Novartis, Pfizer, Boehringer Ingelheim, Mirati, Dynavax
		Supported/Contracted Research/Grant	Merck, Genentech, AstraZeneca, Novartis, Pfizer, Eli Lilly, Bristol-Meyers Squibb, Boehringer Ingelheim, Mirati Therapeutics, Dyanvax
Pilar	Garrido	Other	Roche, Merck, AstraZeneca, Boehringer Ingelheim, Pfizer, Bristol-Meyers Squibb, Eli Lilly and Company, AbbVie, Novartis
		Speakers Bureau	Roche, Merck, Bristol-Meyers Squibb, Pfizer
		Supported/Contracted Research/Grant	Guardant
Pere	Gascón	Honoraria	Sandoz, Hospira, Amgen
		Other	Merck, Sandoz, Hospira
Laurie	Gay	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Gilead Sciences, Foundation Medicine
		Salary	Foundation Medicine
		Employee (full time or part time)	Foundation Medicine
		Other	Roche
Jun	Ge	Employee (full time or part time)	Merck
Sandaruwan	Geeganage	Employee (full time or part time)	Eli Lilly
William	Geese	Employee (full time or part time)	Bristol-Meyers Squibb
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Meyers Squibb
Akihiko	Gemma	Speakers Bureau	AstraZeneca
Carlo	Genova	Honoraria	AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Merck, Roche
Ryan	Gentzler	Speakers or Advisory Board	AstraZeneca
		Supported/Contracted Research/Grant	Merck, Bristol-Myers-Squibb, Celgene
David	Gerber	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Gilead
		Speakers or Advisory Board	Bristol-Meyers Squibb, Samsung-Bioepis
		Speakers Bureau	Guardant
		Other	Karyopharm
		Supported/Contracted Research/Grant	Karyopharm, BerGenBio
Kelly	Gerding	Employee (full time or part time)	Personal Genome Diagnostics
Yaron	Gesthalter	Honoraria	Intuitive Surgical

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Scott	Gettinger	Supported/Contracted Research/Grant	Ariad, AstraZeneca, MedImmune, Bristol-Meyers Squibb, Boehringer Ingelheim, Incyte, Pfizer, Roche, Genentech
		Other	Bristol-Meyers Squibb, Genentech, Ariad, Incyte, Pfizer, Celldex, Alexion Pharmas, Merck, Janssen
		Speakers or Advisory Board	Bristol-Meyers Squibb
Sara	Ghassemifar	Employee (full time or part time)	Merrimack Pharmas
Sharmistha	Ghosh	Other	Pfizer
Don	Gibbons	Supported/Contracted Research/Grant	Janssen
Michael	Giffin	Employee (full time or part time)	Amgen
Moshe	Giladi	Employee (full time or part time)	Novocure
Nicolas	Girard	Other	Bristol-Meyers Squibb, Merck Roche, AstraZeneca
Etienne	Giroux Leprieur	Speakers or Advisory Board	AstraZeneca, Novartis, Roche, Merck
Barbara	Gitlitz	Employee (full time or part time)	Genentech
Fergus	Gleeson	Supported/Contracted Research/Grant	EIT health, National Institute for Health Research
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Optellum
Shobha	Gokul	Employee (full time or part time)	Asuragen
Sarah	Goldberg	Supported/Contracted Research/Grant	AstraZeneca
		Honoraria	AstraZeneca, Bristol-Meyers Squibb, Eli Lilly, Boehringer Ingelheim
		Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb, Eli Lilly, Boehringer Ingelheim Daiichi
Terri	Goldberg	Employee (full time or part time)	Sankyo
Jonathan W.	Goldman	Speakers or Advisory Board	Genentech, Roche, Bristol-Meyers Squibb, Eli Lilly, Pfizer
		Other	Genentech, Roche, Bristol-Meyers Squibb
		Speakers Bureau	Merck
		Honoraria	AstraZeneca
		Supported/Contracted Research/Grant	AstraZeneca, MedImmune, Bristol-Meyers Squibb, Genentech, Roche, Eli Lilly, Merck
Jerome	Goldschmidt Jr.	Other	Amgen
		Honoraria	Amgen
		Speakers Bureau	Bristol-Meyers Squibb, Celgene, Eli Lilly
		Speakers or Advisory Board	Amgen
Daniel	Gomez	Honoraria	Merck, Bristol-Meyers Squibb, AstraZeneca, Varian, Reflexion
		Speakers or Advisory Board	AstraZeneca, Merck
Maciej	Goniewicz	Speakers or Advisory Board	Johnson & Johnson
Jin Mo	Goo	Supported/Contracted Research/Grant	Lunit
Leonid	Gorelik	Employee (full time or part time)	Checkpoint Therapeutics
John	Gosney	Speakers or Advisory Board	AbbVie, AstraZeneca, Bristol-Meyers Squibb, Merck, Pfizer, Roche
		Other	AbbVie, AstraZeneca, Bristol-Meyers Squibb, Merck, Pfizer, Roche
Koichi	Goto	Supported/Contracted Research/Grant	Nippon Boehringer Ingelheim, Chugai Phamaceutical, Eli Lilly
		Honoraria	Nippon Boehringer Ingelheim, Chugai Phamaceutical, Eli Lilly

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Yasushi	Goto	Other	Eli Lilly, Boehringer Ingelheim, Taiho Pharma, GlaxoSmithKline, Pfizer, Novartis, AstraZeneca
		Honoraria	AstraZeneca, Boehringer Ingelheim, Lilly Japan, Chugai Pharma, Taiho Pharma, Ono Pharma, Merck, Pfizer, Bristol-Myers Squiibb Japan, Shionogi Pharma, Novartis, Kyorin
		Supported/Contracted Research/Grant	AbbVie, Eli Lilly, Pfizer
		Speakers Bureau	AstraZeneca, Eli Lilly, Chugai, Taiho Pharma, Boehringer Ingelheim, Ono Pharma, Bristol-Meyers Squibb, Pfizer, Merck, Shionogi Pharma, Novartis
Ramaswamy	Govindan	Speakers or Advisory Board	Merck, Baxalta, Roche, Boehringer Ingleheim, Novartis, Pfizer, Celgene, AstraZeneca, MSK, AbbVie Inivata, Pfizer, NeoHealth, Bristol-Meyers Squibb, Nektar, GlaxcSmithKline
		Other	Genentech, Ariad, Astellas, Bristol-Meyers Squibb, INC Research, AbbVie
		Honoraria	AbbVie, Genentech, Boehringer Ingelheim
Fred	Grannis	Supported/Contracted Research/Grant	International Early Lung Cancer Action Program
		Other	Paolicelli and Phillips Law, International Early Lung Cancer Action Program, Steven Phillip attorney
Jhanelle	Gray	Supported/Contracted Research/Grant	AstraZeneca, Celgene, Eli Lilly, Janssen, Merck, Genentech, Boehringer Ingelheim, Bristol-Meyers Squibb, Array
		Speakers or Advisory Board	AstraZeneca
		Honoraria	Celgene, Eli Lilly, Janssen, AstraZeneca
Laura	Greco	Speakers or Advisory Board	Genentech
Emma	Green	Employee (full time or part time)	Inivata
		Other	Inivata
Laurie	Green	Employee (full time or part time)	Kadmon Corporation, LLC
Jeffrey	Gregg	Speakers or Advisory Board	Foundation Medicine, AstraZeneca, Bristol-Meyers Squibb, Roche
		Speakers Bureau	AstraZeneca, Foundation Medicine
Laurent	Greillier	Speakers or Advisory Board	Roche, AstraZeneca, Bristol-Meyers Squibb, Merck, AbbVie, Novartis, Pfizer, Boehringer Ingelheim
Cesare	Gridelli	Other	Pfizer, Roche
Frank	Griesinger	Speakers or Advisory Board	Ariad, AstraZeneca, Boehringer Ingelheim, Bristol-Myer-Squibb, Celegene, Clovis, Eli Lilly, Merck, Novartis, Pfizer, Roche
		Other	Ariad, AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Celgene, Clovis, Eli Lilly, Merck, Novartis, Pfizer, Roche, Siemens
		Supported/Contracted Research/Grant	Roche, AstraZeneca, Eli Lilly, Bristol-Meyers Squibb, Merck, Celgene, Boehringer Ingelheim, Pfizer, Novartis
Daniel	Grima	Employee (full time or part time)	Cornerstone Research Group
Harry	Groen	Other	Roche-Genentech, Merck, Novartis, Bristol-Meyers Squibb
Francesco	Grossi	Speakers Bureau	Amgen, Celgene, Eli Lilly
		Speakers or Advisory Board	Bristol-Meyers Squibb, Merck, AstraZeneca Pierre Fabre, Roche, Boehringer Ingelheim
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb
		Other	Bristol-Meyers Squibb, Merck, AstraZeneca, Pierre Fabre, Roche, Boehringer Ingelheim, Pfizer, Amgen, Eli Lilly, Celgene
		Honoraria	Bristol-Meyers Squibb, Merck, AstraZeneca, Pierre Fabre, Boehringer Ingelheim, Pfizer, Celgene, Amgen, Roche
Federica	Grosso	Other	PharmaMar, Boehringer Ingelheim
Aaron	Gruver	Employee (full time or part time)	Eli Lilly

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Tao	Gu	Employee (full time or part time)	Bristol-Meyers Squibb
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Meyers Squibb
		Salary	Bristol-Meyers Squibb
Maria	Guerin	Speakers or Advisory Board	AstraZeneca
		Honoraria	AstraZeneca
Ferdinand Morales	Guevara	Employee (full time or part time)	Daiichi Sankyo
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Florian	Guisier	Speakers or Advisory Board	AstraZeneca, Roche, Boehringer Ingelheim
		Honoraria	Bristol-Meyers Squibb, Merck, Roche, AstraZeneca, Boehringer Ingelheim
Honglin	Guo	Employee (full time or part time)	OrigiMed
Zaid	Haddad	Employee (full time or part time)	MagArray
Nahor	Haddish-Berhane	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Janssen
		Salary	Janssen
Eric	Hailman	Employee (full time or part time)	Mersana Therapeutics
Richard	Hall	Speakers or Advisory Board	AstraZeneca, Takeda
		Honoraria	Merck
		Supported/Contracted Research/Grant	Merck, AbbVie, Eli Lilly
Gerald	Hall	Employee (full time or part time)	Eli Lilly
Balazs	Halmos	Speakers or Advisory Board	AstraZeneca, Boehringer Ingelheim, Genentech, Pfizer, Eli Lilly, Foundation Medicine, Guardant Health, Takeda, Novartis, Merck, Bristol-Meyers Squibb
		Supported/Contracted Research/Grant	Merck, AstraZeneca, Mirati Therapeutics, Boehringer Ingelheim, Pfizer, Takeda, Novartis, Eli Lilly
		Other	Foundation Medicine, Guardant Health
		Honoraria	AstraZeneca, Novartis, Takeda, Pfizer, Eli Lilly, Foundation One, Guardant Health, Boehringer Ingelheim, Genentech
Celeste	Hamilton	Employee (full time or part time)	VisionGate
Geoffrey	Hamilton-Fairley	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Oncimmune LLC
Ji-Youn	Han	Other	Roche, Bristol-Meyers Squibb, AstraZeneca, Merck, Takeda, Novartis
		Honoraria	Ono Pharma
Yimei	Han	Employee (full time or part time)	Eli Lilly
Valdimir	Hanes	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Amgen
		Employee (full time or part time)	Amgen
Jeff	Haney	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Ariad
		Employee (full time or part time)	Ariad
Masaki	Hanibuchi	Honoraria	Taiho Pharma, Kyowa Hakko Kirin
Amy	Hanlon Newell	Employee (full time or part time)	Roche
Nasser	Hanna	Supported/Contracted Research/Grant	Merck, Bristol-Meyers Squibb, Genentech, AstraZeneca
Daijiro	Harada	Honoraria	Ono Pharmaceutica, Bristol-Meyers Squibb, Yakult Honsya, Kyowa Hakko Kirin, AstraZeneca, Eli Lilly
David	Harpole	Speakers or Advisory Board	Medtronic, AstraZeneca

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Kimberly	Harrow	Employee (full time or part time)	Xcovery Holding Company
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Xcovery Holding Company
		Salary	Xcovery Holding Company
Stephen	Harrow	Honoraria	AstraZeneca
		Speakers or Advisory Board	AstraZeneca
Akito	Hata	Speakers or Advisory Board	Eli Lilly
AN	Hata	Supported/Contracted Research/Grant	Novartis, Relay Therapeutics, Amgen
Hiroto	Hatabu	Supported/Contracted Research/Grant	Toshiba Medical Systems, Canon, Konica-Minolta
Matthew	Hatton	Speakers or Advisory Board	AstraZeneca
Eric	Haura	Other	Bristol-Meyers Squibb, Janssen Oncology, Roche
		Royalty, Intellectual Property/Patent Holder	Patent
		Supported/Contracted Research/Grant	Eli Lilly, Ignyta, Janssen, Boehringer Ingelheim, Forma Therapeutics
Libor	Havel	Other	Roche
Hidetoshi	Hayashi	Speakers Bureau	Eli Lilly
Yong	He	Speakers or Advisory Board	AstraZeneca, Eli Lilly, Pfizer, Roche
Kai	He	Other	Perthera
		Honoraria	Geneplus
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb, Mirati Therapeutics, Adaptimmune, Genentech, Roche
Graham	Healey	Employee (full time or part time)	Oncimmune LLC
Andreas	Heilmann	Employee (full time or part time)	Foundation Medicine
Rebecca	Heist	Honoraria	Boehringer Ingelheim
		Supported/Contracted Research/Grant	Genentech, Roche, Millenium, Novartis, Celgene, Peregrine, Mirati, Corvus, Incyte, AbbVie, Agios, Debiopharm
Matthew	Hellmann	Other	Bristol-Meyers Squibb, Merck, Genentech Roche, AstraZeneca, MedImmune, Novartis, Janseen, Shattuck Lab, Syndax
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb
		Speakers or Advisory Board	Bristol-Meyers Squibb, Merck, Genentech, AstraZeneca, MedImmune, Novartis, Janssen Pharmas, Mirati Therapeutics, Shattuck Labs
		Royalty, Intellectual Property/Patent Holder	Memorial Sloan Kettering Cancer Center
Todd	Hembrough	Employee (full time or part time)	NantOmics
Roy	Herbst	Speakers or Advisory Board	AstraZeneca, Eli Lilly, Genentech, Roche, Merck, NextCure, Novartis, Pfizer
		Supported/Contracted Research/Grant	AstraZeneca, Eli Lilly, Merck, Genentech
Genevive	Hernandez	Employee (full time or part time)	Genentech
James	Hernandez	Employee (full time or part time)	Personal Genome Diagnostics
Nadine	Hertel	Employee (full time or part time)	Bristol-Meyers Squibb Pharmas
John	Heymach	Royalty, Intellectual Property/Patent Holder	Spectrum Pharmas
		Other	AstraZeneca, AbbVie, Boehringer Ingelheim, Medivation, Ariad, Synta, Oncomed, Novartis, Genentech, Calithera Biosciences
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Cardinal Spine, Bio-Tree, Spectrum Pharmas
		Supported/Contracted Research/Grant	AstraZeneca, Bayer, GlaxoSmithKline, Threshold Pharmas
		Honoraria	Ariad
		Speakers or Advisory Board	AstraZeneca

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Toyoaki	Hida	Supported/Contracted Research/Grant	Ono Pharma, Bristol-Meyers Squibb, Chugai Pharma, Nippon Boehringer Ingelheim, Merck, AstraZeneca, Pfizer, Astellas, Taiho Pharma, Clovis Oncology, Novartis
		Honoraria	Eli Lilly
Prista	Hikmawati	Supported/Contracted Research/Grant	International Office UNS
Katsuya	Hirano	Speakers Bureau	Taiho Pharma
Fred	Hirsch	Other	AstraZeneca, Genentech, HTG Molecular Diagnostics, Eli Lilly, Merck, Clovis Oncology, Ventana Medical Systems, Bristol-Meyers Squibb, Pfizer, Roche
		Royalty, Intellectual Property/Patent Holder	University of Colorado Cancer Center
		Supported/Contracted Research/Grant	Eli Lilly, Genentech, Amgen, Bristol-Meyers Squibb, Celgene
		Speakers or Advisory Board	AbbVie, AstraZeneca, Biocept, Bristol-Meyers Squibb, HTG, Eli Lilly, Loxo, Merck, Novartis, Pfizer, Roche, Genentech, Ventana, Bayer
Cheryl	Ho	Supported/Contracted Research/Grant	BC Cancer Foundation
		Honoraria	AstraZeneca
		Other	Roche
James Chung-man	Ho	Honoraria	AstraZeneca, Roche, Boehringer Ingelheim, Merck, Bristol-Meyers Squibb, Pfizer, Novartis
		Speakers Bureau	AstraZeneca, Roche, Boehringer Ingelheim, Merck, Bristol-Meyers Squibb, Pfizer, Novartis
		Speakers or Advisory Board	AstraZeneca, Roche, Boehringer Ingelheim, Merck, Bristol-Meyers Squibb, Pfizer, Novartis
		Supported/Contracted Research/Grant	AstraZeneca, Roche, Bristol-Meyers Squibb, Pfizer, Merck, Novartis
Tien	Hoang	Employee (full time or part time)	Genentech, Roche
Maximilian	Hochmair	Speakers Bureau	AstraZeneca, Roche, Novartis, Takeda
		Speakers or Advisory Board	Boehringer Ingelheim, AstraZeneca, Merck, Bristol-Meyers Squibb
		Other	Roche
Cyrla	Hoffert	Royalty, Intellectual Property/Patent Holder	Replicor
Kyle	Hogarth	Other	Medtronic
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Auris Surgical Robotics
		Honoraria	Medtronic, Boston Scientific
		Speakers or Advisory Board	Medtronic, Auris Surgical Robotics, Boston Scientific, Grifols, Shire, CSL
Burton	Holmes	Employee (full time or part time)	Roche
Robert	Holt	Employee (full time or part time)	BerGenBio
Allison	Holzhausen	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Xcovery Holding Company
		Salary	Xcovery Holding Company
		Employee (full time or part time)	Xcovery Holding Company
Florian	Honeyball	Honoraria	AstraZeneca
Thomas	Hope	Supported/Contracted Research/Grant	GE Healthcare
Leora	Horn	Other	AbbVie, AstraZeneca, Genentech, Merck, Incyte, Xcovery, Roche
		Supported/Contracted Research/Grant	Xcovery Holding Company, Bristol-Meyers Squibb, Boehringer Ingelheim, AbbVie, Genentech, Merck
Yukio	Hosomi	Speakers Bureau	AstraZeneca, Taiho Pharma, Eli Lilly Japan, Chugai Pharma, Ono Pharma, Bristol-Meyers Squibb, Merck

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Katsuyuki	Hotta	Honoraria	AstraZeneca, Ono Pharma, Boehringer Ingelheim, Nihon Kayaku, Taiho Pharma, Chugai Pharma, Novartis, Bristol-Meyers Squibb, Eli Lilly Japan, Merck, AstraZeneca, Astellas
		Supported/Contracted Research/Grant	Astellas, AstraZeneca, Ono Pharma, Boehringer-Ingelheim, Chugai Pharma, Novartis, Bristol-Meyers Squibb, Eli Lilly Japan, Merck
Karen	Howarth	Supported/Contracted Research/Grant	Inivata
		Employee (full time or part time)	Inivata
		Royalty, Intellectual Property/Patent Holder	Inivata
		Salary	Inviata
Hsin-ju	Hsieh	Employee (full time or part time)	MedImmune, LLC
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	MedImmune, LLC
Tun-Ying	Hsu	Employee (full time or part time)	Merck
Jinwei	Hu	Employee (full time or part time)	OrigiMed
Wenhua	Hu	Employee (full time or part time)	Bristol-Meyers Squibb
Dennis Chin-Lun	Huang	Employee (full time or part time)	Boehringer Ingelheim
Hui	Huang	Employee (full time or part time)	Takeda Pharmas
Min	Huang	Employee (full time or part time)	Merck
Richard	Huang	Employee (full time or part time)	Roche
Xiaodong	Huang	Employee (full time or part time)	Eli Lilly
Xin	Huang	Employee (full time or part time)	Loxo
Yifan	Huang	Employee (full time or part time)	AstraZeneca
Florian	Huemer	Speakers or Advisory Board	Roche, Bristol-Myers-Squibb
		Other	Roche
Rina	Hui	Honoraria	Bristol-Meyers Squibb, Boehringer Ingelheim, Merck, AstraZeneca, Novartis, Roche
		Speakers or Advisory Board	AstraZeneca, Merck, Novartis, Pfizer, Roche, Bristol-Meyers Squibb
		Other	Merck, AstraZeneca, Novartis, Roche, Bristol-Meyers Squibb, Boehringer Ingelheim, Pfizer
Olivier	Huillard	Speakers or Advisory Board	Bristol-Meyers Squibb, Novartis, Sanofi
Martin	Hüllner	Other	GE Healthcare
Annie	Hung	Employee (full time or part time)	Armo BioSciences
Manjusha	Hurry	Employee (full time or part time)	AstraZeneca Canada
Felipe	Hurtado	Employee (full time or part time)	Novartis
Hatim	Husain	Speakers Bureau	AstraZeneca, Bristol-Meyers Squibb, Merck
		Speakers or Advisory Board	AstraZeneca, Foundation Medicine
		Supported/Contracted Research/Grant	Pfizer
David	Hwang	Honoraria	Merck, Pfizer, Takeda
		Speakers or Advisory Board	Merck
Harry	Hwang	Speakers Bureau	Roche, AstraZeneca
		Speakers or Advisory Board	Roche, AstraZeneca
		Honoraria	Roche, AstraZeneca
		Supported/Contracted Research/Grant	Abbott Molecular
David	Hyman	Speakers or Advisory Board	Atara Biotherapeutics, Chugai Pharma, CytomX Therapeutics, Boehringer Ingelheim, AstraZeneca, Pfizer, Bayer, Debiopharm Group, ArQule, Genentech

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A. John	Iafrate	Speakers or Advisory Board	Roche, Chugai
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	ArcherDX
		Royalty, Intellectual Property/Patent Holder	ArcherDX
Shannon	Ibabekci	Employee (full time or part time)	Loxo
Norihiko	Ikeda	Honoraria	AstraZeneca, Chugai, Merck, Ono Pharma, Taiho, Eli Lilly, Pfizer, Johnson & Johnson
Fumio	Imamura	Speakers Bureau	Ono Pharma
		Supported/Contracted Research/Grant	Ono Pharma
Martina	Imbimbo	Honoraria	Bristol-Meyers Squibb
Maurizio	Infante	Honoraria	Merck
Akira	Inoue	Speakers Bureau	AstraZeneca, Eli Lilly, Chugai Pharma., Boehringer Ingelheim
		Honoraria	Chugai, Eli Lilly, Bristol-Meyers Squibb, Nihonkayaku, AstraZeneca, Pfizer, Boehringer Ingelheim
Diana	Ionescu	Honoraria	Merck, Bristol-Meyers Squibb, AstraZeneca
Hidenobu	Ishii	Supported/Contracted Research/Grant	Boehringer Ingelheim
Kumiko	Isse	Employee (full time or part time)	AbbVie
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AbbVie
Kentaro	Ito	Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Chugai Pharma, Ono Pharma, Pfyzer, Merck, Eli Lily
Eiji	Iwama	Honoraria	AstraZeneca, Eli Lilly, Pfizer., Chugai Pharma
Tae	Iwasawa	Honoraria	Ono Pharmas, Astellas, Boehringer Ingelheim, Shionogi, Canon Medical
Salma	Jabbour	Supported/Contracted Research/Grant	Merck, Nestle
David	Jablons	Other	Razor Genomics
Philippe	Jacques	Other	AstraZeneca
Thierry	Jahan	Supported/Contracted Research/Grant	Atomic, Acerta Acerta, Aduro, Bristol-Meyers Squibb, Boehringer Ingelheim, AstraZeneca, Eli Lilly, Epizyme, Merck, Polaris
Mohammad	Jahanzeb	Supported/Contracted Research/Grant	Eli Lilly, Boehringer Ingelheim, Callisto
		Other	Novartis, Ipsen, Roche, Genentech
Yolanda	Jaimes	Employee (full time or part time)	Liquid Genomics
Ariel	Jaimovich	Employee (full time or part time)	Guardant Health
Marko	Jakopovic	Other	Boehringer Ingelheim, AstraZeneca, Roche, Novartis, Merck, Bristol-Meyers Squibb, Pfizer
		Speakers or Advisory Board	Boehringer Ingelheim, AstraZeneca, Roche, Novartis, Merck, Bristol-Meyers Squibb, Pfizer
Seong Bok	Jang	Employee (full time or part time)	Yuhan Corporation
Pasi	Jänne	Other	Araxes Pharmas, Ariad, AstraZeneca, Boehringer Ingelheim, Chugai, Ignyta, Eli Lilly, Loxo, Merrimack, Mirati Therapeutics, Pfizer, Roche, Dana-Farber Cancer Institute
		Speakers or Advisory Board	AstraZeneca, Boehringer Ingelheim, Pfizer, Merrimack Pharmas, Roche, Genentech, Chugai Pharmas, Acea Biosciences, Ignyta, Loxo, Ariad, Eli Lilly, Araxes Pharmas
		Speakers Bureau	Loxo
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Gatekeeper Pharmas
		Supported/Contracted Research/Grant	Astellas Pharmas, AstraZenenca, Daiichi Sankyo, PUMA, Eli Lilly, Boehringer Ingelheim
		Royalty, Intellectual Property/Patent Holder	LabCorp
Ellen	Janssen	Employee (full time or part time)	ICON
Milenka	Jean-Baptiste	Employee (full time or part time)	Evidera
Min-Hua	Jen	Employee (full time or part time)	Eli Lilly and Company

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James	Jett	Employee (full time or part time)	Oncimmune LLC
		Other	Oncimmune LLC
Philip	Jewsbury	Other	AstraZeneca
Fengge	Jiang	Employee (full time or part time)	Amoy Diagnostics
Takahiro	Jikoh	Employee (full time or part time)	Daiichi Sankyo
Thomas	John	Speakers or Advisory Board	Bristol-Meyers Squibb, AstraZeneca, Boehringher Ingelheim, Takeda, Pfizer, Novartis, Merck, Ignyta
		Other	Bristol-Meyers Squibb, AstraZeneca, Boehringer Ingelheim, Takeda, Pfizer, Novartis, Merck
Bruce	Johnson	Royalty, Intellectual Property/Patent Holder	Dana-Farber Cancer Institute
		Other	KEW
		Supported/Contracted Research/Grant	Novartis, Toshiba, Genentech, Roche, Medical Systems
Melissa	Johnson	Supported/Contracted Research/Grant	BerGenBio, Eli Lilly, Merck Serono, Janssen, Mirati Therapeutics, Genmab, Pfizer, AstraZeneca, Genentech, Roche, Stemcentrix, Novartis, Checkpoint Therapeutics, Array BioPharma, Regeneron, Apexigen, AbbVie, Tarveda, Adaptimmune, Syndax, Neovia, Boehringer Ingelheim, Sanofi, Hengrui Therapeutics, Daiichi – Sankyo, Lycera, G1 Therapeutics, Dynavax, OncoMed, Kadmon, BeiGen, Loxo, Mersana
		Speakers or Advisory Board	Astellas, Otsuka Pharmas, Genentech, Roche, Celgene, Boehringer Ingelheim, Sanofi, Mirati, Loxo, AstraZeneca, Mersana
		Other	Astellas, Otsuka Pharmas, Roche
Bonita	Jones	Employee (full time or part time)	Eli Lilly
Greg	Jones	Employee (full time or part time)	Inivata
Gregory	Jones	Speakers or Advisory Board	MDxHealth
Sian	Jones	Employee (full time or part time)	Personal Genome Diagnostics
Mirjana	Josipovic	Other	Varian Medical Systems
Alice	Juang	Employee (full time or part time)	MagArray
Rosalyn	Juergens	Speakers or Advisory Board	Bristol-Meyers Squibb, Merck, Roche, Boehringer Ingelheim, Eli Lilly, Pfizer, Amgen, Novartis, AstraZeneca, Takeda
		Honoraria	Bristol-Meyers Squibb, Merck, Roche, Boehringer Ingelheim, AstraZeneca, MedImmune, Eli Lilly, Takeda, Novartis, Amgen Pfizer
		Speakers Bureau	Amgen
		Other	Boehringer Ingelheim, Bristol-Meyers Squibb, Eli Lilly, Merck, Novartis, Pfizer, Amgen, Roche, AstraZeneca, MedImmune,
		Supported/Contracted Research/Grant	AstraZeneca, MedImmune, Merck, Bristol-Meyers Squibb
Daniela	Juri	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Guardant Health
		Employee (full time or part time)	Guardant Health
Fairooz	Kabbinavar	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Genentech
		Salary	Genentech
		Employee (full time or part time)	Genentech
		Other	Roche
Timor	Kadir	Employee (full time or part time)	Optellum
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Optellum
Carmen	Kahatt	Employee (full time or part time)	PharmaMar S.A.
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	PharmaMar S.A.

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Michael	Kalos	Employee (full time or part time)	Eli Lilly
Rajender	Kamboj	Employee (full time or part time)	Lupin
Sandy	Kamer	Employee (full time or part time)	MagArray
Walid	Kamoun	Employee (full time or part time)	Merrimack Pharmas
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Merrimack Pharmas
		Salary	Takeda
Kuninobu	Kanai	Supported/Contracted Research/Grant	Ono Pharma
Seonmi	Kang	Employee (full time or part time)	Seonmi Kang
Steven	Kao	Honoraria	Roche, Bristol-Meyers Squibb, Merck, AstraZeneca
		Speakers or Advisory Board	AstraZeneca, Pfizer, Boehringer Ingelheim
		Supported/Contracted Research/Grant	Pfizer
Chris	Karapetis	Speakers or Advisory Board	AstraZeneca
Peter	Kasan	Speakers or Advisory Board	Boehringer Ingelheim, Roche, Merck
Elie	Kassouf	Speakers or Advisory Board	Sanofi, Amgen, Celgene, Bristol-Meyers Squibb, Pfizer, Lundbeck, Boehringer Ingelheim, Janssen, AstraZeneca, Novartis
Rahul	Katdare	Employee (full time or part time)	VisionGate
Tatsuya	Kato	Supported/Contracted Research/Grant	Ono Pharmas, Bristol-Meyers Squibb, AstraZeneca, Boehringer Ingerheim, Chugai, Eli Lilly, Kirin Kyowa, Merck, Pfixer, Quintiles, Taiho, Parexel, AbbVie, Astellas
		Honoraria	Ono Pharma, Bristol-Meyers Squibb, AstraZeneca, Boehringer Ingerheim, Chugai, Eli Lilly, Merck, Novartis, Pfizer, Quintiles, Roche, Taiho, Parexel, AbbVie
		Speakers or Advisory Board	Chugai, Eli Lilly, Merck
Terufumi	Kato	Honoraria	AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Chugai, Eli Lilly, Merck, Novartis, Ono Pharma, Pfizer, Quintiles, Taiho
		Supported/Contracted Research/Grant	AbbVie, Astellas, AstraZeneca, Bristol-Meyers Squibb, Chugai, Eli Lilly, Kirin Kyowa, Merck, Ono Pharma, Pfizer, Quintiles, Novartis
		Speakers or Advisory Board	AstraZeneca, Eli Lilly, Merck
		Employee (full time or part time)	Eli Lilly
		Other	Merck
Tomoya	Kawaguchi	Honoraria	Chugai Pharma, AstraZeneca, Boehringer Ingelheim
		Supported/Contracted Research/Grant	AstraZeneca, Chugai Pharma, Boehringer Ingelheim
Laurel	Keefer	Employee (full time or part time)	Personal Genome Diagnostics
Robert	Keith	Speakers Bureau	Boehringer Ingelheim
		Speakers or Advisory Board	Lungevity, American Lung Association - Lung Cancer Medical Advisory Panel
		Royalty, Intellectual Property/Patent Holder	Patent - Use of Prostacyclin Agonists to Prevent Cancer
Laimonas	Kelbauskas	Employee (full time or part time)	VisionGate
Karen	Kelly	Speakers or Advisory Board	AbbVie, AstraZeneca, Genentech, Janssen, Eli Lilly, Merck
		Supported/Contracted Research/Grant	AbbVie, Celgene, Merck, Five Prime, Genentech, Eli Lilly, Lycera, Novartis, Regeneron, Transgene
		Royalty, Intellectual Property/Patent Holder	UpToDate
		Honoraria	Merck
		Other	AbbVie, Genentech, Eli Lilly, Merck, UpToDate
Hirotsugu	Kenmotsu	Honoraria	Boehringer Ingelheim, Chugai Pharma, AstraZeneca
		Supported/Contracted Research/Grant	Boehringer Ingelheim, Chugai Pharma, AstraZeneca
Drew	Kennedy	Employee (full time or part time)	Guardant Health
Keith	Kerr	Other	Bristol-Meyers Squibb
		Speakers or Advisory Board	AstraZeneca, Bristol Meyers Squibb, Merck, Roche, Pfizer

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David	Kerstein	Employee (full time or part time)	Ariad
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Ariad
Sandeep	Khandhar	Other	Medtronic
		Supported/Contracted Research/Grant	Medtronic
		Speakers or Advisory Board	Medtronic
Behzad	Kharabi Masouleh	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Johnson & Johnson
		Employee (full time or part time)	Johnson & Johnson
Leila	Khoja	Employee (full time or part time)	AstraZeneca
Mohsen	Khorshid	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche, Foundation Medicine
		Salary	Roche
		Other	Roche
		Employee (full time or part time)	Roche
Lesli	Kiedrowski	Employee (full time or part time)	Guardant Health
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Guardant Health
Takashi	Kijima	Speakers Bureau	Boehringer Ingelheim, Shionogi, Ono Pharma, Taiho Pharma, Meiji Seika Pharma, Novartis Pharma, Chugai Pharma, Daiichi Sankyo, AstreZeneca, Merck, Pfizer, Eli Lilly
		Supported/Contracted Research/Grant	Ono Pharma
Hironori	Kikkawa	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Anthony	Kim	Speakers or Advisory Board	Medtronic, Genentech
Edward	Kim	Honoraria	Eli Lilly, AstraZeneca, Celgene, Boehringer Ingelheim
		Speakers or Advisory Board	Eli Lilly, AstraZeneca, Celgene, Boehringer Ingelheim
		Other	Eli Lilly, AstraZeneca, Celgene, Boehringer Ingelheim
Hye Ryun	Kim	Other	AstraZeneca, Roche, Boehringer Ingelheim
Min	Kim	Honoraria	Intuitive Surgical, Medtronics, Boston Scientific, Olympus
Miyoung	Kim	Employee (full time or part time)	Boehringer Ingelheim
Sohee	Kim	Employee (full time or part time)	Yuhan Corporation
Young-Chul	Kim	Supported/Contracted Research/Grant	AstraZeneca, Roche
		Speakers or Advisory Board	Caris Life Sciences
		Speakers Bureau	AstraZeneca, Roche
Hedy Lee	Kindler	Speakers or Advisory Board	Merck
Jennifer	King	Speakers or Advisory Board	Grail, AstraZeneca, Genentech, Tesaro, AbbVie
		Supported/Contracted Research/Grant	AstraZeneca
		Speakers Bureau	AstraZeneca
Eilon	Kirson	Employee (full time or part time)	Novocure
Takumi	Kishimoto	Speakers or Advisory Board	Ono Pharma
Roland	Knoblauch	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Janssen
		Salary	Janssen
		Employee (full time or part time)	Janssen
Elizabeth	Knowles	Salary	Elekta

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Kunihiko	Kobayashi	Speakers or Advisory Board	AstraZeneca
		Speakers Bureau	Chugai Pharma., AstraZeneca, Ono Pharma., Eli Lilly
Yoshihisa	Kobayashi	Speakers Bureau	Boehringer Ingelheim
		Supported/Contracted Research/Grant	The Japan Society for the Promotion of Science, Osaka Cancer Society, Novartis
Mark	Kockx	Employee (full time or part time)	Histogenex
Barbara	Koetz	Other	AstraZeneca
Yasuhiro	Koh	Honoraria	Boehringer Ingelheim, AstraZeneca, Kyowa Hakko Kirin, Chugai Pharma, Ono Pharma, Bristol-Meyers Squibb, Thermo Fisher Scientific, Tosoh Corporation
		Supported/Contracted Research/Grant	Boehringer Ingelheim, AstraZeneca, Daiichi Sankyo, Novartis
Alexander	Kohlmann	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Jill	Kolesar	Honoraria	AbbVie
Feng-Ming (Spring)	Kong	Speakers Bureau	Varian Medical
		Honoraria	Varian Medical
Beata	Korytowsky	Employee (full time or part time)	Bristol-Meyers Squibb
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Meyers Squibb
		Salary	Bristol-Meyers Squibb
Marcin	Kowanetz	Employee (full time or part time)	Roche, Genentech
		Royalty, Intellectual Property/Patent Holder	Roche, Genentech
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche
Mark	Kozloff	Speakers Bureau	Genentech, Roche, AbbVie, Amgen, Merck, Eli Lilly
		Other	Genentech, Roche, AbbVie, Merck
Toshiyuki	Kozuki	Honoraria	Kyowa, AstraZeneca, Pfizer, Eli Lilly, Ono, Chugai, Boehringer Ingelheim, Bristol-Meyers Squibb, Taiho, Nippon Kayaku, Merck
		Supported/Contracted Research/Grant	Chugai Pharma, Eli Lily
Johannes	Kratz	Speakers or Advisory Board	Razor
		Other	Razor
Matthew	Krebs	Speakers or Advisory Board	Roche
William	Krimsky	Other	Medtronic, Innovital Systems
		Employee (full time or part time)	Medtronic
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	CSA Medical, Innovital Systems, Peytant Solutions, Gala Therapeutics
		Speakers or Advisory Board	Gala Therapeutics, SOC, Peytant
		Royalty, Intellectual Property/Patent Holder	Medtronic, Merit
		Honoraria	CSA Medical, Merit Medical
Mark	Kris	Honoraria	AstraZeneca
		Other	Genetech Roche, AstraZeneca, Ariad
Vimal	Krishnan	Supported/Contracted Research/Grant	AstraZeneca
Ian	Krop	Speakers or Advisory Board	Daiichi Sankyo, Genentech
Maciej	Krzakowski	Speakers or Advisory Board	Boehringer Ingelheim, AstraZeneca
		Other	Roche

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Nora	Ku	Employee (full time or part time)	Loxo
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Loxo
Akihito	Kubo	Honoraria	Chugai Pharma, Boehringer Ingelheim, Taiho Pharma, AstraZeneca, Novartis, Lilly Japan
		Supported/Contracted Research/Grant	Lilly Japan, Chugai Pharma, Boehringer Ingelheim
Kaoru	Kubota	Honoraria	Chugai, Merck, Taiho, Boehringer Ingerheim, AstraZeneca, Eli Lilly, Ono, KyowaKirin, Novaltis, DaiichSankyo, Eisai, Roche
Geoffrey	Kuesters	Employee (full time or part time)	Merrimack Pharmas
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Merrimack Pharmas
Swati	Kulkarni	Honoraria	AstraZeneca
Rakesh	Kumar	Employee (full time or part time)	MedImmune, LLC
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	MedImmune, LLC
Ansu	Kumar	Employee (full time or part time)	Cellworks Research, Bangalore
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Cellworks Research, Bangalore
Rajesh	Kumawat	Employee (full time or part time)	Lupin Limited
Hiromi	Kumon	Speakers or Advisory Board	Kyorin
		Other	Momotaro Gene
		Royalty, Intellectual Property/Patent Holder	Patent
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Momotaro Gene
		Honoraria	Momotaro Gene
		Supported/Contracted Research/Grant	Kyorin
Pamela	Kunz	Speakers or Advisory Board	Ipsen, Lexicon Pharmas
		Supported/Contracted Research/Grant	Dicerna, Esanex, Oxigene, Advanced Accelerator Applications, Genentech, Incyte, Ipsen, Lexicon Pharmas, Merck
Takayasu	Kurata	Honoraria	Ono Pharma, Eli Lilly, Bristol-Meyers Squibb, AstraZeneca, Chugai, Nippon Boehringer Ingelheim, Merck
		Supported/Contracted Research/Grant	AstraZeneca
Masahiko	Kusumoto	Honoraria	Ono Pharmas, AstraZeneca, Merck
David	Kwiatkowski	Other	AstraZeneca, Genentech, Roche
		Supported/Contracted Research/Grant	AADi
Catherine	Labbe	Honoraria	Bristol-Meyers Squibb, Merck
Laure	Lacoin	Supported/Contracted Research/Grant	Bristol-Myers-Squibb
Marc	Ladanyi	Other	Boehringer-Ingelheim, Afatinib Targeted Therapy
		Speakers or Advisory Board	Foundation Medicine
		Supported/Contracted Research/Grant	Loxo
Rahul	Ladwa	Other	Novartis, Bristol-Meyers Squibb
David	Laidley	Speakers or Advisory Board	Ipsen
		Honoraria	Novartis, Ipsen
		Supported/Contracted Research/Grant	Ipsen, Novartis
Francois	Laliberté	Supported/Contracted Research/Grant	AstraZeneca
		Other	AstraZeneca

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Sivuonthanh	Lam	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche, Genentech
		Salary	Roche, Genentech
		Employee (full time or part time)	Roche, Genentech
		Other	Roche.
Peter	Lambert	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Genentech, Roche
		Salary	Genentech
		Employee (full time or part time)	Genentech
		Supported/Contracted Research/Grant	Roche, Genentech
		Other	Roche
Lorenza	Landi	Speakers or Advisory Board	Bristol-Meyers Squibb AstraZeneca, Pfizer, Boehringer Ingelheim
Joshua	Lang	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Salus Discovery LLC
Corey	Langer	Supported/Contracted Research/Grant	Pfizer, Eli Lilly, Genentech, OSI Pharmas, GlaxoSmithKline, Clovis, Merck, Advantagene, Inovio, Takeda, AbbVie, Celgene, Incyte, Macrogenics
		Honoraria	Bristol-Meyers Squibb, Imclone Systems, Pfizer, Eli Lilly, AstraZeneca, Merck, Novartis, Genentech, Bayer, Celgene, Abbott Labs, Biodesix, Clariant, CarisDx, Ariad, Boehringer Ingelheim, Synta, Clovis
		Other	Amgen, Synta, Peregrine, SWOG, Incyte, VA, Eli Lilly, PIK, PER, NOCR, CCO, RTP
Richard	Lanman	Employee (full time or part time)	Guardant Health
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Guardant Health
		Other	Guardant Health
Si-Houy	Lao-Sirieix	Royalty, Intellectual Property/Patent Holder	AstraZeneca
Sylvie	Laquerre	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Janssen
		Salary	Janssen
		Employee (full time or part time)	Janssen
Janessa	Laskin	Honoraria	Roche, Boehringer Ingelheim, AstraZeneca
		Supported/Contracted Research/Grant	AstraZeneca, Roche, Pfizer
Gary	Latham	Employee (full time or part time)	Asuragen
Christopher	Lathan	Honoraria	Association of Community Cancer Centers
		Speakers or Advisory Board	Eli Lilly, Bristol-Meyers Squibb
		Supported/Contracted Research/Grant	CVS Health
Kelvin	Lau	Honoraria	Medtronic
		Supported/Contracted Research/Grant	Philips
Yvonne	Lau	Employee (full time or part time)	Novartis
Scott	Laurie	Other	Bristol-Meyers Squibb, Novartis, Pfizer, Boehringer Ingelheim, AstraZeneca, BBI
		Honoraria	Novartis, Pfizer, Boehringer Ingelheim, AstraZeneca
Rachael	Lawrance	Employee (full time or part time)	Adelphi Values
		Other	Bristol-Meyers Squibb
Ben	Lawrence	Honoraria	Novartis
		Other	Merck
Anh	Le	Royalty, Intellectual Property/Patent Holder	Abbott Molecular
Catherine	Le	Employee (full time or part time)	Roche

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Trong	Le	Employee (full time or part time)	Bristol-Meyers Squibb
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Meyers Squibb
		Salary	Bristol-Meyers Squibb
Cecile	Le Pechoux	Speakers or Advisory Board	AstraZeneca
Ticiana	Leal	Speakers or Advisory Board	Takeda, AstraZeneca, Novartis, AbbVie, Bristol-Meyers Squibb
Alexandra	Leary	Honoraria	AstraZeneca
		Speakers or Advisory Board	AstraZeneca, Clovis, Gristone, Gamamabs
		Supported/Contracted Research/Grant	Gamamabs, Merus, Clovis, AstraZeneca, Roche, Merck, Pfizer
		Other	AstraZeneca
Shiang	Leaw	Employee (full time or part time)	BeiGene
Anthony	Lee	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Genentech
		Employee (full time or part time)	Genentech
Caleb	Lee	Employee (full time or part time)	Daiichi Sankyo
Dae Ho	Lee	Honoraria	AstraZeneca, Boehringer Ingelheim, CJ Healthcare, Eli Lilly, Merck, Mundipharma, Novartis, Ono Pharma, Pfizer, Roche, Samyang, STCube Pharmas, Ministry of Food and Drug Safety, National Evidence-based Collaborating Agency, Korea, National Cancer Control Planning Board, Takeda, Bristol-Meyers Squibb
		Other	AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, CJ Healthcare, Eli Lilly, Merck, Mundipharma, Novartis, Ono Pharma, Pfizer, Roche, Samyang, STCube Pharmas, Ministry of Food and Drug Safety, National Evidence-based Collaborating Agency, National Cancer Control Planning Board, Takeda
Jay	Lee	Other	Genentech, Roche
Jong-Seok	Lee	Other	Ono Pharma, AstraZeneca
John	Lee	Employee (full time or part time)	Nantkwest
Ki	Lee	Other	AstraZeneca, Eli Lilly, Boehringer Ingelheim, Bristol-Meyers Squibb, Merck, Pfizer
Sue	Lee	Employee (full time or part time)	Regeneron Pharma
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Regeneron Pharma
Martina	Lefterova	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Guardant Health
		Employee (full time or part time)	Guardant Health
Natasha	Leighl	Supported/Contracted Research/Grant	Novartis
		Honoraria	Merck, Bristol-Meyers Squibb
		Other	Novartis, AstraZeneca, Bristol-Meyers Squibb, Merck, Pfizer, Canadian Agency for Drugs and Technologies in Health
Hervé	Lena	Other	AstraZeneca, Roche, Merck, Bristol-Meyers Squibb, Pfizer, Novartis, Eli Lilly, Amgen
Guillaume	Lessene	Supported/Contracted Research/Grant	Servier
Joseph	Leveque	Employee (full time or part time)	Armo BioSciences
Benjamin	Levy	Speakers or Advisory Board	AstraZeneca, Celgene, Merck, Eli Lilly, Genetech, Roche, Takeda
		Supported/Contracted Research/Grant	Celgene, Boehringer Ingleheim
Conrad	Lewanski	Speakers or Advisory Board	Eli Lilly
		Honoraria	Eli Lilly
Christine	Lhomel	Employee (full time or part time)	Roche

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Ang	Li	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Meyers Squibb
		Employee (full time or part time)	Bristol-Meyers Squibb
Bob	Li	Other	Genentech, Roche, Thermo Fischer Scientific, Guardant Health
		Speakers or Advisory Board	Genentech, Guardant Health, Mersana Therapeutics
Chunjie	Li	Employee (full time or part time)	OrigiMed
Gerald	Li	Employee (full time or part time)	Foundation Medicine
Haocheng	Li	Employee (full time or part time)	Roche
Jack	Li	Employee (full time or part time)	Daiichi Sankyo
Jacky Yu-Chung	Li	Speakers Bureau	AstraZeneca, Roche, Genentech
		Supported/Contracted Research/Grant	Roche, Genentech
Jian	Li	Employee (full time or part time)	BeiGene
Jingjin	Li	Employee (full time or part time)	Regeneron Pharma
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Regeneron Pharma
Kitty	Li	Employee (full time or part time)	Guardant Health
Sherry	Li	Employee (full time or part time)	Pfizer
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
Shuanglian	Li	Employee (full time or part time)	Millennium Pharmas, Takeda, Ariad
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Ariad
Xiaodong	Li	Employee (full time or part time)	Merck
Xin	Li	Employee (full time or part time)	BeiGene
Xuemei	Li	Employee (full time or part time)	Bristol-Meyers Squibb
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Meyers Squibb
Yanxia	Li	Employee (full time or part time)	Eli Lilly
Yuping	Li	Other	Amoy Diagnostics
Chris	Liang	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Xcovery Holding Company
		Salary	Xcovery Holding Company
		Employee (full time or part time)	Xcovery Holding Company
Wei	Liao	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	EZLife Bio
Eric	Lim	Speakers Bureau	Abbott Molecular, Pfizer, Roche, Eli Lily, Boehringer Ingelheim, Ethicon
		Supported/Contracted Research/Grant	Medela, ScreenCell, Clearbridge Biomedics, Illumina, Guardant Health
John	Lim	Employee (full time or part time)	TP Therapeutics
Huamao	Lin	Other	Takeda
Jessica	Lin	Honoraria	Chugai, Boehringer Ingelheim
Wei	Lin	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche, Genentech
		Salary	Roche, Genentech
		Employee (full time or part time)	Roche, Genentech
		Other	Roche
Helena	Linardou	Other	Bristol-Meyers Squibb, Roche, Merck

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Philip	Linden	Other	Medtronic
Rolf	Linke	Employee (full time or part time)	SFJ Pharmas Group
Geoffrey	Liu	Honoraria	AstraZeneca, Novartis, Takeda, Bristol-Meyers Squibb, AbbVie, Pfizer, Merck
		Speakers Bureau	AstraZeneca
		Speakers or Advisory Board	AstraZeneca, Roche, Merck, Novartis, Takeda, Bristol-Meyers Squibb, AbbVie
Juan	Liu	Salary	Roche
		Employee (full time or part time)	Roche
		Other	Roche
Stephen	Liu	Speakers or Advisory Board	Genentech, Pfizer, Takeda, Celgene, Eli Lilly, Taiho, Bristol-Meyers Squibb, AstraZeneca, Ignyta
		Supported/Contracted Research/Grant	Genentech, Pfizer, Threshold, Clovis, Corvus, Esanex, Bayer, OncoMed, Ignyta, Merck, Lycera, AstraZeneca, Molecular Partners
		Other	Roche
Qi	Liu	Employee (full time or part time)	Zai Laboratory
Wen-Wei	Liu	Employee (full time or part time)	Roche
Giuseppe	Lo Russo	Honoraria	Ely Lilly, Bristol-Meyers Squibb, AstraZeneca
Edward	Lobenhofer	Employee (full time or part time)	Amgen
John	Longshore	Speakers Bureau	Roche, AstraZeneca, Bristol-Meyers Squibb, Merck, Genentech
		Speakers or Advisory Board	Roche, AbbVie, AstraZeneca, Bristol-Meyers Squibb, Merck, Pfizer
		Supported/Contracted Research/Grant	Roche, AstraZeneca
Billy	Loo	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	TibaRay
		Supported/Contracted Research/Grant	Varian Medical Systems, RaySearch Laboratories
Maria Pilar	Lopez-Criado	Other	Bristol
Fernando	Lopez-Rios	Supported/Contracted Research/Grant	Roche
		Speakers or Advisory Board	Roche, Life Technologies, Bristol-Meyers Squibb, AbbVie, AstraZeneca, Merck, Pfizer
		Speakers Bureau	AbbVie, AstraZeneca, Bristol-Meyers Squibb, Life Technologies, Merck, Pfizer, Roche
		Honoraria	AbbVie, AstraZeneca, Bristol-Meyers Squibb, Life Technologies, Merck, Pfizer, Roche
Jose	Lopez-Vilariño	Employee (full time or part time)	PharmaMar S.A.
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	PharmaMar S.A.
Robert	Lorence	Employee (full time or part time)	Boehringer Ingelheim
James	Lorens	Employee (full time or part time)	BerGenBio
Matthew	Lorenzi	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Janssen
		Salary	Janssen
		Employee (full time or part time)	Janssen
Gyorgy	Losonczy	Other	Roche
Alexander	Louie	Honoraria	Varian Medical Systems, AstraZeneca
Christine	Lovly	Other	Pfizer, Novartis, AstraZeneca, Genoptix, Sequenom, Ariad, Takeda, Foundation Medicine
		Speakers or Advisory Board	Cepheid, Pfizer, Takeda, Novartis, AstraZeneca
		Honoraria	Foundation Medicine, Roche

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Israel	Lowy	Employee (full time or part time)	Regeneron Pharma
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Regeneron Pharma
		Other	Regeneron Pharma
Gerard	Lozanski	Supported/Contracted Research/Grant	Genentech, Stemline Therapeutics
Shun	Lu	Supported/Contracted Research/Grant	AstraZeneca
		Speakers or Advisory Board	Eli Lilly, Hutchison MediPharma, Simcere, Bristol-Meyers Squibb, Roche, Pfizer, AstraZeneca
Zhao Hai	Lu	Employee (full time or part time)	Eli Lilly
Gregory	Lubiniecki	Employee (full time or part time)	Merck
Shuang	Luo	Employee (full time or part time)	Eli Lilly
Xueting	Lv	Employee (full time or part time)	Novartis
Gustavo	Lyons	Speakers Bureau	Johnson & Johnson
Brigette	Ma	Speakers or Advisory Board	Roche, Merck, Boerhinger Ingelheim, Novartis, Bristol-Meyers Squibb
		Honoraria	Roche, Merck, Boerhinger ingelheim, Novartis, Bristol-Meyers Squibb
		Supported/Contracted Research/Grant	Novartis
Mitchell	Machtay	Supported/Contracted Research/Grant	Eli Lilly, ImClone
Philip	Mack	Supported/Contracted Research/Grant	Boehringer Ingelheim
		Other	Guardant Health, Apton Biosystems
		Speakers or Advisory Board	AstraZeneca, Eli Lilly, Pfizer
Hebert	MacMahon	Speakers or Advisory Board	Riverain Technologies, GE Healthcare
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Hologic
		Honoraria	Konica Minolta
		Supported/Contracted Research/Grant	Philips Healthcare
		Contracted/Support Research Grant	University of Chicago
Anant	Madabhushi	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Elucid Bioimaging, Inspirata
		Supported/Contracted Research/Grant	Philips, Inspirata, PathCore
		Speakers or Advisory Board	Inspirata, AstraZeneca, Merck
		Other	Elucid Bioimaging, Inspirata, PathCore
Subha	Madhavan	Employee (full time or part time)	Perthera
Anne	Madroszyk	Speakers or Advisory Board	AstraZeneca, Boehringer Ingelheim
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb, Novartis
		Other	Roche, AstraZeneca, Boehringer Ingelheim
Narendra	Maharaj	Employee (full time or part time)	Lupin
Kathleen	Maignon	Employee (full time or part time)	Flatiron Health
Jyoti	Malhotra	Speakers or Advisory Board	AstraZeneca, Pfizer
Luigi	Manenti	Employee (full time or part time)	Novartis
Helen	Mann	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Michael	Mann	Other	Razor Genomics
Jason	Manro	Employee (full time or part time)	Eli Lilly
Aaron	Mansfield	Speakers or Advisory Board	Genentech, Bristol-Meyers Squibb, AbbVie
		Supported/Contracted Research/Grant	Novartis, NIH
		Other	Roche

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Huzhang	Mao	Employee (full time or part time)	Eli Lilly
Raji	Marati	Employee (full time or part time)	Roche
Robert	Marchesani	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Eli Lilly, Bristol-Meyers Squibb
		Employee (full time or part time)	Eli Lilly
		Other	AstraZeneca
Jack	Mardekian	Salary	Pfizer
		Employee (full time or part time)	Pfizer
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
Aleksandra	Markovets	Employee (full time or part time)	AstraZeneca
Melina	Marmarelis	Supported/Contracted Research/Grant	Novartis, Eli Lilly
Ivonne	Marondel	Employee (full time or part time)	Pfizer
Kristen	Marrone	Speakers or Advisory Board	Compugen, Takeda
Angela	Märten	Employee (full time or part time)	Boehringer Ingelheim
Jean-François	Martini	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Céline	Mascaux	Honoraria	Boehringer Ingelheim, Eli Lilly, Bristol-Meyers Squibb, Roche, AstraZeneca
		Other	Roche, Kephren, AstraZeneca, Merck
		Speakers or Advisory Board	AstraZeneca, Roche, Kephren
Kimberly	Mason	Employee (full time or part time)	Perthera
Ashiq	Masood	Speakers Bureau	Bristol-Meyers Squibb
		Other	Boston Biomedical
Clare	Massey	Employee (full time or part time)	BerGenBio
Elizabeth	Masters	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Noriyuki	Masuda	Honoraria	Ono Pharma, Merck
Christina	Matheny	Employee (full time or part time)	Genentech, Roche
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche
		Royalty, Intellectual Property/Patent Holder	Stanford
Julien	Mazieres	Other	Roche, Bristol-Meyers Squibb, Merck, AstraZeneca, Pfizer, Novartis
		Supported/Contracted Research/Grant	Roche, Genentech, AstraZeneca, Bristol-Meyers Squibb
		Speakers or Advisory Board	Novartis, Roche, Pfizer, Bristol-Meyers Squibb, Eli Lilly, Merck, AstraZeneca
Peter	Mazzone	Speakers or Advisory Board	Exact Sciences, Grail, Oncimmune
		Supported/Contracted Research/Grant	Oncocyte, Veracyte
Caroline	McCoach	Honoraria	Takeda, Guardant
Sherrol	McDonough	Employee (full time or part time)	Thermo Fisher Scientific
Joseph	McGill	Employee (full time or part time)	Daiichi Sankyo
Jessica	McLean	Employee (full time or part time)	Merck
Minesh	Mehta	Supported/Contracted Research/Grant	Novcoure, Bristol-Meyers Squibb, Pharmacyclics
Tarek	Mekhail	Speakers Bureau	AstraZeneca
Diana	Mendus	Employee (full time or part time)	Genentech
Juscilene	Menezes	Employee (full time or part time)	Thermo Fisher Scientific

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Alexander	Menzies	Speakers or Advisory Board	Merck, Bristol-Meyers Squibb, Novartis, Roche, Pierre Fabre
Ina	Menzl	Employee (full time or part time)	Roche
Catalina	Meyer	Employee (full time or part time)	Eli Lilly
Michael	Meyer	Employee (full time or part time)	VisionGate, Syndax
Matthew	Meyerson	Speakers or Advisory Board	OrigiMed
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	OrigiMed
		Supported/Contracted Research/Grant	Bayer
		Royalty, Intellectual Property/Patent Holder	LabCorp
Michael	Michael	Speakers or Advisory Board	Ipsen, Novartis
		Honoraria	Ipsen, Novartis
		Supported/Contracted Research/Grant	Ipsen
David	Micklem	Employee (full time or part time)	BerGenBio ASA
Maria Rita	Migliorino	Speakers or Advisory Board	AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb
Katherine	Mileham	Speakers Bureau	AstraZeneca
		Speakers or Advisory Board	Merck
		Supported/Contracted Research/Grant	Celgene
Kenneth	Miles	Employee (full time or part time)	Miles Medical Centre
		Supported/Contracted Research/Grant	University of Queensland
Vincent	Miller	Employee (full time or part time)	Foundation Medicine
Dawn	Millington	Employee (full time or part time)	Janssen
		Salary	Janssen
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Janssen
Alvin	Milner	Employee (full time or part time)	AstraZeneca
Erene	Mina	Employee (full time or part time)	Thermo Fisher Scientific
Koichi	Minato	Supported/Contracted Research/Grant	Taiho Pharma, Bristol-Meyers Squibb, Quintiles
Mari	Mino-Kenudson	Other	Merrimack Pharmas, H3 Biomedicine
		Honoraria	Merrimac Pharmas, H3 Biomedicine
Miguel	Miranda	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
		Employee (full time or part time)	AstraZeneca
Tara	Mitchell	Speakers or Advisory Board	Incyte, Bristol-Meyers Squibb
		Other	Merck
Upasana	Mitra	Employee (full time or part time)	Cellworks Research India Pvt
Tetsuya	Mitsudomi	Speakers or Advisory Board	Eli LIlly
		Supported/Contracted Research/Grant	Eli Lilly, Boehringer Ingelheim, AstraZeneca, Chugai, The Japan Society for the Promotion of Science
		Other	Bristol-Meyers Squibb, Ono Pharma
		Speakers Bureau	AstraZeneca, Chug, Pfizer, Boehringer Ingelheim
Drew	Moghanaki	Honoraria	Varian Medical Systems
Kosalai	Mohan	Employee (full time or part time)	Regeneron Pharma
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Regeneron Pharma

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Tony	Mok	Speakers or Advisory Board	AstraZeneca, Roche, Genentech, Pfizer, Eli Lilly, Boehringer Ingelheim, Merck, Novartis, Bristol-Meyers Squibb, Taiho, Takeda Oncology Serono, SFJ Pharma, ACEA Biosciences, Vertex Pharma, geneDecode, OncoGenex Technologies, Celgene, Ignyta, Cirina, Fishawack Facilitate, Janssen, ChiMed
		Honoraria	AstraZeneca, Roche, Genentech, Pfizer, Eli Lilly, Boehringer Ingelheim, Merck, Novartis, SFJ Pharma, ACEA Biosciences, Vertex Pharma, Bristol-Meyers Squibb, OncoGenex Pharma, Celgene, Ignyta, Fishawack Facilitate, Takeda Oncology, Janssen, Cirina, Chimed
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Sanomics, Cirina
		Other	Roche., IASLC, ASCO, ChiMed, Chinese Lung Cancer Research Foundation, Chinese Society of Clinical Oncology, Hong Kong Cancer Therapy Society
		Supported/Contracted Research/Grant	AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, SFJ Pharmas Group, Roche, Merck, Clovis Oncology, Bristol-Meyers Squibb, Taiho Pharma, Eisai
		Employee (full time or part time	The Chinese University of Hong Kong
Daniel	Moldaver	Employee (full time or part time)	Cornerstone Research Group
Cliff	Molife	Employee (full time or part time)	Eli Lilly
Arta	Monjazeb	Speakers or Advisory Board	AstraZeneca, Incyte, Dynavax
		Supported/Contracted Research/Grant	Merck, Genentech, Transgene
Isabelle	Monnet	Supported/Contracted Research/Grant	AstraZeneca
Rebecca	Moor	Other	Bristol-Meyers Squibb
Alessandro	Morabito	Honoraria	AstraZeneca, Roche, Boehringer Ingelheim, Pfizer, Merck, Bristol-Meyers Squibb
Jean-François	Morere	Honoraria	Roche
Daniel	Morgensztern	Other	Celgene Corporation, AbbVie, Bristol-Meyers Squibb
Satoshi	Morita	Honoraria	AstraZeneca, Eli Lilly
Denis	Moro-Sibilot	Speakers or Advisory Board	Roche, Eli Lilly, Sanofi, Novartis, Amgen, Pfizer, AstraZeneca, Clovis Oncology, Merck, Ariad, AbbVie, Bristol-Meyers Squibb, Boehringer Ingelheim, Takeda
Clive	Morris	Supported/Contracted Research/Grant	Inivata
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Inivata
		Employee (full time or part time)	Inviata
Don	Morris	Honoraria	Roche, AstraZeneca, Bristol-Meyers Squibb, Cellgene, Takada, Boehringer Ingelheim, Pfizer, Novartis
		Speakers or Advisory Board	Roche, AstraZeneca, Bristol-Meyers Squibb, Cellgene, Takada, Boehringer Ingelheim, Pfizer, Novartis
Eric	Morris	Employee (full time or part time)	Novartis
Stefanie	Mortimer	Employee (full time or part time)	Guardant Health
Peter	Mortimer	Other	AstraZeneca
Rebecca	Mosher	Employee (full time or part time)	Mersana Therapeutics
		Other	Novartis Pharmas, Mersana Therapeutics
Noriko	Motoi	Speakers Bureau	Bristol-Meyers Squibb
		Speakers or Advisory Board	Bristol-Meyers Squibb, Ono Pharmas, Miraca, AstraZeneca, Merck
		Honoraria	Bristol-Meyers Squibb, Ono Pharmas, AstraZeneca, Merck, Novartis, Roche, Agilent, Chugai
		Supported/Contracted Research/Grant	Roche
Nancy	Mueller	Employee (full time or part time)	MedImmune, LLC
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	MedImmune, LLC

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Tariq	Mughal	Speakers Bureau	Sanofi
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Foundation Medicine.
		Honoraria	Sanofi
		Royalty, Intellectual Property/Patent Holder	Oxford University Press
		Other	Roche
Hiroshi	Mukae	Supported/Contracted Research/Grant	Merck, Astellas, Kyorin Pharma, Shionogi, Daiichi Sankyo, Taisho Toyama Pharma, Sumitomo Dainippon Pharma, Pfizer, Boehringer Ingelheim
		Other	Taiho Pharma, Chugai Pharma, Eli Lilly, Fujifilm Pharma, Takeda Pharma, Meiji Seika Pharma, Novartis
Pratik	Multani	Employee (full time or part time)	Ignyta
Haruyasu	Murakami	Speakers Bureau	AstraZeneca
		Honoraria	AstraZeneca, Chugai Pharma, Boehringer Ingelheim
		Supported/Contracted Research/Grant	AstraZenec
Septimiu	Murgu	Other	Educational Consultant Medtronic
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Concordia, Boston Scientific, Merck
		Honoraria	Pinnacle Biologics, Olympus, Boston Scientific, Cook, Auris Robotics
		Speakers or Advisory Board	Auris Robotics, Medtronic
		Royalty, Intellectual Property/Patent Holder	Elsevier
Danielle	Murphy	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Andrea	Murray	Employee (full time or part time)	Oncimmune LLC
Faith	Mutale	Speakers Bureau	Merck, Helsinn
Andrea	Myers	Employee (full time or part time)	Novartis
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Novartis
Sten	Myrehaug	Speakers or Advisory Board	Novartis, Ipsen
		Honoraria	Novartis
		Supported/Contracted Research/Grant	Novartis
		Other	Novartis, Ipsen
Eric	Nadler	Speakers Bureau	AstraZeneca, Merck, Genentech
		Other	AstraZeneca, Merck
Adnan	Nagrial	Speakers or Advisory Board	Merck
		Supported/Contracted Research/Grant	Merck, Bristol-Meyers Squibb
		Other	Bristol-Meyers Squibb
Rebecca	Nagy	Employee (full time or part time)	Guardant Health
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Guardant Health
Jarushka	Naidoo	Supported/Contracted Research/Grant	Merck, AstraZeneca
		Other	Bristol-Meyers Squibb, Takeda, AstraZeneca
Hideyuki	Nakagawa	Speakers Bureau	Eli Lilly

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Kazuhiko	Nakagawa	Supported/Contracted Research/Grant	Ono Pharma, Merck, A2 Healthcare, inVentiv Health, Astellas Pharma, Daiichi Sankyo, Novartis Pharma, AbbVie, Quintiles, ICON Japan, Chugai Pharma, Takeda Pharma, EP-CRSU, Gritstone, Linical, Eli Lilly, Eisai, Bristol-Meyers Squibb, Nippon Boehringer Ingelheim, Taiho Pharma, Parexel, GlaxoSmithKline
		Honoraria	Ono Pharma, AstraZeneca, Nichi-Iko Pharma, Astellas Pharma, Clinical Trial, Taiho Pharma, Bristol-Meyers Squibb, Boehringer Ingelheim, Eli Lilly, Novartis, SymBio Pharma, Pfizer, Chugai Pharma, Nikkei Business Publications, Reno. Medical, Merck, Company, Kissei Pharma, Daiichi Sankyo, AYUMI Pharma Corporation
		Other	EPS Holdings, Showa Yakuhin Kako, Symbio, Kissei, Ayumi
		Speakers or Advisory Board	Astellas Pharma, Ono Pharma, Eli Lilly
Takahiro	Nakajima	Honoraria	AstraZeneca
Yukiko	Nakamura	Honoraria	Chugai Pharma
		Supported/Contracted Research/Grant	Chugai Pharma, Astellas
Yoichi	Nakanishi	Honoraria	Ono Pharma, Bristol-Meyers Squibb, Pfizer, Boehringer Ingelheim, Eli Lilly, Merck, AstraZeneca
		Supported/Contracted Research/Grant	Chugai Pharma, Ono Pharma, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Astellas Pharma, Taiho Pharma, Eli Lilly, AsahiKasei
Takashi	Nakano	Honoraria	Merck, Olympus, Ishihara Sangyo, Kyorin, Pharma, Boehringer Ingelheim, Ono Pharma
Kazuhisa	Nakashima	Honoraria	Chugai Pharma, Boehringer Ingelheim
Yuko	Nakayama	Speakers or Advisory Board	AstraZeneca
Julian	Nam	Employee (full time or part time)	Roche
Hervé	Naman	Honoraria	Roche
Tony	Nash	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Ronald	Natale	Speakers or Advisory Board	AstraZeneca
		Employee (full time or part time)	AstraZeneca
		Supported/Contracted Research/Grant	AbbVie, Bristol-Meyers Squibb, AstraZeneca, Merck, SynDeRx
Faith	Nathan	Employee (full time or part time)	Bristol-Meyers Squibb
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Meyers Squibb
Natalya	Nazarenko	Employee (full time or part time)	Ipsen BioPharmas
Joel	Neal	Other	Ariad, Takeda, AstraZeneca, Genentech, Roche, Eli Lilly
		Speakers or Advisory Board	Ariad, Takeda, AstraZeneca, Genentech, Roche, Eli Lily, Clovis
		Supported/Contracted Research/Grant	Boehringer Ingelheim, Exelixis, Genentech, Roche, Merck, Nektar Therapeutics, Novartis, Ariad, Takeda
Alan	Nelson	Employee (full time or part time)	VisionGate
Michele	Nguyen	Employee (full time or part time)	Loxo
Alan	Nicholas	Employee (full time or part time)	Genentech
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Genentech
Andrew	Nicholson	Other	Merck, Boehringer Ingelheim, Novartis, AstraZeneca, Bristol-Meyers Squibb, Roche, AbbVie
		Supported/Contracted Research/Grant	Pfizer, Roche
		Speakers or Advisory Board	Pfizer, Abbvie
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Merck
Monique	Nilsson	Royalty, Intellectual Property/Patent Holder	Spectrum Pharma

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Mizuki	Nishino	Supported/Contracted Research/Grant	Merck, Toshiba Medical Systems, AstraZeneca
		Other	Daiichi Sankyo
		Honoraria	Roche
Kazuto	Nishio	Honoraria	Boehringer Ingelheim
		Supported/Contracted Research/Grant	Boehringer Ingelheim
		Speakers or Advisory Board	Eli Lilly
Makoto	Nishio	Honoraria	Ono Pharma, Bristol-Meyers Squibb, Pfizer, Chugai Pharma, Eli Lilly, Taiho Pharma, AstraZeneca, Boehringer Ingelheim, Merck, Novartis, Daiichi Sankyo Healthcare
		Speakers or Advisory Board	Ono Pharma, Bristol-Meyers Squibb, Pfizer, Chugai Pharma, Eli Lilly, Taiho Pharma, AstraZeneca, Boehringer Ingelheim, Merck, Novartis, Sankyo Healthcare
		Supported/Contracted Research/Grant	Merck, Novartis, Ono Pharma, Chugai Pharma, Bristol-Meyers Squibb, Taiho Pharma, Eli Lilly, AstraZeneca, Pfizer, Astellas
		Other	Novartis, Daiichi Sankyo Healthcare, Taiho Pharma, Bristol-Meyers Squibb, Boehringer Ingelheim, Ono Pharma, Eli Lilly, Chugai Pharma, AstraZeneca, Merck, Pfizer, Roche
		Speakers Bureau	Ono Pharma, Bristol-Myers Squibb, Pfizer, Chugai Pharma, Eli Lilly, Taiho Pharma, AstraZeneca, Boehringer Ingelheim, Merck, Novartis
Yasuhiko	Nishioka	Honoraria	Taiho Pharma
		Supported/Contracted Research/Grant	Taiho Pharma
Naoyuki	Nogami	Speakers or Advisory Board	Eli Lilly
Hiroshi	Nokihara	Honoraria	Taiho Pharma, Chugai Pharma, Eli Lilly, AstraZeneca, Boehringer Ingelheim, Ono Pharma, Bristol-Meyers Squibb, Novartis Pharma, Merck
		Supported/Contracted Research/Grant	Novartis, Daiichi Sankyo, IQVIA Services, Astellas Pharma, AstraZeneca, Ono Pharma, Pfizer, Taiho Pharma, Chugai Pharma, Eli Lilly
Helene	Nordahl Christensen	Employee (full time or part time)	AstraZeneca
Kim	Norris	Speakers or Advisory Board	Takeda
		Other	Takeda
Kaname	Nosaki	Honoraria	AstraZeneca, Chugai Pharma, Eli Lilly, MSD, Nippon Boehringer Ingelheim, Ono Pharma, Pfizer Japan, Taiho Pharma
		Supported/Contracted Research/Grant	Merck, Novartis
Silvia	Novello	Speakers or Advisory Board	Takeda
		Speakers Bureau	Boehringer Ingelheim, AstraZeneca, Roche, Merck, Bristol-Meyers Squibb, Eli Lilly, Takeda, Pfizer
Ruslan	Novosiadly	Employee (full time or part time)	Eli Lilly
Petr	Novotny	Employee (full time or part time)	Optellum
Anna	Nowak	Speakers or Advisory Board	Bayer, AstraZeneca, Sellas Life Sciences, Trizell, Boehringer Ingelheim, Epizyme, Roche, Merck
		Other	AstraZeneca, Boehringer Ingelheim, Epizyme
		Supported/Contracted Research/Grant	AstraZeneca, Douglas Pharma
Toshihiro	Nukiwa	Speakers or Advisory Board	Asahi Kasei, Boehringer Ingelheim
Rafael	Nuñez	Employee (full time or part time)	PharmaMar
Esmond	Nwokeji	Employee (full time or part time)	Bristol-Meyers Squibb
Kenneth	O'Byrne	Honoraria	Pfizer, Roche, AstraZeneca, Boehringer-Ingelheim, Bristol-Meyers Squibb, Merck, Eli Lilly, Novartis, Teva
		Speakers Bureau	Pfizer, Roche, AstraZeneca, Boehringer-Ingelheim, Bristol-Meyers Squibb, Merck
		Royalty, Intellectual Property/Patent Holder	Queensland University of Technology
		Supported/Contracted Research/Grant	Tesaro
		Speakers or Advisory Board	Pfizer, Roche, AstraZeneca, Boehringer-Ingelheim, Bristol-Meyers Squibb, Merck, Lilly Oncology, Novartis, Teva

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Justin	Odegaard	Employee (full time or part time)	Guardant Health
Luc	Odier	Speakers or Advisory Board	Eli Lilly
		Supported/Contracted Research/Grant	Pfizer, Amgen, AstraZeneca
John	O'Donnell	Employee (full time or part time)	Bristol-Meyers-Squibb
Vance	Oertel	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Xcovery Holding Company
		Salary	Xcovery Holding Company
		Employee (full time or part time)	Xcovery Holding Company
Filiz	Oezkan	Other	Epigenomics, Genentech, Roche
		Honoraria	Novartis
		Supported/Contracted Research/Grant	Genentech, Roche
Martin	Oft	Employee (full time or part time)	Armo BioSciences
Yuichiro	Ohe	Other	AstraZeneca, Chugai Pharma, Eli Lilly, Ono Pharma, Novartis
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Ono Pharma
		Honoraria	AstraZeneca, Chugai Pharma, Lilly Japan, Ono Pharma, Bristol-Meyers Squibb Japan, Daiichi Sankyo, Nippon Kayaku, Boehringer Ingelheim, Bayer, Pfizer, Merck, Taiho Pharma, Novartis, Kyowa Hakko Kirin, Sanofi, Kyorin, Kissei
		Supported/Contracted Research/Grant	AstraZeneca, Lilly, Chugai, Taiho, Pfizer, Merck, Novartis, Kyorin, Dainippon-Sumitomo, Ignyta, Bristol-Meyers Squibb, Nipponkayaku, Japan Agency for Medical Research and Development, Ono Pharma, Kissei
		Speakers or Advisory Board	AstraZeneca, Chugai, Ono Pharma, Kissei, Kyorin
Carol	O'Hear	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche
		Salary	Genentech
		Employee (full time or part time)	Genentech
Satoshi	Oizumi	Honoraria	AstraZeneca, Eli Lilly, Ono Pharma
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb, Pfizer
Morihito	Okada	Speakers Bureau	Taiho Pharma, Johnson & Johnson, Covidien, Eli Lilly, Chugai Pharma
		Supported/Contracted Research/Grant	Taiho Pharma, Nippon Kayaku, Chugai Pharma, Covidien, Johnson & Johnson, Daiichi Sankyo, Yakult Honsha, Eli Lilly, Nihon Medi-Physics, Pfizer, Mochida Pharma, Shionogi Pharma, Ono Pharma
		Honoraria	Ono Pharma
Hiroaki	Okamoto	Supported/Contracted Research/Grant	Takeda, Ono Pharma, Astrazeneca, Merck, Chugai Pharma, Taiho Pharma, Bristol-Meyers Squibb, Eli Lilly, Daiich Sankyo
Isamu	Okamoto	Speakers Bureau	Taiho Pharma
		Honoraria	Nippon Boehringer Ingelheim
		Supported/Contracted Research/Grant	Nippon Boehringer Ingelheim, AstraZeneca, Ono Pharma, Chugai Pharma, Bristol-Meyers Squibb, Merck, Eli Lilly, Taiho Pharma, Pfizer
		Speakers or Advisory Board	Eli Lilly
Kyoichi	Okishio	Speakers Bureau	Ono Pharma, Bristol-Meyers Squibb
Carlos	Oliveira	Employee (full time or part time)	Biodesix
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Biodesix
James	Oliviero	Employee (full time or part time)	Checkpoint Therapeutics
Steven	Olsen	Employee (full time or part time)	Guardant Health

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Anthony	Olszanski	Speakers or Advisory Board	Bristol-Meyers Squibb, Merck
		Other	Takeda
Yukie	Omori	Employee (full time or part time)	Eli Lilly
Umang	Ondhia	Employee (full time or part time)	Roche
Teng Jin	Ong	Employee (full time or part time)	Celgene Corporation
Akira	Ono	Honoraria	Chugai Pharma
		Supported/Contracted Research/Grant	Chugai Pharma
Erik	Orava	Employee (full time or part time)	AstraZeneca
Peter	Ordentlich	Employee (full time or part time)	Syndax
Francisco	Orlandi	Other	AstraZeneca, Roche, Genentech, Bristol-Meyers Squibb, Merck, Eli Lilly, Pfizer
		Speakers Bureau	AstraZeneca, MedImmune
		Supported/Contracted Research/Grant	AstraZeneca, MedImmune, Amgen, Genentech, Roche, Astellas Medivation, Merck, Bristol-Meyers Squibb, Celltrion, Boehringer Ingelheim
Raymond	Osarogiagbon	Supported/Contracted Research/Grant	Association of Community Cancer Centers
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Foundation Medicine, Pfizer, Eli Lilly
		Royalty, Intellectual Property/Patent Holder	Patent
		Other	Association of Community Cancer Centers
Kenji	Otsuka	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Otsuka Holdings
Gregory	Otterson	Speakers or Advisory Board	Novartis, Takeda, Genentech, Pfizer, Amgen
		Supported/Contracted Research/Grant	Pfizer, Bristol-Meyers Squibb, Merck, Novartis, Genentech, AstraZeneca, Ignyta, Clovis
Sai-Hong	Ou	Speakers Bureau	Roche, Genentech, AstraZeneca, Takeda
		Speakers or Advisory Board	Pfizer, Roche, Genentech, Novartis, AstraZeneca, Takeda, Foundation Medicine
		Honoraria	Pfizer, Genentech, Roche, Ariad, Takeda, Novartis, AstraZeneca, Foundation Medicine
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	TP Therapeutics
		Supported/Contracted Research/Grant	Pfizer, Roche, MedImmune, AstraZeneca, Clovis Oncology, Ariad, Ignyta, Peregrine Pharma, GlaxoSmithKline, Astellas Pharma, Chugai Pharma
Qiuxiang	Ou	Employee (full time or part time)	Geneseeq Technology
Dwight	Owen	Other	L&M Policy Research
Scott	Owen	Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb, Roche, Merck
		Honoraria	AstraZeneca
		Other	Roche Canada
Sherry	Owens	Employee (full time or part time)	Incyte
Taofeek	Owonikoko	Speakers or Advisory Board	AbbVie, Bristol-Meyers Squibb, G1 Therapeutics
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb, AbbVie, United Pharma, G1 Therapeutics
Geoffrey	Oxnard	Speakers or Advisory Board	Inivata, GRAIL, DropWorks, AstraZeneca, Takeda/Ariad
		Other	Loxo, Inivata, AstraZeneca
		Royalty, Intellectual Property/Patent Holder	Co-author of patent held by DFCI describing a plasma genotyping approach
		Honoraria	Guardant, Sysmex
Randall	Oyer	Honoraria	Association of Community Cancer Centers
Masahiro	Ozaki	Employee (full time or part time)	Canon Medical Systems Corporation

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Mustafa	Özgüroğlu	Speakers or Advisory Board	Astellas
		Honoraria	Janssen
Jose	Pacheco	Speakers or Advisory Board	AstraZeneca, Novartis
		Honoraria	Ariad Pharma
		Supported/Contracted Research/Grant	Janssen, AstraZeneca and Pfizer
Sukhmani	Padda	Supported/Contracted Research/Grant	Forty-Seven, EpicentRx
		Speakers or Advisory Board	G1 therapeutics, Janssen, AstraZeneca, AbbVie
		Other	Physician Education Resource, MedScape
Damian	Page	Employee (full time or part time)	Roche, Novartis
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche, Novartis
		Other	Roche
		Salary	Roche
Venkata	Palle	Employee (full time or part time)	Lupin
Xiaoyun	Pan	Employee (full time or part time)	Takeda
Zhiying	Pan	Employee (full time or part time)	Amgen
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Amgen
Kaimin	Pang	Employee (full time or part time)	Boehringer Ingelheim
Vassiliki	Papadimitrakopoulou	Speakers or Advisory Board	Nektar Therapeutics, AstraZeneca, Arrys, Merck, Loxo, Araxes Pharma, Roche, Janssen Research Foundation, Bristol-Meyers Squibb, Clovis Oncology, Eli Lilly, Novartis, Takeda Pharma, AbbVie, TRM Oncology, Pfizer
		Supported/Contracted Research/Grant	Eli Lilly, Novartis, Merck, AstraZeneca, Roche, Nektar Therapeutics, Janssen, Bristol-Meyers Squibb, Checkmate, Incyte, Oregon Health Science, ACEA Biosciences, American Association of Cancer Research, Hope Foundation, Cancer Prevention and Research Institute of Texas, Genentech, Guardant Health
Mauro Giulio	Papotti	Speakers Bureau	Pfizer, Merck, Roche, AstraZeneca
		Speakers or Advisory Board	AbbVie
Drew	Pardoll	Other	Aduro, Compugen, GlaxoSmithKline, MedImmune, AstraZeneca, Merck, Potenza Therapeutics, Sanofi, Tizona, DNatrix, Amgen, Rock Springs Capital, Janssen, Bayer
		Speakers or Advisory Board	Immunomic Therapeutics, WindMil Therapeutics
Joseph	Park	Employee (full time or part time)	Amgen
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Amgen
Keunchil	Park	Other	Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Eli Lilly, Hanmi, Kyowa Kakko Kirin, Novartis, Ono Pharma, Roche, Bristol-Meyers Squibb, GlaxoSmithKline, Merck, GlaxoSmithKline
		Supported/Contracted Research/Grant	AstraZeneca
		Speakers or Advisory Board	AstraZeneca, Astellas, Boehringer Ingelheim, Bristol-Meyers Squibb, Clovis, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Hanmi, KHK, Merck, Novartis, Roche
Rahul	Parulkar	Employee (full time or part time)	Nantomics
Ugo	Pastorino	Royalty, Intellectual Property/Patent Holder	Gensignia Life Science
Greg	Pate	Employee (full time or part time)	Roche
Bhavin	Patel	Employee (full time or part time)	MagArray
Jyoti	Patel	Speakers or Advisory Board	AbbVie, AstraZeneca, Bristol-Meyers Squibb, Takeda, Roche
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb
		Other	Genentech

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Sabina	Patel	Other	AstraZeneca
Sandip	Patel	Speakers or Advisory Board	AstraZeneca
		Supported/Contracted Research/Grant	Xcovery Holding Company
		Other	Merck, Incyte
Melissa	Pavilack	Employee (full time or part time)	AstraZeneca
Nick	Pavlakis	Speakers or Advisory Board	Bristol-Meyers Squibb, Merck, Astra Zeneca, Roche, Novartis, Boehringer Ingelheim, Merck, Pfizer, Ipsen, Amgen
		Supported/Contracted Research/Grant	Bayer
Dean	Pavlick	Employee (full time or part time)	Foundation Medicine
Luis	Paz-Ares	Other	Novartis, Roche, Pfizer, Bristol-Meyers Squibb, Merck, Boehringer Ingelheim, AstraZeneca, Amgen, Clovis, Takeda
		Honoraria	Eli Lilly, Roche, Novartis, Bristol-Meyers Squibb, Merck, Pfizer, Amgen, Takeda, Boehringer Ingelheim, AstraZeneca, Clovis Oncology, Astillas
		Speakers or Advisory Board	Bristol-Meyers Squibb, Merck, AstraZeneca, Roche, Lilly, Merck, Pfizer, Novartis, Takeda, Incyte, Boehringer Ingelheim, Celgene
Laura	Peek	Employee (full time or part time)	Oncimmune
Tobias	Peikert	Speakers or Advisory Board	Epizyme
Nir	Peled	Honoraria	AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Eli Lilly, Merck, Novartis, Pfizer, Roche, NovellusDx, FMI, Gaurdant360
		Other	AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Eli Lilly, Merck, Novartis, Pfizer, Roche, NovellusDx, FMI, Gaurdant360
Gerson	Peltz	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Frederique	Penault-Llorca	Speakers or Advisory Board	Pfizer
John	Penrod	Employee (full time or part time)	Bristol-Meyers Squibb
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Meyers Squibb
		Salary	Bristol-Meyers Squibb
Maurice	Pérol	Honoraria	AstraZeneca
		Speakers or Advisory Board	Pfizer
Francesco	Perrone	Honoraria	Amgen, AstraZeneca, Bayer, Bristol-Meyers Squibb, Boehringer Ingelheim, Eli Lilly, Ipsen, Novartis, Pfizer, Sandoz, Tesaro AstraZeneca, Baxter, Eli Lilly, Merck, Roche
Heiko	Peschl	Salary	EIT health, National Institute for Health Research
Solange	Peters	Speakers or Advisory Board	Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Eli Lilly, Roche, Janssen, Merck, Pfizer, Regeneron, Takeda
Emanuel	Petricoin	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Perthera
See	Phan	Employee (full time or part time)	Genentech
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche
Andrew	Phillips	Employee (full time or part time)	AbbVie
Lyndsey	Pickup	Employee (full time or part time)	Optellum
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Optellum

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Rathi	Pillai	Supported/Contracted Research/Grant	Bristol-Meyers Squibb
		Speakers or Advisory Board	AstraZeneca
Zosia	Piotrowska	Other	AstraZeneca, Boehringer Ingelheim, Ariad, Novartis, Guardant Health, Takeda, AbbVie
		Speakers or Advisory Board	AstraZeneca, Ariad, Takeda, Novartis, Boehringer Ingelheim, AbbVie
		Supported/Contracted Research/Grant	Novartis
		Honoraria	Guardant Health
J	Pipas	Employee (full time or part time)	Merrimack Pharmas
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Merrimack Pharmas
Bilal	Piperdi	Employee (full time or part time)	Merck
Robert	Pirker	Speakers Bureau	Boehringer Ingelheim
		Speakers or Advisory Board	Boehringer Ingelheim, AstraZeneca, Eli Lilly
		Honoraria	Merck, Genmab and Regeneron
Yazdi	Pithavala	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Vincent	Plagnol	Employee (full time or part time)	Inivata
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Inivata
		Royalty, Intellectual Property/Patent Holder	Inivata
David	Planchard	Other	AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Merck, Novartis, Roche, Pfizer, Celgene
		Speakers or Advisory Board	AstraZeneca, Boehringer, Bristol-Meyers Squibb, Merck, Celgene, Novartis, Pfizer, Roche Celtes
		Speakers Bureau	Boehringer Ingelheim, Merck, Pfizer, Novartis, Roche, Celgene
Lukas	Plank	Supported/Contracted Research/Grant	AstraZeneca, Boehringer Ingelheim, Roche
		Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Roche
Miklos	Pless	Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb, Roche, Merck, Boehringer
Adam	Pluzanski	Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Merck, Roche
		Speakers or Advisory Board	AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Merck, Roche
Katerina	Politi	Supported/Contracted Research/Grant	AstraZeneca, Roche, Kolltan, Symphogen
		Honoraria	AstraZeneca, Merck, Novartis, Tocagen
		Royalty, Intellectual Property/Patent Holder	Molecular MD
Anna	Polli	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Rodney	Pommier	Speakers or Advisory Board	Novartis Oncology, Ipsen
		Honoraria	Novartis Oncology, Ipsen
Greg	Pond	Employee (full time or part time)	Roche Canada
Lynne	Poole	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
		Other	AstraZeneca
		Employee (full time or part time)	AstraZeneca

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Sanjay	Popat	Other	Boehringer Ingelheim, Epizyme, Bristol-Meyers Squibb, Clovis Oncology, Roche, Eli Lilly, Takeda, AstraZeneca, Novartis, Pfizer, Merck, Guardant Health, AbbVie
		Honoraria	Boehringer Ingelheim, AstraZeneca, Roche, Eli Lilly, Novartis, Takeda, Guardant Health, Bristol-Meyers Squibb, Pfizer, Chugai Pharma, Merck, Abbvie
		Supported/Contracted Research/Grant	Boehringer Ingelheim, Epizyme, Bristol-Meyers Squibb, Clovis Oncology, Roche, Eli Lilly, Takeda
		Speakers Bureau	Pfizer, AstraZeneca, Boehringer Ingelheim, Roche, Merck, Chugai
		Speakers or Advisory Board	Boehringer Ingelheim, AstraZeneca, Roche, Novartis, Pfizer, Bristol-Meyers Squibb, Merck, Guardant Health, AbbVie, Takeda, Chugai
Bryce	Portier	Employee (full time or part time)	Roche Diagnostics
Pieter E.	Postmus	Speakers or Advisory Board	Celgene, AstraZeneca, Roche, Bristol-Meyers Squibb, Boehringer Ingelheim, Janssen, Merck, Clovis
Vaclav	Potesil	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Optellum
John	Powderly	Supported/Contracted Research/Grant	Genentech, Bristol-Meyers Squibb, Curius, Corvus, Merck, Macrogenics
		Speakers Bureau	Genentech, Bristol-Meyers Squibb
		Other	Bristol-Meyers Squibb
		Royalty, Intellectual Property/Patent Holder	T cell immunotherapy development
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	BioCytics, LionBiotech, Juno, Blue Bird, Kite Pharma, ZioPharma
Courtney	Powell	Employee (full time or part time)	Roche
Masha	Poyurovsky	Employee (full time or part time)	Kadmon Corporation LLC
Chris	Presley	Employee (full time or part time)	VisionGate
Michael	Pritchett	Honoraria	Biodesix, Medtronic, AstraZeneca, Johnson & Johnson
		Speakers or Advisory Board	Biodesix, Medtronic, AstraZeneca
		Speakers Bureau	Medtronic, AstraZeneca
Claudia	Proto	Honoraria	Bristol-Meyers Squibb, Merck
Mariano	Provencio	Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb, Fabre, Merck, Pierre, Roche
		Other	Bristol-Meyers Squibb
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb
Xiangping	Qian	Employee (full time or part time)	NeuPharma
Jingxin	Qiu	Speakers or Advisory Board	Merck
Syed	Quadri	Employee (full time or part time)	AbbVie
Susan	Quinn	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Katie	Quinn	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Guardant Health
		Employee (full time or part time)	Guardant Health
Christina	Raabe	Employee (full time or part time)	Boehringer Ingelheim
Shahrooz	Rabizadeh	Employee (full time or part time)	Nanth Health
Frederick	Racke	Employee (full time or part time)	Quest Diagnostics
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Quest Diagnostics
Janna	Radtchenko	Employee (full time or part time)	Cardinal Health
Luis	Raez	Supported/Contracted Research/Grant	Bristol-Meyers Squibb, Pfizer, Roche, Genentech, Syndax, Novartis
Judith	Raimbourg	Other	Bristol-Meyers Squibb, Amgen, Leo Pharma

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Suresh	Ramalingam	Other	AbbVie, Amgen, AstraZeneca, Bristol-Meyers Squibb, Celgene, Genentech, Roche, Nektar, Takeda, Loxo, Eli Lilly, Merck, Novartis
		Speakers or Advisory Board	AbbVie, Amgen, AstraZeneca, Bristol-Meyers Squibb, Celgene, Genentech, Roche, Nektar, Takeda, Loxo, Eli Lilly, Merck, Novartis
Robert	Ramirez	Speakers or Advisory Board	AstraZeneca, Biotheranostics, Advanced Accelerator Applications, Novartis
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Advanced Accelerator Applications
		Honoraria	Merck, Genetech, AstraZeneca, Ipsen, Guardant
		Speakers Bureau	Guardant Health, Merck, AstraZeneca, Ipsen BioPharmas, Inc
Erik	Rasmussen	Employee (full time or part time)	Eli Lilly, Amgen
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Amgen
Marianne	Ratcliffe	Employee (full time or part time)	AstraZeneca
Tobias	Raum	Employee (full time or part time)	Amgen
Victoria	Raymond	Employee (full time or part time)	Guardant Health
Dan	Raz	Supported/Contracted Research/Grant	Merck
Neal	Ready	Other	Bristol-Meyers Squibb
Martin	Reck	Speakers Bureau	Roche, Eli Lilly, AstraZeneca, Bristol-Meyers Squibb, Celgene, Merck, Boehringer-Ingelheim, Novartis, Pfizer, Abbot
		Speakers or Advisory Board	Roche, Eli Lilly, AstraZeneca, Bristol-Meyers Squibb, Celgene, Merck, Boehringer Ingelheim, Novartis, Pfizer, Abbot
		Other	AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Lilly, Merck, Practa, Roche
		Honoraria	AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Celgene, Eli Lilly, Merck, Pfizer, Proacta, Novartis, Roche, Abbott
Karen	Reckamp	Other	Amgen, Ariad, Astellas Pharma, Euclises, Tesaro, Boehringer Ingelheim, Takeda
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb, Pfizer, Novartis, Ariad, Clovis Oncology, Xcovery, Gilead Sciences, Pfizer, Adaptimmune, Genentech, Roche, Boehringer Ingelheim, AbbVie
Sandeep	Reddy	Employee (full time or part time)	NantHealth
Jordi	Remon	Other	Inivata
Dennis	Revicki	Other	Takeda
Thereasa	Rich	Employee (full time or part time)	Guardant Health
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Myriad Genetics
Eduardo	Richardet	Other	Bristol-Meyers Squibb
Bill	Richardson	Employee (full time or part time)	Roche
Otis	Rickman	Other	Medtronic, Medtronic, BD, Olympus, AbbVie
		Honoraria	Veran Medical
		Supported/Contracted Research/Grant	Olympus, BD
Todd	Riehl	Employee (full time or part time)	Roche/Genentech
Gregory	Riely	Supported/Contracted Research/Grant	Novartis, Genentech Roche, Millennium, GlaxoSmithKline, Pfizer, Infinity Pharmas, Ariad
		Speakers or Advisory Board	Genetech
		Other	Ariad Pharmas, GlaxoSmithKline, Infinity Pharmas, Millennium Pharmas, Inc., Novartis Pharmas Corporation, Pfizer, Roche Laboratories, Genentech, Merck
Jonathan	Riess	Supported/Contracted Research/Grant	Merck, Boehringer Ingelheim, AstraZeneca
		Speakers or Advisory Board	Takeda, Celgene, Biodesix, AbbVie

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Petra	Rietschel	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Regeneron Pharma
		Honoraria	Regeneron Pharma
		Employee (full time or part time)	Regeneron Pharma
James	Rigas	Speakers or Advisory Board	AstraZeneca
Erika	Rijavec	Honoraria	AstraZeneca
Ed	Riley	Employee (full time or part time)	AbbVie
David	Rimm	Speakers or Advisory Board	AstraZeneca, Agendia, Agilent, Bethyl Labs, Biocept, Bristol-Meyers Squibb, Cell signaling technology, Cepheid, Merck, Optrascan, Perkin Elmer, Ultivue
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	PixelGear
		Supported/Contracted Research/Grant	Navigate, Novartis, Gilead Sciences, Perkin Elmer
Andreas	Rimner	Supported/Contracted Research/Grant	Varian Medical Systems, Boehringer Ingelheim, AstraZeneca, Pfizer
		Honoraria	Varian Medical Systms, Bristol-Meyers Squibb, AstraZeneca, Pfizer, Merck
		Speakers or Advisory Board	AstraZeneca, Merck
Naiyer	Rizvi	Honoraria	Roche, AstraZeneca, Novartis, Merck, Pfizer, Lilly, Bristol-Meyers Squibb
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Gritsone Oncology, Armo Biosciences
		Speakers or Advisory Board	Merck, AstraZeneca, Roche, Bristol-Meyers Squibb, Novartis, Pfizer, Eli Lilly, AbbVie, Regeneron
		Other	Merck, AstraZeneca, Roche, Bristol-Meyers Squibb, Novartis, Pfizer, Eli Lilly, AbbVie, Regeneron
Michael	Roach	Supported/Contracted Research/Grant	Varian
Kate	Roberts	Other	Roche
Laurie	Roberts	Employee (full time or part time)	Evidera
Jacqulyne	Robichaux	Royalty, Intellectual Property/Patent Holder	Spectrum Pharma
Cliff	Robinson	Speakers Bureau	Varian Medical Systems
		Speakers or Advisory Board	Radiologica
Andrew	Robinson	Speakers or Advisory Board	Merck, Kirkland
		Other	Merck, Kirkland,
Gaetano	Rocco	Speakers Bureau	Baxter, Medtronic
Heinrich	Roder	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Biodesix
		Employee (full time or part time)	Biodesix
Joanna	Roder	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Biodesix
		Employee (full time or part time)	Biodesix
Brent	Roeck	Employee (full time or part time)	Spectrum Pharma
Julia	Roeper	Honoraria	Roche, Boehringer Ingelheim
Kimberly	Rohan	Speakers Bureau	Merck, Genentech, AstraZeneca
		Speakers or Advisory Board	AstraZeneca
Simon	Roitt	Supported/Contracted Research/Grant	Inivata
		Employee (full time or part time)	Inivata
Lee	Rosen	Supported/Contracted Research/Grant	Regeneron Pharma
Nitzan	Rosenfeld	Employee (full time or part time)	Inivata
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Inivata

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Mark	Rosenzweig	Employee (full time or part time)	Foundation Medicine
Jeffrey	Ross	Employee (full time or part time)	Foundation Medicine
Kenneth	Roth	Employee (full time or part time)	Eli Lilly
S	Rothenberg	Employee (full time or part time)	Loxo
Jeffrey	Rothenstein	Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb, Merck, Pfizer, Roche
Sacha	Rothschild	Supported/Contracted Research/Grant	AstraZeneca, Bristol-Meyers Squibb, Merck
		Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb, Merck, Novartis, Pfizer, Roche
Julia	Rotow	Other	Revolution Medicines
Etienne	Rouleau	Salary	Lundbeck
		Honoraria	AstraZeneca, Roche, Bristol-Meyers Squibb
		Speakers Bureau	AstraZeneca
		Supported/Contracted Research/Grant	AstraZeneca
		Other	AstraZeneca, Roche
John	Ruckdeschel	Employee (full time or part time)	EMX International
		Other	ProLung
Charles	Rudin	Speakers or Advisory Board	AbbVie, Amgen, AstraZeneca, Bristol-Meyers Squibb, Genentech, Harpoon, Genetics
		Other	Bristol-Meyers Squibb, AbbVie, Seattle Genetics, Harpoon Therapeutics, Genentech Roche, AstraZeneca
Mary	Ruisi	Employee (full time or part time)	Merck
Valerie	Rusch	Other	Da Vinci Surgery, Bristol-Meyers Squibb
		Supported/Contracted Research/Grant	Genelux
Kris	Sachsenmeier	Other	AstraZeneca
Matilde	Saggese	Employee (full time or part time)	AstraZeneca
Nobuhiko	Saijo	Speakers Bureau	Ono Pharma, Bristol-Myers Squibb, AstraZeneca, Merck
Pierre	Saintigny	Supported/Contracted Research/Grant	AstraZeneca, Roche, Novartis
		Speakers or Advisory Board	HTG
Tomohito	Saito	Supported/Contracted Research/Grant	Ono Pharma, Bristol-Myers Squibb
		Other	Ono Pharma
Gabriella	Salvatore	Employee (full time or part time)	Millennium Pharma, Cambridge, MA, Takeda
Ayman	Samkari	Employee (full time or part time)	Merck
Rachel	Sanborn	Speakers or Advisory Board	Genetics, AstraZeneca, Celldex, AbbVie, Takeda
		Honoraria	AstraZeneca
		Supported/Contracted Research/Grant	Merck, Bristol-Meyers Squibb, Medimmune
Alan	Sandler	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche, Genentech
		Salary	Roche, Genentech
		Employee (full time or part time)	Roche, Genentech
		Other	Roche
Mansee	Sangani	Employee (full time or part time)	Novartis
Randeep	Sangha	Honoraria	Pfizer, Boehringer Ingelheim, AstraZeneca, Roche, Genentech, Lundbeck, Bristol-Meyers Squibb, Merck, AbbVie, Takeda
		Speakers or Advisory Board	Boehringer Ingelheim, AstraZeneca, Roche, Genentech, Lundbeck, Eli Lilly, Bristol-Meyers Squibb, Merck, Novartis, AbbVie, Takeda
		Other	Bristol-Meyers Squibb
Serap	Sankoh	Employee (full time or part time)	Syndax

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Ademi	Santiago-Walker	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Johnson & Johnson
		Employee (full time or part time)	Johnson & Johnson
Sergio	Santillana	Employee (full time or part time)	Merrimack Pharma
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Merrimack Pharma
Antonio	Santo	Speakers or Advisory Board	Merck
Catarina	Santos	Employee (full time or part time)	Optellum
Edgardo	Santos	Speakers Bureau	Genentech, Pfizer, Novartis, Amgen, Takeda, Boehringer Ingelheim, Celgene, Merck, AstraZeneca
Orestes	Santos Morales	Employee (full time or part time)	Center of Molecular Immunology
Indrani	Sarkar	Employee (full time or part time)	Genentech
Andreas	Sashegyi	Employee (full time or part time)	Eli Lilly
Masafumi	Sata	Speakers or Advisory Board	Ono Pharma, AstraZeneca
Miyako	Satouchi	Honoraria	Chugai, Eli Lilly, AstraZeneca, Pfizer, Taiho, Boehringer Ingelheim, Ono Pharma, Bristol-Myers Squibb, Merck, Novartis
		Supported/Contracted Research/Grant	Chugai, Eli Lilly Japan, Merck, AstraZeneca, Pfizer, Bristol-Myers Squibb, Ono, Novartis, Astellas
Laura	Saunders	Employee (full time or part time)	AbbVie
Mark	Sausen	Employee (full time or part time)	Personal Genome Diagnostics
Eric	Sbar	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Giorgio	Scagliotti	Honoraria	AstraZeneca, Roche, Pfizer, Merck, Eli Lilly, AbbVie, Novartis, Clovis
		Speakers or Advisory Board	Eli Lilly, Merck
		Speakers Bureau	Eli Lilly, Merck
		Other	Bayer
David	Schaer	Employee (full time or part time)	Eli Lilly
Jürgen	Scheele	Employee (full time or part time)	Merck
Devin	Schellenberg	Speakers or Advisory Board	AstraZeneca
		Honoraria	Pfizer
		Supported/Contracted Research/Grant	Varian Medical Systems
Erin	Schenk	Other	Elsevier
Michael	Schenker	Supported/Contracted Research/Grant	Amgen, Bristol-Meyers Squibb, Roche, Novartis, Merck, Bayer, Eli Lilly, Pfizer, AbbVie, CMed, Astellas, Nektar, AstraZeneca, Boehringer Ingelheim, Mylan, Bioven, Pharma Mar, Eisai, Daichii Sankyo
Arnaud	Scherpereel	Speakers or Advisory Board	Bristol-Meyers Squibb, Merck, Boehringer Ingelheim, AstraZeneca, Roche
		Other	Bristol-Meyers Squibb, Merck, Boehringer Ingelheim, AstraZeneca, Eli Lilly, Epizyme, Bayer, Roche
Joan	Schiller	Speakers or Advisory Board	AstraZeneca, Roche, Merck
		Supported/Contracted Research/Grant	Merck, Genetech, Bristol-Meyers Squibb, Xcovery
		Other	Lung Cancer Research Foundation
Peter	Schmid	Employee (full time or part time)	Roche
		Honoraria	AstraZeneca, Bayer, Boehringer Ingelheim, Celgene, Eisai, Novartis, Pfizer, Puma, Roche, Genentech
		Supported/Contracted Research/Grant	Astellas, AstraZeneca, Medivation, Novartis, Oncogenex, Roche, Genentech

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Emmett	Schmidt	Employee (full time or part time)	Merck
		Salary	Merck
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Merck
Roland	Schott	Speakers or Advisory Board	Roche
Alexa	Schrock	Employee (full time or part time)	Foundation Medicine
Jody	Schulz	Employee (full time or part time)	Thermo Fisher Scientific
Katja	Schulze	Employee (full time or part time)	Genentech
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche, Genentech
Ed	Schuuring	Speakers or Advisory Board	AstraZeneca, Roche, Pfizer, Novartis, Bristol-Meyers Squibb, Amgen, BioCartis, Abbot, Bio-rad, Illumina
		Supported/Contracted Research/Grant	Pfizer, Biocartis, Bristol-Meyers Squibb, Roche, Boehringer Ingelheim
Lee	Schwartzberg	Speakers or Advisory Board	Bristol-Myers Squibb, Merck
		Honoraria	Eisai, Helsinn, Tesaro
		Supported/Contracted Research/Grant	Tesaro
Joerg	Schwock	Honoraria	Merck, Olympus
Andrew	Scott	Supported/Contracted Research/Grant	AbbVie
		Speakers or Advisory Board	Life Science Pharma
		Royalty, Intellectual Property/Patent Holder	mAb806
Jeffrey	Scott	Employee (full time or part time)	IntegraConnect
Marietta	Scott	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Vieri	Scotti	Speakers or Advisory Board	Boehringer Ingelheim
Eva	Segelov	Honoraria	Ipsen
Tanguy	Seiwert	Honoraria	Merck, Bristol-Meyers Squibb, AstraZeneca, Innate Pharma
Nobuhiko	Seki	Speakers Bureau	Eli Lilly, AstraZeneca, Chugai Pharma, Boehringer Ingelheim, Taiho Pharma, Daiichi Sankyo, Ono Pharma, Bristol-Myers Squibb, Merck
		Speakers or Advisory Board	Eli Lilly
Giovanni	Selvaggi	Employee (full time or part time)	Bristol-Myers Squibb
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Myers Squibb
		Salary	Bristol-Myers Squibb
Suresh	Senan	Speakers or Advisory Board	AstraZeneca, Eli Lilly, Merck
		Employee (full time or part time)	VU University Medical Center
		Honoraria	Eli Lilly
		Supported/Contracted Research/Grant	Varian Medical Systems, ViewRay
Lecia	Sequist	Speakers or Advisory Board	AstraZeneca, Genentech, Pfizer, Bristol-Meyers Squibb, Merrimack Pharma, Blueprint Medicines
		Other	Merrimack, Novartis, Boehringer Ingelheim
		Supported/Contracted Research/Grant	AstraZeneca, Novartis, Genentech, Boehringer Ingelheim, Merck, Merrimack, Guardant Health
Takashi	Seto	Honoraria	Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Chugai Pharma, Eli Lilly, Merck, Nippon Boehringer Ingelheim, Ono Pharma, Pfizer, Taiho Pharma, Takeda
		Supported/Contracted Research/Grant	AstraZeneca, Bayer, Chugai Pharma, Daiichi Sankyo, Eli Lilly, Kissei Pharma, Merck, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
David	Shames	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche, Genentech
		Salary	Roche, Genentech
		Employee (full time or part time)	Roche, Genentech
		Royalty, Intellectual Property/Patent Holder	UT Southwestern, Genentech
		Other	Roche
Geetha	Shankar	Employee (full time or part time)	Genentech, Roche
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche
Yang W.	Shao	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Geneseeq Technology
		Employee (full time or part time)	Geneseeq Technology
Geoffrey	Shapiro	Speakers or Advisory Board	Pfizer, Eli Lilly, Vertex Pharma, Roche, G1 Therapeutics
		Supported/Contracted Research/Grant	Pfizer, Eli Lilly
Sharad	Sharma	Employee (full time or part time)	Lupin
Alan	Sharpe	Employee (full time or part time)	AstraZeneca
Alice	Shaw	Speakers or Advisory Board	Pfizer, Novartis, Genentech, Roche, Ariad, Takeda, Ignyta, Blueprint Medicines, Loxo, Daiichi Sankyo, Merck, Taiho Pharma, KSQ Therapeutics, Natera
		Honoraria	Pfizer, Novartis, Roche, Genentech, Foundation Medicine, Takeda
		Supported/Contracted Research/Grant	Pfizer, Novartis, Roche, Genentech
Jay	Shaw	Employee (full time or part time)	Thermo Fisher Scientific
Pamela	Shaw	Employee (full time or part time)	Mesana Therapeutics
Jenny	Sheng	Employee (full time or part time)	Pfizer
Frances	Shepherd	Honoraria	Bristol-Myers Squibb, Eli Lilly, AstraZeneca, Roche, Genentech, Merck, Novartis, Pfizer
		Other	Bristol-Myers Squibb, Eli Lilly, Pfizer, AstraZeneca, MedImmune, Roche, Merrimack
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Eli Lilly, AstraZeneca
		Speakers or Advisory Board	Eli Lilly, AstraZeneca, Merck
Ashwini	Shewade	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche
		Salary	Genentech
		Employee (full time or part time)	Genentech
		Other	Roche
Weiwei	Shi	Employee (full time or part time)	OrigiMed
Ryota	Shiga	Employee (full time or part time)	Daiichi Sankyo
Jin-Yuan	Shih	Honoraria	AstraZeneca, Roche, Boehringer Ingelheim, Eli Lilly, Pfizer, Novartis, Merck, Ono Pharma, Bristol-Myers Squibb
Michelle	Shiller	Speakers Bureau	AstraZeneca, Merck
		Speakers or Advisory Board	AbbVie, Agendia, AstraZeneca, Genomic Health, Merck
		Honoraria	AbbVie, Agendia, AstraZeneca, Genomic Health, Merck, Molecular Match
Shani	Shilo	Honoraria	Novartis, Takeda
		Speakers or Advisory Board	Novartis, Takeda
		Other	Bristol-Myers Squibb
Nicole	Shipitofsky	Employee (full time or part time)	Daiichi Sankyo

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Lu	Shun	Speakers Bureau	AstraZeneca, Eli Lilly, Roche, Pfizer
		Speakers or Advisory Board	AstraZeneca, Hutchison MediPharma, Simcere, Bristol-Myers Squibb, Roche, Pfizer
		Supported/Contracted Research/Grant	AstraZeneca
Yu	Shyr	Speakers or Advisory Board	Roche
Salvatore	Siena	Speakers or Advisory Board	Roche, Amgen, Ignyta, Bayer, Novartis, Merck
Diego	Signorelli	Honoraria	AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb
Alan	Sihoe	Supported/Contracted Research/Grant	Medela
John	Simmons	Employee (full time or part time)	Personal Genome Diagnostics
George	Simon	Speakers or Advisory Board	Takeda
		Supported/Contracted Research/Grant	Merck
Hélène	Simon	Honoraria	Roche
Brian	Simpson	Employee (full time or part time)	Tracon Pharma
Jasmeet	Singh	Employee (full time or part time)	Daiichi Sankyo
Neeraj	Singh	Employee (full time or part time)	Cellworks Research
Simron	Singh	Honoraria	Ipsen, Novartis, Pfizer
		Other	Ipsen, Novartis
		Supported/Contracted Research/Grant	Novartis, Merck
Sumeet	Singh	Other	Roche Canada
Veena	Singh	Other	Biocept
		Employee (full time or part time)	Biocept
Shankar	Siva	Speakers Bureau	Varian, Astellas, Bristol-Meyers Squibb
		Speakers or Advisory Board	Janssen, Astellas
		Supported/Contracted Research/Grant	Varian, Merck
		Other	Bristol-Meyers Squibb, AstraZeneca
Stan	Skrzypczak	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Guardant Health
		Employee (full time or part time)	Guardant Health
Tania	Small	Employee (full time or part time)	Novartis
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Novartis
		Supported/Contracted Research/Grant	Novartis
		Other	Novartis
Marie-Anne	Smit	Employee (full time or part time)	Amgen
Derek	Smith	Employee (full time or part time)	Roche
Steve	Smith	Employee (full time or part time)	Loxo
Michael	Snee	Supported/Contracted Research/Grant	IQVIA
Jeremy	Snider	Employee (full time or part time)	Flatiron Health
Stephanie	Snow	Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb, Eli Lilly, Merck, Novartis, Roche
Mark	Socinski	Supported/Contracted Research/Grant	Genentech, Pfizer, Spectrum, Bristol-Meyers Squibb
		Speakers Bureau	Genentech, Bristol-Meyers Squibb, AstraZeneca
Benjamin	Solomon	Speakers or Advisory Board	AstraZeneca, Bristol-Myers Squibb, Merck, Pfizer, Roche, Genentech, Novartis
		Honoraria	Bristol-Myers Squibb, AstraZeneca
		Supported/Contracted Research/Grant	Pfizer
		Royalty, Intellectual Property/Patent Holder	Veristrat
		Other	AstraZeneca, Roche, Merck, Bristol-Myers Squibb, Novartis

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Qingtao	Song	Employee (full time or part time)	Amoy Diagnostics
Andreas	Sonyi	Employee (full time or part time)	Eli Lilly
Ross	Soo	Supported/Contracted Research/Grant	AstraZeneca
		Honoraria	AstraZeneca, Bristol-Meyers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Celgene, Ignyta, Roche, Taiho
Will	Sopwith	Supported/Contracted Research/Grant	IQVIA
Jean-Charles	Soria	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
		Honoraria	AstraZeneca, Bristol-Meyers Squibb, Pfizer, Roche, Sanofi, Pierre Fabre
		Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb, Pfizer, Roche, Sanofi, Pierre Fabre
Arturo	Soto-Matos	Employee (full time or part time)	PharmaMar
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	PharmaMar
Pierre Jean	Souquet	Other	Roche
		Speakers or Advisory Board	Roche, Eli Lilly, Pfizer, Boehringer Ingelheim, AstraZeneca, Novartis
		Honoraria	Bristol-Myers Squibb, Takeda
		Supported/Contracted Research/Grant	AstraZeneca, Novartis, Boehringer Ingelheim
Lior	Soussan Gutman	Employee (full time or part time)	Oncotest Teva Pharmas
Jessica	Spahn	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Genentech, Roche
		Salary	Genentech
		Employee (full time or part time)	Genentech
ErnstJan	Speel	Honoraria	Pfizer
Jonathan	Spicer	Other	Bristol-Myers Squibb
		Speakers or Advisory Board	Bristol-Myers Squibb, AstraZeneca
		Honoraria	AstraZeneca
James	Spicer	Supported/Contracted Research/Grant	Bristol-Meyers Squibb
Alexander	Spiers	Honoraria	Medtronic
David	Spigel	Other	Genentech, Roche, Celgene, Bristol-Myers Squibb, Eli Lilly, AstraZeneca, Pfizer, Clovis Oncology, Novartis, Boehringer Ingelheim
		Supported/Contracted Research/Grant	Genentech, Roche, Novartis, Celgene, Bristol- Myers Squibb, Eli Lilly, AstraZeneca, Pfizer, Clovis Oncology, Boehringer Ingelheim, Peregrine Pharma, Oncogenex, OncoMed, Amgen, Verastem, Daiichi Sankyo, University of Texas Southwestern Medical Center-Simmons Cancer Center, Merck
Alexander	Spira	Other	AbbVie, AstraZeneca, Bristol Myers, Eli Lilly, Takeda, Ariad, Clovis Oncology, Roche
		Supported/Contracted Research/Grant	Genentech, Merck, AstraZeneca
Virote	Sriuranpong	Supported/Contracted Research/Grant	Boehringer Ingelheim
Rolf	Stahel	Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Roche
		Speakers or Advisory Board	AbbVie, AstraZeneca, Bristol-Meyers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Pfizer, Roche
Elizabeth	Stankevich	Employee (full time or part time)	Regeneron Pharma
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Regeneron Pharma, Celgene, Bristol-Myers Squibb, Merck
Victoria	Stefaniak	Employee (full time or part time)	Eli Lilly

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David	Stewart	Supported/Contracted Research/Grant	Celgene, Boehringer Ingelheim, AstraZeneca, Novartis, Bristol-Myers Squibb
		Speakers or Advisory Board	Roche
		Other	Boehringer Ingelheim
Brendon	Stiles	Employee (full time or part time)	Pfizer, Pharmaceutical Product Development
		Speakers or Advisory Board	Merck, AstraZeneca, Lung Cancer Research Foundation
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer, Pharmaceutical Product Development
		Other	Lung Cancer Research Foundation
Thomas	Stinchcombe	Speakers or Advisory Board	Genentech, AstraZeneca, Novartis, Takeda
Martin	Stockler	Supported/Contracted Research/Grant	AbbVie, Amgen, AstraZeneca, Bayer, Bristol-Meyers Squibb, Celgene, Merck, Pfizer, Roche
Shanna	Stopatschinskaja	Employee (full time or part time)	TP Therapeutics
Jonathan	Strosberg	Speakers or Advisory Board	Novartis, Advanced Accelerator Applications
		Honoraria	Ipsen, Lexicon
Deepa	Subramaniam	Speakers Bureau	AstraZeneca
		Speakers or Advisory Board	Bristol-Meyers Squibb
Janakiraman	Subramanian	Other	Alexion, Biocept, Paradigm, AstraZeneca, Pfizer
		Speakers Bureau	AstraZeneca, Boehringer Ingelheim, Eli Lilly
		Supported/Contracted Research/Grant	Biocept, Paradigm
		Speakers or Advisory Board	AstraZeneca, Pfizer
Sucha	Sudarsanam	Salary	NeoGenomics, Laboratories
Shunichi	Sugawara	Honoraria	AstraZeneca, Chugai Pharma, Nippon Boehringer Ingelheim, Taiho Pharma, Pfizer, Eli Lilly, Novartis, Kyowa Hakko Kirin, Bristol-Myers Squibb, Ono Pharma, Merck
		Speakers Bureau	Eli Lilly
Masahiro	Sugihara	Employee (full time or part time)	Daiichi Sankyo
Shawn	Sun	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche
		Salary	Roche
		Employee (full time or part time)	Roche
Daniel	Sussman	Employee (full time or part time)	VisionGate
Kazumi	Suzukawa	Employee (full time or part time)	Eli Lilly
Aurélie	Swalduz	Supported/Contracted Research/Grant	Pfizer, Boehringer Ingelheim
		Speakers or Advisory Board	Roche
Zsuzsanna	Szalai	Speakers or Advisory Board	Boehringer Ingelheim, Bristol-Myers Squibb, Roche, Pfizer, AstraZeneca, Chiesi, Merck
Aleksandra	Szczesna	Other	Roche
Christopher	Szeto	Employee (full time or part time)	Nantomics
Eric	Sztejman	Other	Medtronic
Maria	Taboada	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Motoko	Tachihara	Honoraria	Eli Lilly
Hisashi	Tachizaki	Employee (full time or part time)	Canon Medical Systems Corporation
Kosei	Tajima	Employee (full time or part time)	Genentech
Kazuhisa	Takahashi	Speakers Bureau	AstraZeneca, Eli Lilly
		Supported/Contracted Research/Grant	AstraZeneca, Eli Lilly
Shunji	Takahashi	Supported/Contracted Research/Grant	Daiichi Sankyo
		Honoraria	Daiichi Sankyo

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Toshiaki	Takahashi	Supported/Contracted Research/Grant	Eli Lilly, Merck, Ono Pharma, AstraZeneca, Chugai Pharma
		Speakers Bureau	Eli Lilly Japan, Ono Pharma, Roche Diagnostics, Novartis Pharma
		Speakers or Advisory Board	Merck, AstraZeneca, Chugai Pharma, Eli Lilly
		Honoraria	AstraZeneca, Chugai Pharma, Eli Lilly, Boehringer Ingelheim, Ono Pharma, Pfizer Japan
Yuichiro	Takeda	Supported/Contracted Research/Grant	Ono Pharma
Mitsuhiro	Takenoyama	Honoraria	AstraZeneca, Bristol-Myers Squibb, Chugai Pharma, Covidien Japan, Eli Lilly, Kyowa Hakko Kirin, Merck, Boehringer Ingelheim, Ono Pharma, Taiho Pharma
		Supported/Contracted Research/Grant	AstraZeneca, Bristol-Myers Squibb, Chugai Pharma, Eli Lilly, Kyowa Hakko Kirin, Ono Pharma
Denis	Talbot	Honoraria	Pierre Fabre, Eli Lilly, Pfizer, Novartis, AstraZeneca, Celgene, Boehringer Ingelheim, Bristol-Meyers Squibb, Roche
		Other	Novartis, Merck, Ipsen, Eli Lilly, Roche
Akihiro	Tamiya	Supported/Contracted Research/Grant	Ono Pharma, Bristol-Myers Squibb
		Speakers Bureau	Ono Pharma, Bristol-Myers Squibb, Chugai Pharma, AstraZeneca, Eli Lilly, Boehringer Ingelheim
		Honoraria	Chugai Pharma, AstraZeneca, Bristol-Myers Squibb, Eli Lilly Pharma, Ono Pharma
Bo	Tan	Employee (full time or part time)	Eli Lilly
Daniel	Tan	Honoraria	National Cancer Centre Singapore, Pfizer, Merck, AstraZeneca, Loxo, Boehringer Ingelheim, Bristol-Meyers Squibb
		Speakers or Advisory Board	AstraZeneca, Pfizer, Novartis, Merck
		Supported/Contracted Research/Grant	GSK, AstraZeneca, Novartis
Fenlai	Tan	Employee (full time or part time)	Bettapharma Pharma
Seng Chuen	Tan	Employee (full time or part time)	Merck
Hiroshi	Tanaka	Speakers or Advisory Board	AstraZeneca, Chugai pharma, Merck
		Speakers Bureau	Eli Lilly, Ono Pharma, Pfizer, Novartis, T Hiho Pharma, Bristol-Myers Squibb
		Supported/Contracted Research/Grant	Astellas, Merck
Fumihiro	Tanaka	Speakers Bureau	Chugai Pharma
		Supported/Contracted Research/Grant	Chugai Pharma
Yoshihiko	Taniguchi	Supported/Contracted Research/Grant	Ono Pharma, Bristol-Myers Squibb
		Speakers Bureau	Chugai Pharma, Merck
Aiyang	Tao	Employee (full time or part time)	Novartis
Ahmad	Tarhini	Other	Merck, Incyte
		Speakers or Advisory Board	Merck, Incyte
Janis	Taube	Speakers or Advisory Board	Amgen, AstraZeneca, Merck
Mahesh	Tawney	Employee (full time or part time)	Eli Lilly
Fiona	Taylor	Employee (full time or part time)	Adelphi Values
		Other	Bristol-Myers Squibb
Paul	Taylor	Other	Bristol-Myers Squibb, Pierre Fabre
Mustapha	Tehfe	Speakers or Advisory Board	Celgene, Eli Lilly, Pfizer, Ipsen, Merck, Taiho Pharma, AstraZeneca, Bristol-Myers Squibb
		Speakers Bureau	Celgene
Ricardo	Terra	Speakers or Advisory Board	Johnson & Johnson, Medtronic, H.Strattner, Intuitive
		Speakers Bureau	AstraZeneca, Boehringer, Merck, Medtronic, H.Strattner
		Supported/Contracted Research/Grant	Johnson & Johnson
Nick	Thatcher	Speakers or Advisory Board	Eli Lilly, Boehringer Ingelheim, Otsuka, Roche
		Supported/Contracted Research/Grant	Amgen

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Alia	Thawer	Other	Novartis
		Honoraria	Pfizer
		Supported/Contracted Research/Grant	Ipsen, Pfizer
Charles	Theuer	Employee (full time or part time)	Tracon Pharma
Michael	Thomas	Other	Novartis, Eli Lilly, Pfizer, Bristol-Meyers Squibb, Roche, AstraZeneca, Boehringer Ingelheim, Merck
		Speakers or Advisory Board	Merck, Bristol-Meyers Squibb, Eli Lilly, Novartis, Roche, Celgene, AstraZeneca
Matthew	Thompson	Supported/Contracted Research/Grant	IQVIA
Erik	Thunnissen	Speakers or Advisory Board	Pfizer, Bristol-Meyers Squibb, Merck
		Other	Diaceutics
		Supported/Contracted Research/Grant	Pfizer
		Honoraria	Oncologia, Histogenix, AstraZeneca, Ventana
Holger	Thurm	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Markus	Tiemann	Speakers or Advisory Board	Novartis, Boehringer Ingelheim, AstraZeneca, Roche
Robert	Timmerman	Supported/Contracted Research/Grant	Varian Medical Systems, Accuray, Elekta Oncology
Marcello	Tiseo	Other	AstraZeneca, Bristol-Meyers Squibb, Boehringer Ingelheim, Eli Lilly, Novartis, Otsuka, Pierre Fabre, Merck, Pfizer, Roche
Alexander	Todd	Employee (full time or part time)	AstraZeneca
Kanae	Togo	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Dianne	Tomita	Employee (full time or part time)	Amgen
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Amgen
Betty	Tong	Speakers or Advisory Board	Medtronic
Xiaoling	Tong	Employee (full time or part time)	Geneseeq Technology
Aracelis	Torres	Employee (full time or part time)	Flatiron Health
Shinichi	Toyooka	Honoraria	AstraZeneca, Chugai Pharma, Daiichi Sankyo, Astellas Pharma, Boehringer Ingelheim, Taiho Pharma, Ono Pharma, Bayer, Medtronic, Johnson & Johnson, Kyorin
		Supported/Contracted Research/Grant	Taiho Pharma
Ryo	Toyozawa	Speakers Bureau	Kyowa Hakko Kirin, Ono Pharma, AstraZeneca, Eli Lilly, Merck, Chugai Pharma, Nippon Boehringer Ingelheim
		Honoraria	AstraZeneca, Chugai Pharma, Eli Lilly, Kyowa Hakko Kirin, Merck, Nippon Boehringer Ingelheim, Ono Pharma
Diana	Tran	Employee (full time or part time)	Cornerstone Research Group
Spyros	Triantos	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Janssen
		Salary	Janssen
		Employee (full time or part time)	Janssen

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Anne	Tsao	Speakers or Advisory Board	Bristol-Meyers Squibb, Eli Lilly, Genentech, Roche, Novartis, Ariad, Merck, Seattle Genetics, Astra-Zeneca, Boehringer Ingelheim, Sellas Life Science, Takeda, Polaris, Astellas Pharma, Imedex
		Supported/Contracted Research/Grant	Eli Lilly, Millennium, Polaris, Genentech, Merck, Boehringer Ingelheim, Bristol-Meyers Squibb, Ariad, Epizyme, Genetics
		Other	Bristol-Meyers Squibb, Eli Lilly, Genentech, Roche, Novartis, Ariad, Merck, Seattle Genetics, AstraZeneca, Boehringer Ingelheim, Sellas Life Sciences, MedImmune
		Honoraria	Bristol-Meyers Squibb, Astra-Zeneca, Novartis, Boehringer Ingelheim, Genentech, Roche, Takeda, Ariad, Eli Lilly
		Royalty, Intellectual Property/Patent Holder	John Wiley
Ming	Tsao	Honoraria	Merck, AstraZeneca, Bristol-Myers Squibb, Pfizer, Roche, Ventana
		Supported/Contracted Research/Grant	Merck, Pfizer, Roche, Ventana, AstraZeneca
		Speakers or Advisory Board	AstraZeneca, Pfizer, Merck, Roche, Ventana, Bristol-Myers Squibb, AbbVie, Celgene
Masahiro	Tsuboi	Speakers or Advisory Board	Merck, AstraZeneca
		Honoraria	AstraZeneca KK, Eli Lilly, Boehringer Ingelheim, Daikichi-Sankyo, Chudai Pharma, Taiho Pharma, Teijin Pharma, Johnson & Johnson
Koji	Tsuta	Supported/Contracted Research/Grant	Ono Pharma
Michael	Tu	Other	Roche, AstraZeneca
Brian	Tuch	Employee (full time or part time)	Loxo
Ken	Tuell	Employee (full time or part time)	Bristol-Myers Squibb
Tal	Twito	Employee (full time or part time)	Oncotest Teva Pharmas
Dusty	Tyree	Employee (full time or part time)	Roche
Luis	Ubillos	Speakers Bureau	Roche, Tecnofarma
		Speakers or Advisory Board	Roche, Tecnofarma, Servier, Bayer
Hibiki	Udagawa	Honoraria	Chugai
Yoshiko	Urata	Supported/Contracted Research/Grant	Chugai
		Honoraria	Taiho, Novartis
Tiziana	Usari	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Joshua	Usher	Employee (full time or part time)	Liquid Genomics
Anil	Vachani	Honoraria	MagArray
Shireen	Vali	Employee (full time or part time)	Cellworks Group
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Cellworks Group
		Other	Cellworks Group
Eric	Vallieres	Speakers or Advisory Board	AbbVie, AstraZeneca, Spiration
		Speakers Bureau	Synthes
		Other	Spiration, Olympus
Eliezer	Van Allen	Speakers or Advisory Board	Tango Therapeutics, Invitae, Genome Medical
		Other	Bristol-Myers Squibb, Novartis
Marc	van der Schee	Employee (full time or part time)	Owlstone Medical
		Royalty, Intellectual Property/Patent Holder	Owlstone Medical
Bram	van Ginneken	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Thirona
		Supported/Contracted Research/Grant	MeVis Medical Systems

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Peter	Van Vlasselaer	Employee (full time or part time)	Armo BioSciences
Feng	Vang	Employee (full time or part time)	Guardant Health
Johan	Vansteenkiste	Supported/Contracted Research/Grant	University Hospitals KU Leuven, Merck
		Speakers or Advisory Board	Apotex, AstraZeneca, Apotex, Boehringer Ingelheim, Merck, Novartis, Roche
		Other	AstraZeneca, Merck, Bristol-Meyers Squibb, Roche
		Honoraria	AstraZeneca, Bristol-Meyers Squibb, Merck, Roche
Nebibe	Varol	Employee (full time or part time)	Bristol-Myers Squibb
Sumath	Vasista	Employee (full time or part time)	Cellworks Research, Bangalore
Anne Marie	Velasco Roth	Employee (full time or part time)	Thermo Fisher Scientific
Vamsidhar	Velcheti	Speakers or Advisory Board	Genentech, Bristol-Myers Squibb, Celgene, AstraZeneca, Takeda Oncology Foundation Medicine, Merck, Fulgent Genetics
		Other	Clovis Oncology, Genertech, Bristol-Myers Squibb, Merck, Celgene, Foundation Medicine, AstraZeneca, MedImmune, Genoptix, Trovagene, Eisai, OncoPlex Diagnostics
		Supported/Contracted Research/Grant	Genentech, Bristol-Myers Squibb, Merck, Celgene, Foundation Medicine, AstraZeneca, MedImmune, Genoptix, Atreca, Heat Biologics, Leap Therapeutics, Eisai, OncoPlex Diagnostics, NantOmics, Alkermes, Trovagene
Victor	Velculescu	Speakers or Advisory Board	Personal Genome Diagnostics, Ignyta
Galina	Velikova	Supported/Contracted Research/Grant	European Organisation for Research and Treatment of Cancer, YCR Cancer Research, National Institute for Health Research, Breast Cancer Now
		Honoraria	Novartis, Roche
Alain	Vergnenegre	Speakers or Advisory Board	Merck, Roche, Bristol-Meyers Squibb, Pierre Fabre Oncology, Janssen, Teva, AstraZeneca, Boehringer Ingelheim
Karim	Vermaelen	Supported/Contracted Research/Grant	Bristol-Myers Squibb
		Other	Bristol-Myers Squibb, Merck, Roche
Giulia	Veronesi	Speakers or Advisory Board	Medtronic
		Honoraria	Verbsurgical, Abmedica
Cecile Rose	Vibat	Employee (full time or part time)	Biocept.
Donna	Vickery	Employee (full time or part time)	Bristol-Myers Squibb
Michele	Vigliotti	Employee (full time or part time)	Daiichi Sankyo
Victoria	Villaflor	Speakers or Advisory Board	Takeda, Genentech
Liza	Villaruz	Speakers or Advisory Board	Pfizer
Augusto	Villegas	Speakers Bureau	Celgene, Alexion, Bristol-Meyers Squibb
		Speakers or Advisory Board	AstraZeneca
Sylvie	Vincent	Employee (full time or part time)	Millennium Pharma, Takeda Pharma
Carla	Visseren-Grul	Employee (full time or part time)	Eli Lilly
Nicholas	Vogelzang	Honoraria	Boehringer Ingelheim
Everett	Vokes	Other	Genentech
Jan	Von Der Thüsen	Speakers or Advisory Board	AbbVie, Bristol-Meyers Squibb, Merck, Roche
Ute	Von Wangenheim	Employee (full time or part time)	Boehringer Ingelheim
Anagh	Vora	Employee (full time or part time)	Thermo Fisher Scientific
Pieter	Vuylsteke	Employee (full time or part time)	Agfa HealthCare
Catherine	Wadsworth	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca

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Momen	Wahidi	Other	Medtronic, Olympus, Boston Scientific
		Honoraria	CSA, PneumoX, Veran, Intuitive, Medtronic, Uptake
		Employee (full time or part time)	Vida
Satoshi	Wakai	Employee (full time or part time)	Canon Medical Systems Corporation
Heather	Wakelee	Honoraria	ACEA, Genentech, Novartis, AstraZeneca
		Supported/Contracted Research/Grant	Clovis, Exelixis, AstraZeneca, MedImmune, Genentech, Roche, Bristol-Meyers Squibb, Gilead, Novartis, Xcovery, Pfizer, Celgene, Pharmacyclics, Eli Lilly, Acea, Merck
		Speakers or Advisory Board	ACEA Biosyciences, Pfizer, Novartis, Genentech, Roche, AstraZeneca, Merck
Kazushige	Wakuda	Honoraria	AstraZeneca, Chugai Pharma, Boehringer Ingelheim
		Supported/Contracted Research/Grant	AstraZeneca
Andrew	Walding	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Jill	Walker	Employee (full time or part time)	AstraZeneca
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	AstraZeneca
Ryan	Walton	Employee (full time or part time)	AstraZeneca
Aodi	Wang	Employee (full time or part time)	OrigiMed
Ben	Wang	Employee (full time or part time)	Merrimack Pharma
Buhai	Wang	Speakers or Advisory Board	AstraZeneca, Boehringer Ingelheim, Roche
		Speakers Bureau	Eli Lilly
Fufeng	Wang	Employee (full time or part time)	Nanjing Geneseeq Technology
Kai	Wang	Employee (full time or part time)	OrigiMed
Kongming	Wang	Employee (full time or part time)	Daiichi Sankyo
Lisa	Wang	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche
		Salary	Genentech
		Employee (full time or part time)	Genentech
		Other	Roche
Sherry	Wang	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Tao	Wang	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Weifeng	Wang	Employee (full time or part time)	OrigiMed
Xiaonan	Wang	Employee (full time or part time)	Nanjing Geneseeq Technology
Yu	Wang	Employee (full time or part time)	Boehringer Ingelheim
Zuobai	Wang	Employee (full time or part time)	BeiGene
Saiama	Waqar	Supported/Contracted Research/Grant	Spectrum Pharma, Eli Lilly, Pfizer, Genentech/Roche, Daiichi Sankyo, Newlink Genetics, Puma Biotechnology, Novartis, Xcovery, Synermore biologics, Celgene, Vertex, Bristol-Myers Squibb, Stem CentRx, Hengrui Therapeutics, Checkpoint Therapeutics, Ignyta, AstraZeneca, Merck
Jeffery	Wasser	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Merck, Pfizer, Bristol Meyers Squibb, Johnson & Johnson
Chenlu	Wei	Employee (full time or part time)	BeiGene
Uri	Weinberg	Employee (full time or part time)	Novocure

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Glen	Weiss	Speakers Bureau	Merck, Novartis, Medscape, Pharmatech, Amgen, Pfizer
		Speakers or Advisory Board	Blend Therapeutics, IDEA Pharma, Igynta, Angiex, Circulogene, Paradigm, Viomics, GLG Counsel
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Circulogene
		Employee (full time or part time)	Cancer Treatment Centers of America
		Other	NantWorks, Cambridge HealthTech Institute, Tesaro
Jared	Weiss	Supported/Contracted Research/Grant	AstraZeneca, Astellas, Celgene, Merck, Pfizer, Novartis
		Speakers or Advisory Board	Biodesix, AstraZeneca, Eli Lilly, Merck, Genentech, Clovis Oncology, Inivata, BioMarck Pharma
Ashley	Wells	Employee (full time or part time)	Guardant Health
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Guardant Health
Xiaohui	Wen	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Roche
		Salary	Roche
		Employee (full time or part time)	Roche
		Royalty, Intellectual Property/Patent Holder	Roche
Howard (Jack)	West	Other	Ariad, Genentech, Roche, Takeda
		Speakers Bureau	Ariad, Bristol-Myers Squibb, Eli Lilly
		Speakers or Advisory Board	AbbVie, Ariad, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Merck, Roche, Genentech, Takeda, Spectrum
Paul	Wheatley-Price	Speakers or Advisory Board	AstraZeneca, Novartis, Eli Lilly Oncology, Bristol-Meyers Squibb, Merck, Takeda
James	White	Employee (full time or part time)	Personal Genome Diagnostics
Loretta	Williams	Supported/Contracted Research/Grant	Merck
		Salary	Merck
Keith	Wilner	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Robin	Wiltshire	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Pfizer
		Employee (full time or part time)	Pfizer
Katherine	Winfree	Employee (full time or part time)	Eli Lilly
Marie	Wislez	Speakers or Advisory Board	AstraZeneca, Boehringer Ingelheim, Roche
		Other	Pfizer, Novartis, Roche, Chugai
Ignacio	Wistuba	Other	Genentech, Roche, Eli Lilly, Bristol-Myers Squibb, Ariad, HTG Molecular Diagnostics, Asuragen, Pfizer, AstraZeneza, MedImmune
		Speakers Bureau	Pfizer, Boehringer Ingelheim, Merck, Bristol-Myers Squibb, Genentech, Roche
		Supported/Contracted Research/Grant	Genentech, Merck, OncoPlex Diagnostics, Myriad Genetics, HTG Molecular Diagnostics, Silicon Biosystems, Adaptimmune, Pfizer, MedImmune, DepArray, Bristol-Myers Squibb, Adaptive, Takeda, Amgen
		Speakers or Advisory Board	Genentech, Roche, Bristol-Myers Squibb, AstraZeneca/Medimmune, Pfizer, HTG Molecular, Asuragen, Merck, GlaxoSmithKline, Bayer
B	Wolf	Employee (full time or part time)	Blueprint Medicines Corp
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Blueprint Medicines Corp

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Jürgen	Wolf	Speakers or Advisory Board	AbbVie, AstraZeneca, Bristol-Meyers Squibb, Boehringer Ingelheim, Chugai, Ignyta, Eli Lilly, Merck, Novartis, Pfizer, Roche
		Supported/Contracted Research/Grant	Bristol-Meyers Squibb, Merck, Novartis, Pfizer
		Honoraria	AbbVie, AstraZeneca, Bristol-Meyers Squibb, Boehringer Ingelheim, Chugai, Ignyta, Eli Lilly, Merck, Novartis, Pfizer, Roche
Marianne	Wolfsteiner	Employee (full time or part time)	PRA Health Sciences
		Other	Celgene
Eugene	Woltering	Speakers or Advisory Board	Interscience Institute
Philip	Wong	Speakers or Advisory Board	AstraZeneca, Bristol-Meyers Squibb
		Supported/Contracted Research/Grant	Nexplasmagen, Instadesign
Antoinette	Wozniak	Speakers or Advisory Board	AstraZeneca, Takeda, Boehringer Ingelheim, HUYA, BeyondSpring
		Supported/Contracted Research/Grant	Boehringer Ingelheim
Jennifer	Wu	Supported/Contracted Research/Grant	AstraZeneca
Xue	Wu	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Geneseeq Technology
		Employee (full time or part time)	Geneseeq Technology
Yi-Long	Wu	Speakers or Advisory Board	AstraZeneca, Roche, Pfizer, Eli Lilly, Boehringer Ingelheim, Sanofi
		Speakers Bureau	AstraZeneca, Roche, Boehringer Ingelheim, Eli Lilly, Pfizer, Sanofi
		Honoraria	AstraZeneca, Eli Lilly, Pfizer, Roche
		Other	AstraZeneca, Boehringer Ingelheim, Merck, Roche
		Supported/Contracted Research/Grant	Boehringer Ingelheim, Roche
Alan	Wu	Employee (full time or part time)	MagArray
Fan	Xia	Employee (full time or part time)	BeiGene
Shuang	Xie	Employee (full time or part time)	Merck
Bin	Xu	Honoraria	Merck, AstraZeneca
Lu	Xu	Employee (full time or part time)	Merck
Xia	Xu	Employee (full time or part time)	Merck
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Tadaaki	Yamada	Supported/Contracted Research/Grant	Ono Pharma, Boehringer Ingelheim, Takeda
Masafumi	Yamaguchi	Honoraria	AstraZeneca, Chugai Pharma, Covidien Japan, Daiichi Sankyo, Eli Lilly, Kyowa Hakko Kirin, Ono Pharma, Taiho Pharma
Noboru	Yamamoto	Speakers Bureau	Bristol-Meyers Squibb, Pfizer, AstraZeneca, Eli Lilly, Ono Pharma, Chugai
		Speakers or Advisory Board	Eisai, Takeda, OncoTherapy Science, Otsuka, Boehringer Ingelheim
		Supported/Contracted Research/Grant	Quintiles, Astellas, Chugai, Esai, Taiho, Bristol-Meyers Squibb, Pfizer, Novartis, Daiichi-Sankyo, Bayer, Boehringer Ingelheim, Kyowa-Hakko Kirin, Takeda, Ono Pharma
Nobuyuki	Yamamoto	Speakers or Advisory Board	Eli Lilly, Quintiles, Astellas, Chugai, Esai, Taiho, Bristol-Meyers Squibb, Pfizer, Novartis, Daiichi-Sankyo, Bayer, Boehringer Ingelheim, Kyowa-Hakko Kirin, Takeda, Ono, Takeda, OncoTherapy Science
		Supported/Contracted Research/Grant	Eli Lilly
		Honoraria	AstraZeneca, Pfizer, Chugai Pharma, Bristol-Myers Squibb Japan, Ono Pharma, Eli Lilly Japan
Takeharu	Yamanaka	Supported/Contracted Research/Grant	Taiho, Takeda
		Honoraria	Taiho, Takeda, Chugai, Boehringer Ingelheim
Hiroaki	Yanagimoto	Supported/Contracted Research/Grant	Ono Pharma

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James Chih-Hsin	Yang	Other	Boehringer Ingelheim, Eli Lilly, Bayer, Roche, Genentech, Chugai, Astellas, Merck, Novartis, Celgene, Merrimack, Yuhan Pharma, Bristol-Meyers Squibb, Ono Pharma, Daiichi Sankyo, Takeda, AstraZeneca, Hansoh Pharma
		Speakers or Advisory Board	Boehringer Ingelheim, Eli Lilly, Roche, Genentech, Chugai, Astellas, Merck, Pfizer, Novartis, Takeda, Celgene, Merrimack, Yuhan Pharma, Bristol-Meyers Squibb, Ono Pharma, Daiichi Sankyo, AstraZeneca, Hansoh Pharma
		Honoraria	Novartis, Roche, Genentech, Eli Lilly and Company, Merck, Celgene, Pfizer, Ono Pharma, Bristol-Myers Squibb, Hansoh, Takeda, Boehringer Ingelheim, Astellas, Merimack, Yuhan Pharma
Lulu	Yang	Employee (full time or part time)	Eli Lilly
Rong	Yang	Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Myers Squibb
		Employee (full time or part time)	Bristol-Myers Squibb
Ming	Yao	Employee (full time or part time)	OrigiMed
Zane	Yang	Employee (full time or part time)	Spectrum Pharma
Luan Di	Yao	Employee (full time or part time)	Eli Lilly
Kazuhiro	Yasufuku	Speakers or Advisory Board	Concordia, Olympus America
		Supported/Contracted Research/Grant	Olympus Corporation, Siemens, Veran Medical Technologies, Novadaq
		Other	Intuitive Surgical, Medtronic, Johnson & Johnson, Auris Surgical Robotics
Yasushi	Yatabe	Other	Merck, Chugai-Pharma, AstraZeneca, Bristol-Meyers Squibb, Pfizer, Roche, ThermoFisher, Dako
		Honoraria	AstraZeneca, Merck, Bristol Myers, Chugai-pharma, Pfizer, Roche
Kiyotaka	Yoh	Speakers or Advisory Board	Chugai Pharma, AstraZeneca, Eli Lilly
		Honoraria	Boehringer Ingelheim, Taiho Pharma, Novartis
		Supported/Contracted Research/Grant	Bayer, Eli Lilly, AstraZeneca, Pfizer, Taiho Pharma
Takashi	Yokoi	Honoraria	Chugai Pharma, Bristol-Myers Squibb, Ono Pharma, AstraZeneca, Eli Lilly, Boehringer Ingelheim, Taiho Pharma
Toshihide	Yokoyama	Speakers Bureau	Eli Lilly
Sue	Yom	Supported/Contracted Research/Grant	Bristol-Myers Squibb, Merck, Genentech
		Royalty, Intellectual Property/Patent Holder	Springer, UpToDate
Ichiro	Yoshino	Honoraria	Pfizer, Shionogi, Astellas Pharma, Nippon Boehringer Ingelheim, Daiichi Sankyo Company, Chugai Pharma, Teijin Pharma
Hiroshige	Yoshioka	Speakers or Advisory Board	Chugai, Eli Lilly
Ming	You	Employee (full time or part time)	Nanjing Geneseeq Technology
Jenean	Young	Employee (full time or part time)	Genentech
Channing	Yu	Employee (full time or part time)	Daiichi Sankyo
Helena	Yu	Other	AstraZeneca, Boehringer Ingelheim, Eli Lilly
		Supported/Contracted Research/Grant	AstraZeneca, Astellas Pharma, Eli Lilly, Clovis Oncology, Incyte, Daiichi, Novartis
Heng	Yu	Employee (full time or part time)	MagArray
Wei	Yu	Employee (full time or part time)	Genentech, Roche
Yong	Yuan	Employee (full time or part time)	Bristol-Meyers Squibb
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Bristol-Myers Squibb
		Salary	Bristol-Myers Squibb
Kenneth	Yuen	Employee (full time or part time)	Guardant Health
Gerard	Zalcman	Speakers or Advisory Board	Roche, Boehringer Ingelheim, Pfizer, Bristol-Meyers Squibb, Merck, Oncology
		Honoraria	Roche, Eli Lilly, Pfizer, Bristol-Meyers Squibb, AstraZeneca, Boehringer Ingelheim

FIRST NAME	LAST NAME	NATURE OF RELEVANT FINANCIAL RELATIONSHIP	NAME OF COMPANY(S)
Alona	Zer	Honoraria	Bristol-Meyers Squibb, Eli Lilly, Roche
Bin	Zhang	Employee (full time or part time)	Ipsen BioPharmas
Dan	Zhang	Employee (full time or part time)	Zai Laboratory
Hui	Zhang	Employee (full time or part time)	Daiichi Sankyo
Li	Zhang	Speakers or Advisory Board	Merck, Boehringer Ingelheim
Steven	Zhang	Other	Takeda
Sylvia	Zhao	Employee (full time or part time)	Novartis
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Novartis
Cheng	Zheng	Employee (full time or part time)	Novartis
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	Novartis
Anna	Zhou	Other	Cornerstone Research Group
Caicun	Zhou	Honoraria	Roche, Eli Lilly, Boehringer Ingelheim, Merck, Hengrui, Qiru, Sanofi, Pfizer
HaoJin	Zhou	Employee (full time or part time)	Merck
Edward	Zhu	Employee (full time or part time)	Loxo
Guanshan	Zhu	Employee (full time or part time)	Amoy Diagnostics
Huiping	Zhu	Employee (full time or part time)	Asuragen
Jian	Zhu	Other	Ariad
Viola	Zhu	Speakers or Advisory Board	AstraZeneca, Biocept, Roche, Genentech, Takeda
		Ownership Interest (stocks or stock options, or other ownership interest Excluding diversified mutual funds)	TP Therapeutics
Christoph	Zielinski	Speakers or Advisory Board	Roche, Novartis, Bristol-Meyers Squibb, Merck, Ariad, Boehringer Ingelheim, Imugene, Fibrogen, AstraZeneca
Robert	Zielinski	Honoraria	Bristol-Myers Squibb

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IASLC 2019
Meetings Schedule

IASLC 19th Lung Cancer Targeted Therapies Meeting
February 20-23, 2019 | Santa Monica, California
#LCTT19

IASLC Small Cell Lung Cancer Meeting 2019
April 3-5, 2019 | New York, New York
#SCLC19

2019 European Lung Cancer Congress
April 10-13, 2019 | Geneva, Switzerland | #ELCC19

IASLC Mesothelioma Meeting 2019
July 10-12, 2019 | New York, New York | #MESO19

IASLC 20th World Conference on Lung Cancer
September 7-10, 2019 | Barcelona, Spain
#WCLC2019

IASLC North America Conference on Lung Cancer 2019
October 9-12, 2019 | Chicago, Illinois | #NACLC19

IASLC Latin America Conference on Lung Cancer 2019
October 18-19, 2019 | Mexico City, Mexico
#LACLC19

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